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Nutraceuticals: Chemoradiation Sensitizers and Adverse Effect Resolvers

Oroma B

Obstetrics and Gynecology Locum Tenens, PO Box 59, Salinas, CA 93902-0059, USA

Corresponding author: Oroma Nwanodi B

o.nwanodi@juno.com

Obstetrics and Gynecology Locum Tenens, PO Box 59, Salinas, CA 93902-0059, USA.

Tel: 3143042946

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Abstract

Background: Conventional cancer treatment is associated with resistant cancer development, treatment and quality of life limiting adverse effects, and patients' inability to complete intended treatment plans. Conventional cancer treatment's adverse effects lead 36.1% of cancer patients to seek integrative cancer treatments, which can provide a 15 percentage-point improvement in their health status. Therefore, a review of the extent of nutraceuticals applicable to conventional chemoradiation sensitization and adverse effect amelioration, as well as, for chemoprevention is valuable.

Methods: PubMed searches in September 2016 and January 2017, and hand searches in August 2016 and January 2017 were performed for English language, free full text articles published from 2012 onwards. Search terms were combinations of the key words: Homeopathy, nutraceuticals, phytochemicals, cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, prevention, and treatment. Adjuvant characteristics, adverse effects, and chemoradiation sensitization treatments were taken from these searches.

Findings: Organosulphurs are immunologic chemosensitizers. Terpenes can inhibit or reverse drug resistance. Epigallocatechin modulates estrogen receptor expression. Polyunsaturated fatty acids are cancer cell membrane chemoradiation sensitizers. Esterified vitamin E analogues and Ayurvedic Triphala radiosensitize the MCF-7 breast cancer cell line. Curcumin and resveratrol also radiosensitize cancer cells. Withaferin A is synergistic with cisplatin permitting reduced cisplatin doses while maintaining cisplatin's effectiveness. Conventional cancer treatment associated hand-foot syndrome, hematologic toxicity, mucositis, pain, sleep dysfunction, and overall toxicity respond to several nutraceuticals.

Conclusion and significance: The evidence for concurrent nutraceutical use with conventional chemoradiation to reduce conventional chemoradiation doses, and to prevent or limit conventional chemoradiation associated adverse effects exists. *In vitro*, and murine and human *in vivo* evidence suggests that nutraceuticals are effective chemoradiation sensitizers and adjuvants, with synergistic potential. Expanded scope positive human trials would facilitate a broader and deeper role for nutraceuticals in integrative cancer treatment.

Keywords: Adverse effects; Breast cancer; Cervical cancer; Cancer prevention; Cancer treatment; Chemosensitization; Endometrial cancer; Epigallocatechin-3-gallate; Naturopathic medicine; Nutraceuticals; Ovarian cancer; Phytochemicals; Polyphenols; Radiation sensitization

Abbreviations: AMPK: p-AMP-activated protein kinase; AP-1: Activating protein 1, a gene expression regulating transcription factor; B16 melanoma: A murine tumor cell line with multiple sub-lines (one of which is B16-B16) used to study solid tumors and metastasis; BAX: B-cell lymphoma 2 associated X protein; BBI: Bowman-Birk inhibitor; Bcl_2: B-cell lymphoma 2 protein; Brk: Breast tumor kinase, a catalytic nonreceptor tyrosine kinase; BCRP: Breast cancer

resistance protein; caSki: Epidermoid cervical carcinoma cell line; COX-2: Cyclooxygenase-2; c-fos: A proto-oncogene, the human homolog of the retroviral oncogene v-fos; cyclinD1: A protein with the retinoblastoma protein binding motif, Cyclin-dependent kinase and cyclin-dependent kinase inhibitor binding domains; CSC: Cancer stem cells; CYP450: Cytochrome P450 – an isozyme family that biotransforms medications; DIM: Diindolylmethane; DNA: Deoxyribonucleic acid; EGCG: Epigallocatechin-3-gallate; EGFR: Epidermal growth factor receptor; ER: Estrogen receptor; ERK: Extracellular signal regulated kinase; fra-1: bZIP family oncogenic transcription factor; FRAP1 (mTOR): A serine/threonine kinase crucial to cellular growth and proliferation; GFR: Growth factor receptors Includes the epidermal growth factor receptor (EGFR) family: (ErbB1), HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4; HeLa: An immortalised cervical cancer cell line taken from Henrietta Lacks; HESA-A: A patented immunomodulating medication including *Apium graveolens* L. (celery), *Carum carvi* L. (caraway) and *Penaeus latisculatus* (king prawn); HLA: Human leukocyte antigen; HPV: Human Papilloma Virus; I3C: Indole-3-carbinol; IC_{50}: Inhibitory concentration at which response to, or binding of an inhibitor is halved; IL-1β: Interleukin-1β, an agonist for innate immunity and inflammation; IL-4: Interleukin-4, a cytokine that induces naïve helper T cell differentiation; IL-6: A milieu-dependent anti- or pro-inflammatory protein; LDL: Low density lipoprotein; mTOR: Mammalian (mechanistic) target of rapamycin; mTORC1: Mammalian (mechanistic) target of rapamycin complex 1, a protein synthesis controller; mTORC2 Mammalian (mechanistic) target of rapamycin complex 2, a cellular metabolism and cytoskeleton regulator; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2: Nuclear factor (erythroid-derived 2)-like 2 transcription factor; ObGyns Obstetrician-gynecologists; PI3K: Phosphotydyl inositol-3-phosphate kinase; p21WAFI/CIP1: cyclin-dependent kinase inhibitor 1, mediator of the p53-dependent G1/S cell cycle checkpoint; P-gp: P-glycoprotein; PKM1: Pyruvate kinase isozyme M1; PKM2: Pyruvate kinase isozyme M2; PUFA: Polyunsaturated fatty acids; QOL: Quality of life; RAPTOR: Regulatory-associated protein of mTOR; RICTOR: Rapamycin-insensitive companion of mTOR; ROS: Reactive oxygen species; TNBC: Triple negative breast cancer; TNF-α: Tumor necrosis factor-α; TRAIL: TNF receptor apoptosis inducing ligand; VEGF: Vascular endothelial growth factor; VEGFR-2: VEGF receptor subtype 2; VEGFR-3: VEGF receptor subtype 3 and VEGF-C: VEGF protein C, which binds to VEGFR-2 and VEGFR-3.

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Nutraceuticals: Chemoradiation Sensitizers and Adverse Effect Resolvers

Introduction

Nutraceuticals and phytochemicals play a role in preventing and limiting the adverse sequelae of chemotherapy and radiotherapy, without reducing chemotherapeutic and radiotherapy effectiveness [1-3]. Cancer treatment adverse effect amelioration is the primary reason 28.3% of early-stage breast cancer patients in Villejuif, France, use integrative therapies [4]. Although chemoradiation adverse effect treatments form 23.9% of overall European integrative cancer center treatments, 36.1% of Dutch parents of pediatric cancer patients choose integrative treatments for adverse effects of their children's conventional cancer treatments [5,6]. Integrative medicine use is attributed to a 35% reduced health status deterioration, compared to 50% in nonusers [7]. Improved quality of life (QOL) and symptomology are a goal of 75% of Swiss parents seeking integrative cancer treatment for their children, which is consistent with practitioners' goals [5,8]. Relapse prevention, which should include increased treatment efficacy only forms 6.3% of European Integrative Cancer Center therapeutic aims [5]. However, increased bodily ability to fight cancer is the reason why 50.7% of cancer patients use integrative medicine [5].

Integrative cancer treatment for chemoradiation adverse effect amelioration is recommended by 42.9%, and practiced by 40.3% of 310 Hessian region obstetrician-gynecologists (ObGyns) who responded to a survey at an educational meeting [9]. Only 8.7% of these ObGyns reported that integrative therapies would be unreasonable for cancer

treatment adverse effects remediation [9]. Integrative cancer treatment targets chemoradiation associated nausea and vomiting, neuropathy, lymphedema, leukopenia, mucositis, and xerostomia [5]. Cancer associated anxiety and depression, fatigue, iatrogenic menopause, muscle disorder, pain, secondary infections, and sleep disturbances are also addressed by integrative cancer treatment [5]. Integrative cancer treatment can also treat diarrhea and constipation, irrespective of causation [5]. Herbal medicine, minerals, oligotherapy, phytotherapy, plants, probiotics, propolis, and vitamins form up to 65% of the integrative therapies used by early-stage breast cancer patients [4].

Apparently, integrative cancer treatments should have much to offer gynecologic cancer patients. The curative oncologic potential of homeopathy and nutraceuticals is addressed in two separate studies. Therefore, this study seeks to elucidate the extent of nutraceuticals as chemoradiation sensitizers, with an emphasis on gynecologic cancers. Nutraceuticals as adverse effect ameliorators, and nutraceuticals' adverse effects will also be addressed.

Methods

PubMed searches in September 2016 and January 2017, and hand searches in August 2016 and January 2017 were performed for English language, free full text articles published from 2012 onwards. Search terms were combinations of the key words: homeopathy, phytochemicals, breast cancer, cancer, cervical cancer, endometrial cancer, ovarian cancer, prevention, and treatment, as shown in **Figure 1.** Adjuvant characteristics, adverse effects, and chemoradiation sensitization treatments were taken from these searches. These searches retrieved 172 articles, of which 47 articles had a homeopathy focus, 86 articles were focused on phytochemicals, and 39 articles were from content driven hand searches. Cumulatively, 31 articles were excluded for strictly homeopathy related content, 2 articles were editorials, and 1 article was a letter to the editor. There were 15 duplicate articles, 2 redundant articles, and 43 extraneous articles, resulting in a total of 94 excluded and 78 included articles.

Nutraceutical chemoradiation sensitizers

Sensitizing treatments prevent resistance, the innate responses to a treatment that diminish the treatment's effectiveness. Nutraceutical and conventional chemoradiation mechanism of action patterns may be complementary and synergistic, yielding greater treatment effectiveness than the sum effectiveness of each treatment as a single agent. It is biologically plausible that if a DNA damaging treatment and a treatment that prevents DNA repair mechanisms are administered concurrently, the two treatments will be synergistic [10]. Radiation sensitizers that get cells to sensitive parts of the cell cycle are given starting with radiation onset and may be continued after the last radiation treatment. DNA repair inhibitors are also continued post-radiation. Chemosensitizers can also function by tumor microenvironment alteration, creating a hostile environment for cancer stem cells (CSC) [11].

Diindolylmethane (DIM), the metabolite of the organosulphur indole-3-carbinol (I3C), negates conventional chemotherapeutic's activation of nuclear factor kappa-β (NF-κβ), a proinflammatory transcription factor, thereby making pancreatic cancer chemosensitive to conventional chemotherapeutics [12]. The anti-inflammatory phytonutrients, apigenin, baicalein, curcumin, epigallocatechin-3-gallate (EGCG), genistein, luteolin, oridonin, quercetin, and wogonin suppress NF-κB, inhibit proinflammatory cytokines including tumor necrosis factor-α (TNF-α, an acute inflammation cytokine) and IL-6 (a milieu-dependent anti- or pro-inflammatory protein), may stabilize p53 protein, and sensitize TNF receptor apoptosis inducing ligand (TRAIL) induced apoptosis, preventing or delaying chemotherapy resistance [11]. Quercetin and EGCG also overcome chemoresistance by apoptosis induction [13]. Quercetin additionally reduces chemoresistance by inhibiting heat shock factors and P-glycoprotein (P-gp) [13,14]. Quercetin has a 1.65 cervical cancer radiosensitizing enhancement ratio [15].

The isoflavone genistein also overcomes chemoresistance by increasing multidrug resistance (MDR) protein 1 affinity for glutathione and modulating breast cancer resistance protein (BCRP) [13]. Genistein also radiosensitizes for HeLa and CaSki cervical cancers [15]. Baicalein, kaempferol, and rutin inhibit P-gp [13,14]. Kaempferol and luteolin reverse BCRP-mediated chemotherapy resistance [13]. Silibinin, a polyphenol and major active constituent of silymarin from milk thistle seeds, reduces chemoresistance by BCRP interaction, apoptosis induction, down regulating cyclin expression, and inhibiting angiogenesis and P-gp [13].

Genistein and I3C synergistically inhibit human HT-29 colon cancer cells [12]. The cruciferous vegetable derived benzyl- and phenethyl-isothiocyanates irreversibly inhibit N-acetyltransferases thereby decreasing carcinogenic aromatic amines' metabolic activation, and reducing the development of environmental carcinogen triggered cancers [16]. *In vitro* studies of the phytoalexin isoflavone glyceollin I have achieved a 68% decrease in invasion and an 83% decrease in migration of letrozole-resistant breast cancer cells [17].

The terpene linalool chemosensitizes human breast adenocarcinoma by reversing doxorubicin resistance [12]. The antioxidative terpene α-Pinene inhibits MDR associated protein 2- and BCRP-mediated transport [12]. Rice bran oil tricin and tocotrienols, and defatted rice bran chemically sulfated polysaccharide SRBPS2a decrease MDA-MB-468 breast adenocarcinoma cell line tumors' volume, decrease breast tumors in general, with maximal inhibition of EMT-6 breast carcinoma cell line tumors [18]. Phenolic extracts inhibit MDA-MB-468 and HBL100 breast cancer [18]. Denatured rice bran hemicellulose increases yeast-mediated caspase-dependent apoptosis in Michigan Cancer Foundation-7 (MCF-7) invasive breast ductal carcinoma cell line, ZR75-1 ductal carcinoma, and HCC-70 triple negative (estrogen receptor [ER] negative, progesterone receptor negative, and HER2 negative) breast cancer (TNBC) cell lines [18]. Denatured rice bran hemicellulose also prevents U266 multiple myeloma cell line G_0-G_1 phase cell entry [18]. Rice bran, rice bran oil, and defatted rice bran reduce the incidence and quantity of

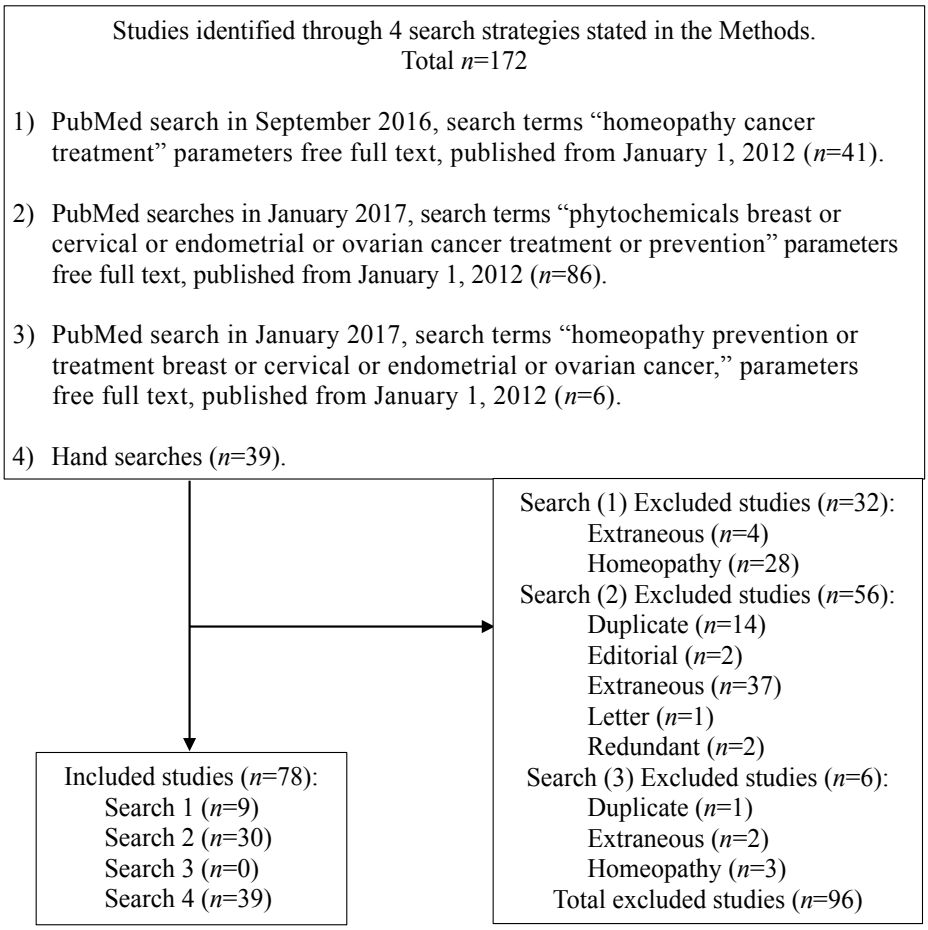

Figure 1 Literature selection flowchart.

colorectal cancer tumors [18]. Fermented brown rice and bran similarly affect lung cancer [18].

About 20% of breast cancers are poor prognosis, estrogen receptor-α (ERα) negative[19]. ER-β inhibits breast cell growth, whereas ER-α is proliferative [20]. Glyceollin I decreases Zinc Finger E-Box binding Homeobox 1 expression 3.39-fold, affecting a ER-independent pathway crucial to TNBC [17]. The tea derived polyphenol EGCG is an antiangiogenic chemosensitizer [21]. EGCG induces ERα expression in ERα-negative breast cancer cells, allowing an estrogen antagonist such as Tamoxifen, to be used in ER-α negative breast cancer treatment [19]. B-sitosterol is synergistic with tamoxifen, potentiating tamoxifen's activating effect on ceramides metabolism [22]. EGCG activates wild-type p53, p21, and B-cell lymphoma 2 (Bcl_2) associated X proteins (Bax) in prostate cancer, but only Bax in breast cancer [23]. EGCG, more so than other tea-derived polyphenols - catechin, epicatechin and epigallocatechin - is anti-proliferative to the MDA-MB-231 TNBC cell line via pro-oxidant cytotoxicity using copper ions, which are often elevated in cancer [24].

The organosulphur isothiocyanate sulforaphane is synergistic with exemestane, a synthetic steroidal irreversible inhibitor of the terminal and rate-limiting aromatase reaction in estrogen biosynthesis. Sulforaphane inhibits vascular endothelial growth factor receptor 2 (VEGFR-2) transcription [21]. Vascular endothelial growth factor (VEGF) is an angiogenesis signaling protein. Exemestane treats ER+ breast cancer [25]. Concurrent sulforaphane and exemestane synergistically inhibit lipopolysaccharide activated inducible nitric oxide synthase in mouse peritoneal macrophages, and NF-KB activation in U937 myeloid monocyte lymphoma cell line [25]. *In vitro* studies have shown that sulforaphane is synergistic with gemcitabine against MCF-7 cells, combination index <1, $p<0.05$, allowing lower gemcitabine dose [26]. In this case, sulforaphane downregulated Bcl2 and cyclooxygenase-2 (COX-2), producing apoptotic and anti-inflammatory effects respectively [26]. Sulforaphane also radiosensitizes head and neck cancer cells, and chemosensitizes for arsenic trioxide and doxorubicin [26].

Single agent or adjuvant oridonin and wogonin are apoptotic to paclitaxel-resistant epithelial ovarian cancer (EOC) cells, and to carboplatin-paclitaxel resistant EOC cells [11]. *In vitro* studies indicate that apigenin, genistein, kaempferol, luteolin, and quercetin may be anti-angiogenic via VEGF production inhibition [11,13]. Apigenin, genistein, kaempferol, luteolin, and quercetin may also suppress ovarian cancer cell metastasis [11,13]. Oridonin and wogonin may suppress ovarian CSC via surface marker epithelial cell adhesion molecule downregulation [11]. Wogonin modulates COX-2 expression, interleukin (IL)-1β production,

and VEGF-C-induced VEGFR-3 phosphorylation [21]. For neural stem cell expressed indoleamine 3,5-dioxygenase-1 inhibition to create an immunologic anti-cancer microenvironment, apigenin, wogonin, chrysin, baicalein, genistein, and quercetin, (in order of decreasing inhibitory activity), can be effective [27]. Kaempferol, a flavanol polyphenol, down-regulates c-Myc in epithelial ovarian cancer cell line OVCAR-3, resulting in synergism with cis-platinum [11]. Ellagic acid dosed at 100 µM or more, is a dose dependent pre-radiation pro-oxidant to HeLa cervical cancer cells, which then lose cellular viability 1 hour post 3 Gray radiation [28]. Ellagic acid is unique in preventing epigenetic modifications in MCF-7 via DNA methyltransferase inhibition [29].

Cancer cells are deficient in polyunsaturated fatty acids (PUFA), which partially contributes to chemoradiation resistance. PUFA supplementation, such as arachidonic acid supplementation, increases PUFA content in tumor cell membranes, radiosensitizing cancer cells [28]. Renal cancer cell lines have been radiosensitized by PUFA supplementation [30]. Fish oil supplementation to lung cancer chemotherapy increases the response rate (p=0.008), increases benefit (p=0.02), increases the number of chemotherapy cycles received (p=0.02), and increases 1-year survival from 38.7% to 60% (p=0.15) [31]. Tocopherol succinate (an esterified vitamin E analogue), when used with gamma radiation increases MCF-7 breast cancer cell line apotosis [28]. Ayuverdic Triphala formulation with gamma radiation also radiosensitizes MCF-7 [28]. The cannabinoid receptor agonist, aminoalklylindole WIN55,212-2 (WIN2), has stereoisomer specific radiation synergistic antiproliferative activity against MCF-2, MDA-MB231 cell lines ($p<0$.05) [32]. The radiation-WIN2 combination displayed autophagy and senescence [32]. WIN2 displayed dose-dependent ceramide metabolism inhibition [32].

Curcumin, a turmeric derived polyphenol, radiosensitizes prostate cancer cells by down regulating pro-survival factors [33]. Curcumin overcomes chemoresistance by angiogenesis, DNA repair, and NF-kB signaling inhibition, proapoptotic signaling proteins upregulation, and mitochondrial dysfunction [13]. Curcumin's downregulation of NF-kB and increased reactive oxygen species (ROS) generation allow chemosensitization to cisplatin [15]. Quercetin and wogonin also chemosensitize to cisplatin [15]. Curcumin's downregulation of NF-kB and serine kinases allows chemosensitization to taxol and paclitaxel [15]. Curcumin sensitizes the DLD-1, HCT116, and LoVo colon cancer cell lines to silymarin, creating 5-fold increased caspase3/7 antiproliferative activity compared to single agent silymarin [34]. Curcumin chemosensitizes drug resistant cervical cancer to vinblastine, mitoxantrone, and etoposide [15]. Curcumin and isoliquiritigenin (a chalcone) are directly toxic to neural stem cells that express indoleamine 3,5-dioxygenase-1 [27].

Turmeric is synergistic with docetaxel in lung cancer treatment, may improve tolerability of bleomycin and cisplatin, sensitize cancer cells for taxanes (as noted for curcumin above), and reduce resistance to vincas [35]. Similarly, the polyphenol diarylheptanoid hirsutenone from *Alnus hirsute* var. sibirica tree bark, dosed at 10 µM *in vitro*, preferentially sensitizes chemoresistant p53 wild-type C13 and OVCAR-433 ovarian cancer cells to cisplatin [36]. Hirsutenone is less effective with p53-defective A2780cp, Hey, Occ-1, and SKOV3 ovarian cancer cell lines [36]. Hirsutenone-dependent, protein kinase B modulated, phosphatidylinositol 3-kinase inhibition is linked to cisplatin and ubiquitin-proteasome-dependent X-linked inhibitor of apoptosis degradation, and increased mitochondria to nucleus translocation of apoptosis-inducing factor [36].

Trametes versicolor (Coriolus or Polyporus), accounts for 25% of Japanese cancer care cost [37]. The *Trametes versicolor* extract polysaccharide Kureha, gives an HLA type associated proven survival advantage in gastrectomy and esophagectomy patients [38]. *Trametes versicolor is* also used in integrative breast cancer treatment [39]. *Ganoderma lucidum* (Reishi or Ling Zhi), contains ganoderic acid and triterpenoids that inhibit cancer cell growth [40]. *Viscum album* has antitumor activity for hepatocellular carcinoma, and may reduce malignant ascites volume [41]. *Teucrium polium* L., induced spontaneous regression of alveolar soft part cancer [41].

The Ferula species derived monoterpene conferone is a potent P-glycoprotein inhibitor that reverses MDR when concurrently given with vinblastine to Madin Darby canine kidney cells with the *MDR1* gene, which encodes for the efflux protein, P-glycoprotein (MDCK-MDR1), and to the bladder carcinoma 5637-cell line [42]. Without vinblastine, conferone lacks notable anti-tumor activity [42]. Independently, confereone has moderate cytotoxic activity against ovarian cancer CH1 and lung cancer A549 cell lines [42]. The Ferula species derived phytoestrogenic monoterpenes stylosin and tschimgine may have independent anti-cancer activity against the 5637 and MCF-7 cell lines, and have moderate cytotoxic activity against the melanoma SK-MEL-28 cell line [42]. The activity of conferone, stylosin, and tschimgine against CHI lymphoblastoid, A549 alveolar basal epithelial carcinoma, and SK-MEL-28 mutant B-raf and wildtype N-Ras cell lines lacks structure-activity relationships [42]. Therefore, conferone, stylosin, and tschimgine are believed to be chemopreventive and/or chemosensitizing, not directly cytotoxic [42]. The Ferula species derived monoterpenes galbanic acid and farnesiferol may also be potent P-glycoprotein inhibitors to reverse MDR [42].

Pretreatment of the MDA-MB-231 and T47D cell lines with the polyphenol enterolactone radiosensitizes by increasing breast cancer radiation-induced apoptosis, chromosomal aberrations, and micronuclei formation, and reducing radiation-induced DNA damage repair [43]. *In vitro* studies of melatonin, a polyphenol, show decreased HeLa cell viability [44]. Melatonin synergistically increased the cytotoxicity of cisplatin, 5-fluorouracil, and doxorubicin against HeLa cells by increasing caspase-3 activation, ROS overproduction driven entry into mitochondrial apoptosis, and increased DNA fragmentation [44]. Curcumin also modulates HeLa cells by down regulating Human papilloma virus (HPV) 18 transcription, reversing *c*-fos and fra-1 expression, and inhibiting AP-1 binding [15].

Resveratrol, a phytoalexin polyphenol mainly found in grapes, berries, peanuts, pines, and herbs, alters cell cycle progression and has a cytotoxic response to ionizing radiation [28,45]. Resveratrol at 250 μM, inhibits HSP27, induces caspase 3 and 9 dependent apoptosis (p<0.005), and increases mitochondrial permeability in MCF-7 cells (p<0.005), facilitating cytotoxic doxorubicin treatment sensitization (p<0.05) [46]. This is consistent with HSP27 overexpression in doxorubicin resistant MDA-MB-231 cells, and in HER2 stability that reduces trastuzumab susceptibility [46]. Resveratrol also reduces chemoresistance by inhibiting angiogenesis and MAP kinase [13].

Withaferin A, from *Withnia somnifera* (ashwagandha), reduces EOC growth by 70 to 80% and inhibits metastasis by inhibiting CSC [47,48]. In mouse models, Withaferin A in combination with 0.75 the normal dose of cisplatin achieves identical anti-cancer results as normal dose cisplatin. The *in vivo* human goal is to prevent or reduce platinum-resistance incidence, which occurs in up to 70% of cases [47]. Withaferin A has synergistic cytotoxicity with doxorubicin for U2OS osteogenic sarcoma and MCF-7 breast cancer cell lines [49]. *In vivo* xenografts of A2780, A2780/CP70, and CaOV3 epithelial ovarian cancer cell lines treated with Withaferin A and doxorubicin have a 70 to 80% greater reduction in cancer growth than if either agent is used alone, p<0.05 [49]. Withaferin A and doxorubicin at one-ninth the standard dose display time- and dose-dependent anti-proliferation and cell death induction that surpasses that of standard dose doxorubicin [49]. Combining doxorubicin with the synthetic curcumin analog HO-3867 increased cytotoxicity, permitting reduced doxorubicin dose, in turn decreasing myocardial toxicity [49]. Curcumin nano-complexed with doxorubicin overcomes murine *in vivo* adenosine triphosphate transport associated MDR human and murine acute leukemia, multiple myeloma, ovarian and prostate cancer phenotypes [50]. Curcumin-doxorubicin nanocomplex doses comparable to those at which free doxorubicin and pegylated liposomal doxorubicin cause cardiotoxicity and bone marrow suppression are nontoxic [50].

Milk derived cysteine containing whey proteins are physiologically active beyond the gastrointestinal tract, facilitating antioxidant glutathione synthesis, and phase II detoxification [51]. Mice models show that dairy products reduce tumors by a factor of 0.2 to 0.7 [52]. Soy derived Bowman-Birk inhibitor (BBI) is also a chemoradiation sensitizer, synergistic with cisplatin [51].

Nutraceuticals as cancer preventives

Soy protein intake is inversely associated with breast cancer recurrence and mortality, irrespective of ER status and tamoxifen use [53]. Soy isoflavone intakes of more than 43.75 mg/day have a 0.48 odds ratio (OR) for ER-positive breast cancer incidence, when compared to an intake of less than 18.76 mg/day [54]. Similarly, consumption of soy milk fermented with *Lactobacillus casei* strain Shirota, four or more times weekly has an OR of 0.65 for ER-positive breast cancer development when compared to an intake of less than 4 times weekly [54]. Soy milk fermented with *Streptococcus thermophilus* 14085 or *Bifidibacterium infantis* 14603 inhibits HT-29 epithelial morphology and caco-2 heterogenous epithelial colorectal cancer cell lines [54]. In mice models, soy milk fermented with *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Streptococcus lactis*, or *Bifidobacteria* inhibited the ER-positive MCF-7 breast cancer [54]. Compared to nonfermented rice bran, ferrulic acid content is increased in rice bran fermented with *Saccharomyces boulardii*, which decreases lymphoma cell viability [18]. *Aspergillus oryzae* fermented brown rice decreases bladder, esophageal, and tongue cancer incidence and the number of tongue tumors [18]. Fermented brown rice and bran decrease hepatocellular carcinoma incidence [18]. *Lentinus edodes* cultured rice bran exo-biopolymer inhibits B16-B16 melanoma [18]. Human epidemiological studies attribute whey-rich dairy products with cancer risk reduction [51].

Phytosterols increase antioxidant enzyme activity and inhibit carcinogen, ROS, and pro-inflammatory cytokine production [52]. Phytosterols are anti-angiogenic. Phytosterols are pro-apototic by increasing caspase-3 and mitogen activated protein kinase enzymes, decreasing prostaglandin series 2, Bcl2, phosphotydyl inositol-3-phosphate kinase and protein kinase B [52]. The highest quartile phytosterol intake is associated with a 50% reduction (95% CI 0.31 to 0.70) in lung cancer [20]. The highest phytosterol intake is also associated with a 0.33 OR (95% CI 0.17 to 0.65) of stomach cancer incidence [20]. In some Iranian women, after adjustment for confounders, the highest quartile phytochemical index intake (mean 41.6 ± 10.2), is associated with significantly reduced breast cancer risk (OR=0.08, 95% confidence interval [CI] 0.01-0.84) [53]. An *in-utero* blueberry diet reduces the breast glandular terminal end buds, which are most susceptible to carcinogen transformation [29]. From adolescence through late menopause, berry-polyphenols are antiestrogenic and modulate breast cancer development pathways, including growth factor receptor (GFR) activation [29]. Given the above, apigenin and luteolin rich celery heart, parsley, and thyme; quercetin rich apple and onion; EGCG and ellagic acid rich green tea; ellagic acid rich freeze-dried organic berry; genestein rich soybean; curcumin rich tumeric; and oridonin rich *Rabdosia rubescens* (Dong Ling Cao) would be recommended as part of an ovarian cancer prevention diet [11]. A diet high in carotenoids, fiber, lignans (coffee, carrots, cucumbers, and strawberries), poultry, stigmasterol (>23 mg per day), and vegetables is known to be chemoprotective for ovarian cancer [55]. Consistent with this, an Italian pooled analysis of 1,411 cases and 3,668 controls, showed that a high vegetable, fruit, nut, fish, unsaturated fats; moderate alcohol; and low meat, dairy, cereals and potatoes diet can reduce endometrial cancer risk to a 0.43 OR, 95% CI 0.34 to 0.56 [56]. However, a prospective study of 112,088 women did not find that a diet high in vegetables or fruits reduced endometrial cancer risk [57].

Tea as a functional food is being studied as a chemopreventive for breast, fibrosarcoma, gastric cancer, glioblastoma, head and neck cancers, neuroblastoma, and prostate cancer as its constituent polyphenols inhibit VEGF, NF- κβ, c-fos and cyclinD1 promoter activity, Bax, and stabilize p53 [21]. The combination

of EGCG 200 mg, epigallocatechin 37 mg, and epicatechin 31 mg, as an oral capsule and/or vaginal ointment achieves a mean 69% clearance of HPV-related cervical lesions [15]. Kaemferol, a flavanol polyphenol, is chemopreventive for ovarian cancer by COX-2 and IL-4 inhibition, Src kinase suppression, and NF-κβ downregulation [21].

Oleanolic acid, is a pentacyclic triterpene found in apples, dates, grapes, olives/olive oil, pomegranates, rosemary, and sage [58]. Oleanolic acid has demonstrated *in vitro* antiproliferative potential against breast cancer and melanoma cell lines [58,59]. Oleanolic acid inhibits MCF-7, MDA-MB-231, and Hs578T cell growth by increasing AMPK expression, upregulating p53 and p21WAFI/CIP1 expression, while down regulating ERα expression, inhibiting mTORC1, mTORC2, regulatory-associated protein of mTOR (RAPTOR), rapamycin-insensitive companion of mTOR (RICTOR), and mTOR/ FRAP1 [58]. Oleanolic acid also suppressed aerobic glycolysis by increasing PKM1 and decreasing PKM2 and mTOR [58]. Oleanolic acid also inhibits MDA-MB-231 cell invasion and migration by decreasing breast tumor kinase (Brk), paxillin, and Ras-related C3 botulinum toxin substrate 1 phosphorylation [58]. Curcumin dosed at 8 mg daily is a cervical cancer chemopreventive for 25% of women. Vaginal capsules and vaginal cream have been trialed, with 81.3% and 87.7% HPV clearance rates, respectively [15].

Beneficial estrogen metabolism is promoted by the cruciferous indole I3C and its metabolite DIM, in-turn protecting against estrogen-enhanced breast, cervical, and endometrial cancers [12]. DIM and I3C are chemoprotective against BT549, MCF-7, MCF-10A, MDA-MB-231, and T47D breast cancer cell lines [12]. DIM exhibits dose and time dependent BRCA1 upregulation [12].

Nutraceuticals for chemoradiation adverse effect resolution

Over 60 nutraceuticals including phytochemicals and vitamins interact with oncologic target molecules [60]. Phytochemicals offer cancer patients clinically (but not statistically) significant pain relief [61]. In non-smokers, antioxidants, including glutathione, and N-acetyl-cysteine, have been shown to reduce chemotherapy toxicity without reducing chemotherapeutic effectiveness [1].

Mistletoe dose-dependently inhibits cell-cycles and triggers apoptosis [62]. Meta-analysis of supportive mistletoe for nonmetastatic colorectal cancer at German and Swiss tumor centers showed fewer adjuvant therapy-related adverse reactions (p<0.001), fewer persisting symptoms (p<0.001), and possible survival benefit [62]. Intravenous mistletoe is recommended for improved overall health, improved tolerance of chemotherapy, and stabilizing pathologic processes [63]. Most studies on mistletoe remedies have not used standardized QOL assessment [64]. When studies on mistletoe remedies have used standardized QOL measures, mistletoe remedies have not been found to provide a significant QOL improvement in comparison to standard care [64].

Middle Eastern integrative cancer treatment research includes nutraceuticals [41]. Honey can be prophylactically applied to radiation-treated areas to mucositis [41]. Kefir and yogurt can reduce colorectal cancer chemotherapy related sleep disturbances [41]. *Triticum aestivum* (wheatgrass juice) had reduced hematological toxicity of breast cancer treatment [41]. *Lawsonia inermis* (topical henna) treats hand-foot syndrome due to capecitabine [41]. HESA-A, herbal-marine formulation containing *Apium graveolens* L. (celery), *Carum carvi* L. (caraway) and *Penaeus latisculatus* (king prawn) improved pain and Kamofsky performance scale scores in colon and breast cancer patients [41].

Nutraceuticals: Adverse effects

Integrative medicine synergism raises conventional cancer treatment efficacy [5]. However, nutraceuticals can also negatively affect conventional cancer treatment [65]. For instance, antioxidant harm has been substantiated for smokers receiving radiotherapy [66]. Lung and prostate cancer risk is significantly raised by vitamin E and high dose β-carotene [21]. However, it is unclear if this risk exists when mixed tocopherols are the vitamin E source, instead of solely α-tocopherols. Nonetheless, these findings are concerning. Moreover, as 40% or fewer integrative medicine users discuss their integrative medicine use with their oncologists, appropriate counseling may not occur [41].

Genistein can be pro-estrogenic in breast cancer, so should be avoided by breast cancer patients [21]. The antiestrogens anastrazole, exemestane, letrozole, and tamoxifen, were used by 38% of Scottish breast cancer patients also taking chamomile, echinacea, garlic, ginseng, grapefruit, pomegranate, or peppermint, all of which affect cytochrome P450 (CYP450) [65]. Ellagic acid is a CYP450 inhibitor capable of reducing anastrazole, exemestane, letrozole, imatinib, and irinotecan levels, while increasing tamoxifen levels [6,65]. Cell repair, including Poly ADP-Ribose Polymerase 1 (PARP-1) mediated cell repair, and signaling pathways can be negatively affected by nutraceuticals [4]. Similarly, excessive anti-angiogenic nutraceutical consumption will inhibit angiogenesis in healthy tissue [21]. Patients prescribed methotrexate or other vitamin antagonists must be counseled against use of nutraceuticals rich in the targeted vitamin [6].

Nuances of nutraceutical and phytochemical use must be understood. Co-administration requirements, dose dependent and whole-body organ system effects should be recognized. For instance, while I3C and DIM are chemoprotective for estrogen-associated cancers, I3C and DIM have been associated with hepatic cancers in rainbow trout [12]. Omega-3-PUFAs should be limited to 5 to 6.9 grams daily due to anticoagulation, glycemic dysfunction, and increased low density lipoprotein (LDL) [67].

In a study of French early-stage breast cancer patients, integrative medicine use was associated with an average 0.6 more important or very important adverse effects than was nonuse [4]. Importantly, integrative medicine use was significantly associated with increased vaginal dryness (p=0.06), fewer hot flushes (p=0.03), and more uncategorized adverse effects (p=0.03) [4]. Minor adverse effects associated

with polyphenols are abdominal pain, diarrhea, fatigue, insomnia, and nausea [68]. Adverse effects can be dose and comorbidity dependent. Confusion resulted with consumption of 6 grams daily of green tea extract in an advanced stage prostate cancer patient, but maximum daily green tea extract intake should be 750 mg/day [68]. Grade 4 nephrotoxicity and emesis occur with quercetin dosed at 1,400 mg/m^2 weekly, whereas average daily quercetin intake is about 16 mg/day [68].

Future research

Resveratrol at 250 μM, should undergo *in vivo* murine trials with MCF-7, doxorubicin resistant MDA-MB-231, and trastuzumab unsusceptible HER2 positive cancers [46]. Pretreatment with enterolactone should undergo *in vivo* murine radiosensitization trials with MDA-MB-231 and T47D cell lines [43]. Quercetin and genistein should undergo broader *in vivo* radiosensitization trials. Hirsutenone should undergo *in vivo* trials with chemoresistant p53 wild-type C13 and OVCAR-433 [36]. Phase II trials of BBI for oral cancer prevention are indicated, given successful phase I trials [51].

Having completed *in vitro* cell line and *in vivo* mice trials, apigenin, baicalein, chrysin, genistein, quercetin, and wogonin, should be ready for human trials of VEGF and indoleamine 3,5-dioxygenase-1 inhibition [27]. Because DIM effectively inhibits NF-κβ, which is increased in ovarian cancer [69], DIM could be an ovarian cancer chemosensitization trial candidate. *In vivo* studies of glyceollin I of more than 40 days duration are needed to ascertain if glyceollin I can reduce tumor weight [17]. Having completed numerous *in vitro* human cell line studies, and mice and rat *in vivo* studies, rice bran derivatives should be considered for clinical trials [18]. Poly-catechins such as sinecatechins could be trialed for intravaginal HPV lesions.

Chemoradiation sensitizers candidates should undergo randomized controlled comparative effectiveness studies. For instance, curcumin, hirsutenone, and withaferin A could be studied for cisplatin and/or doxorubicin chemosensitization and synergism equivalence. The curcumin doxorubicin nano-complex should be considered for human *in vivo* trials against acute leukemia, multiple myeloma, ovarian and prostate cancer [50]. Curcumin, ellagic acid, tocopherol succinate, and tumeric, could be studied for ionizing radiation sensitization equivalence. Immune response modulation astaxanthin, resveratrol, the *Lentinus edodes* derived polysaccharide L-II and lentinan, and the polysaccharide fractions of *Ganoderma lucidum* and *Astragalus membranaceus* can be investigated for chemosensitization and synergism [70].

Many nutraceuticals may be anti-angiogenic chemoradiation sensitizers. *Artemisia annua* (Chinese wormwood), *Viscum album* (European mistletoe), *Curcuma longa* (turmeric), *Scutellaria baicalensis* (Chinese skullcap), *Vitis vinifera* (grape seed extract), *Magnolia officinalis* (Chinese magnolia tree), *Camellia sinensis* (green tea), *Ginkgo biloba* (ginkgo), *Poria cocos* (tuckahoe), *Zingiber officinalis* (ginger), *Panax ginseng* (ginseng), *Rabdosia rubescens hora* (rabdosia), and Chinese destagnation herbs are all anti-angiogenic nutraceuticals [21]. These nutraceuticals could be further studied specifically for anti-angiogenic benefits. Anti-angiogenesis could be explored as a factor in mistletoe's colon cancer survival benefit [21].

Cancer prevention

Dietary studies should examine overall diets and the quality of consumed products, instead of portions of diet: Fruits and vegetables in isolation from the overall diet and the quality of the consumed fruits and vegetables may not provide the best data going forward. Consumption of nonorganic "dirty dozen" fruits and vegetables should not have the same chemopreventive effect as consumption of all organic alternatives, including organic frozen berries. Prospective studies of berries and berry polyphenols in high-risk women from the *in-utero* environment through late menopause could determine if berries and berry polyphenols offer breast cancer primary and secondary chemoprevention [29].

Curcumin, EGCG, genistein, green tea extract, quercetin, red clover, resveratrol and soy should undergo breast, colorectal, and prostate cancer chemoprevention clinical trials in both healthy populations and populations at risk of a primary or secondary malignancy [68]. Retrial of selenium with mixed tocopherols (not all α-) vitamin E is warranted for prostate cancer prevention.

Numerous mechanism specific chemoprevention and therapeutic trials are possible: Curcumin and I3C for the phosphatase and tensin homology pathways (breast, endometrial, thyroid, and prostate cancers); diguelin for the insulin-like growth factor-receptor pathways (breast, colon, lung, pancreatic, and prostate cancers, melanoma, rhabdomyosarcoma, and EOC); EGCG against retinoblastoma protein pathways (squamous cell lung cancers); apigenin, genistein, and resveratrol for growth differentiation factor 15 pathways (breast, bladder, colorectal, ovarian, pancreatic, and prostate cancers, and glioblastomas); luteolin and p53 pathways (bladder, lung, head and neck, and cisplatin resistant cancers); porphyrins for Hippo pathways (neurofibromatosis and schwanommas); resveratrol for AT-rich interactive domain 1A pathways (breast, endometrial, gastric, ovarian, and renal cancers, endometriosis and medulloblastomas); withaferin A for Notch pathways (breast and lung cancers, melanoma and T-cell acute lymphoblatic leukemia [23].

Ongoing trials

There are several trials underway. Chemosensitization trials include immune modulation of prostate cancer by dietary soy [71]. Green tea and EGCG are being investigated for colon carcinogenesis modulation [72]. Combined primary and secondary prevention trials include Phyllanthusmin C, a diphyllin lignin for natural killer cell primary and secondary prevention of acute myeloid leukemia [73]. Primary prevention trials include Silibinin and I3C for inflammation-driven lung cancer chemoprevention [74]. Benzyl isothiocyanate and sulforaphane for breast cancer chemoprevention trial [75,76], and black raspberry phytochemicals for oral cancer chemoprevention [77]. Sulforaphane is also undergoing skin cancer chemoprevention via nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and epigenetics trials [78].

Conclusion

The evidence for concurrent nutraceutical use with conventional chemoradiation to reduce conventional chemoradiation doses, and to prevent or limit conventional chemoradiation associated adverse effects exists. *In vitro*, and murine and human *in vivo* evidence suggests that nutraceuticals are effective chemoradiation sensitizers and adjuvants, with additive and synergistic potential. Expanded scope positive human trials would facilitate a broader and deeper role for complementary nutraceuticals as part of integrative cancer treatment protocols.

References

1 Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, et al. (2007) Impact of antioxidant supplementation on chemotherapeutic efficacy: A systematic review of the evidence from randomized controlled trials. Cancer Treat Rev 33: 407-418.

2 King N, Balneaves LG, Levin GT, Nguyen T, Nation JG, et al. (2015) Surveys of cancer patients and cancer health care providers regarding complementary therapy use, communication, and information needs. Integr Cancer Ther 14: 515-524.

3 Wanchai A, Armer JM, Stewart BR (2010) Complementary and alternative medicine use among women with breast cancer: A systematic review. Clin J Oncol Nurs 14: E45-E55.

4 Saghatchian M, Bihan C, Chenailler C, Mazouni C, Dauchy S, et al. (2014) Exploring frontiers: Use of complementary and alternative medicine among patients with early-stage breast cancer. The Breast 23: 279-285.

5 Rossi E, Vita A, Baccetti S, Di Stefano M, Voller F, et al. (2015) Complementary and alternative medicine for cancer patients: results of the EPAAC survey on integrative oncology centres in Europe. Support Care Cancer 23: 1795-1806.

6 Singendonk M, Kaspers GJ, Naafs-Wilstra M, Schouten-van Meeteren A, Loeffen J, et al. (2013) High prevalence of complementary and alternative medicine use in the Dutch pediatric oncology population: A multicenter survey. Eur J Pediatr 172: 31-37.

7 Klafke N, Mahler C, von Hagens C, Rochon J, Schneeweiss A, et al. (2015) A complex nursing intervention of complementary and alternative medicine (CAM) to increase quality of life in patients with breast and gynecologic cancer undergoing chemotherapy: study protocol for a partially randomized patient preference trial. Trials 16: 1.

8 Magi T, Kuehni CE, Torchetti L, Wengenroth L, Lüer S, et al. (2015) Use of Complementary and Alternative Medicine in Children with Cancer: A Study at a Swiss University Hospital. PLoS ONE 10: e0145787.

9 Münstedt K, Maisch M, Tinneberg HR, Hübner J (2014) Complementary and alternative medicine (CAM) in obstetrics and gynaecology: a survey of office−based obstetricians and gynaecologists regarding attitudes towards CAM, its provision and cooperation with other CAM providers in the state of Hesse, Germany. Arch Gynecol Obstet 290: 1133-1139.

10 Flores-Pérez A, Rafaelli LE, Ramírez-Torres N, Aréchaga-Ocampo E, Frías S, et al. (2014) RAD50 targeting impairs DNA damage response and sensitizes human breast cancer cells to cisplatin therapy. Cancer Biol Ther 15: 777-788.

11 Chen SS, Michael A, Butler-Manuel S (2012) Advances in the treatment of ovarian cancer – a potential role of anti-inflammatory phytochemicals. Discov Med 13: 7-17.

12 Acharya A, Das I, Singh S, Saha T (2010) Chemopreventive properties of indole-3-carbinol, diindolylmethane and other constituents of cardamom against carcinogensis. Recent Patents on Food, Nutrition and Agriculture 2: 166-177.

13 Hussain SA, Sulaiman AA, Balch C, Chauhan H, Alhadidi QM, et al. (2016) Natural polyphenols in cancer chemoresistance. Nutrition and Cancer 68: 879-891.

14 Mohana S, Ganesan M, Agilan B, Karthikeyan R, Srithar G, et al. (2016) Screening dietary flavonoids for the reversal of P-glycoprotein-mediated multidrug resistance in cancer. Mol BioSyst 12: 2458-2470.

15 Moga MA, Dimienescu OG, Arvatescu CA, Mironescu A, Dracea L, et al. (2016) The role of natural polyphenols in the prevention and treatment of cervical cancer – an overview. Molecules 21: E1055.

16 Duval R, Xu X, Bui LC, Mathieu C, Petit E, et al. (2016) Identification of cancer chemopreventive isothiocyanates as direct inhibitors of the arylamine N-acetyltransferase-dependent acetylation and bioactivation of aromatic amine carcinogens. Oncotarget 7: 8688-8699.

17 Carriere PP, Llopis SD, Naiki AC, Nguyen G, Phan T, et al. (2015) Glyceollin I reverses epithelial to mesenchymal transition in letrozole resistant breast cancer through ZEB1. Int J Environ Res Pub He 13: 10.

18 Henderson AJ, Ollila CA, Kumar A, Borresen EC, Raina K, et al. (2012) Chemopreventive properties of dietary rice bran: Current status and future prospects. Advanced Nutrition 3: 643-653.

19 Li Y, Meeran SM, Patel SN, Chen H, Hardy TM, et al. (2013) Epigenetic reactivation of estrogen receptor-α (ERα) by genistein enhances hormonal therapy sensitivity in ERα-negative breast cancer. Mol Cancer 12: 1.

20 Grattan BJ (2013) Plant sterols as anticancer nutrients: Evidence for their role in breast cancer. Nutrients 5: 359-387.

21 Wang Z, Dabrosin C, Yin X, Fuster MM, Arreola A, et al. (2015) Broad targeting of angiogenesis for cancer prevention and therapy. Semin Cancer Biol 35: S224-S243.

22 Bin Sayeed MS, Ameen AA (2015) Beta-sitosterol: A promising but orphan nutraceutical to fight against cancer. Nutrition and Cancer 67: 1216-1222.

23 Amin ARM, Karpowicz PA, Carey TE, Arbiser J, Nahta R, et al. (2017) Evasion of anti-growth signaling: A key step in tumorigenesis and potential target for treatment and prophylaxis by natural compounds. Semin Cancer Biol 35: S55-S77.

24 Farhan M, Khan HY, Oves M, Al-Harrasi A, Rehmani N, et al. (2016) Cancer therapy by catechins involves redox cycling of copper ions and generation of reactive oxygen species. Toxins 8: 37.

25 Liu H, Talalay P (2013) Relevance of anti-inflammatory and antioxidant activities of exemestane and synergism with sulforaphane for disease prevention. PNAS 110: 19065-19070.

26 Hussain A, Mohsin J, Prabhu SA, Begum S, El-Ain Nusri Q, et al. (2013) Sulforaphane inhibits growth of human breast cancer cells and augments the therapeutic index of the chemotherapeutic drug, gemcitabine. Asian Pac J Cancer P 14: 5855-5860.

27 Chen SS, Corteling R, Stevanato L, Sinden J (2012) Polyphenols inhibit indoleamine 3,5-dioxygenase-1 enzymatic activity – a role of immunomodulation in chemoprevention. Discov Med 14: 327333

28 Girdhani S, Bhosle SM, Thulsidas SA, Kumar A, Mishra KP (2005) Potential of radiosensitizing agents in cancer chemo-radiotherapy. J Cancer Res Ther 1: 129-131

29 Aiyer HS, Warri AM, Woode DR, Hilakivi-Clarke L, Clarke R (2012) Influence of Berry-Polyphenols on Receptor Signaling and Cell-Death Pathways: Implications for Breast Cancer Prevention. J Agr Food Chem 60: 5693-5708.

30 Smyth AL, McGlynn H (2005) Modification of the radiosensitivity of renal cancer cell line as a consequence of polyunsaturated fatty acid supplementation. Nutr Res 25: 65-77.

31 Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman T, et al. (2011) Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. Cancer 117: 3774-3780.

32 Emery SM, Alotaibi MR, Tao Q, Selley DE, Lichtman AH, et al. (2014) Combined antiproliferative effects of the aminoalkylindole WIN55,212-2 and radiation in breast cancer cells. J Pharmacol Exp Ther 348: 293-302.

33 Chendil D, Ranga RS, Meigooni D, Satishkumar S, Ahmed MM (2004) Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3. Oncogene 23: 1599-1607.

34 Montgomery A, Adeyeni T, San K, Heuertz RM, Ezekiel UR (2016) Curcumin Sensitizes Silymarin to Exert Synergistic Anticancer Activity in Colon Cancer Cells. J Cancer 7: 1250-1257.

35 Yin H, Guo R, Xu Y, Zheng Y, Hou Z, et al. (2012) Synergistic antitumor efficiency of docetaxel and curcumin against lung cancer. Acta Biochim Biophys Sin (Shanghai) 44: 147-153.

36 Farrand L, Kim JIY, Byun S, Im-aram A, Lee JL, et al. (2014) The diarylheptanoid hirsutenone sensitizes chemoresistant ovarian cancer cells to cisplatin via modulation of apoptosis-inducing factor and x-linked inhibitor of apoptosis. J Biol Chem 289: 1723-1731.

37 Standish LJ, Wenner CA, Sweet ES, Bridge C, Nelson A, et al. (2008) Trametes versicolor Mushroom Immune Therapy in Breast Cancer. Journal of the Society for Integrative Oncology 6: 122-128.

38 Cassileth BR, Deng G (2004) Complementary and alternative therapies for cancer. The Oncologist 9: 80-89.

39 Standish LJ, Dowd F, Sweet E, Dale L, Weaver M, et al. (2016) Breast cancer integrative oncology care and its costs. Integr Cancer Ther April-June: 1-11.

40 Wachtel-Galor S, Yuen J, Buswell JA, Benzie IFF (2011) Ganoderma lucidum (Lingzhi or Reishi): A medicinal mushroom. In: Benzie IFF, Wachtel-Galor S (eds). Herbal medicine: Biomolecular and clinical aspects.

41 Ben-Ayre E, Ali-Shtayeh MS, Nejmi M, Schiff E, Hassan E, et al. (2012) Integrative oncology research in the Middle East: Weaving traditional and complementary medicine in supportive care. Support Care Cancer 20: 557-564.

42 Valiahdi SM, Iranshahi M, Sahebkar A (2013) Cytotoxic activities of phytochemicals from Ferula species. BioMed Central 21: 39.

43 Bigdeli B, Goliaei B, Masoudi-Khoram N, Jooyan N, Nikoofar A, et al. (2016) Enterolactone: A novel radiosensitizer for human breast cancer cell lines through impaired DNA repair and increased apoptosis. Toxicol Appl Pharm 15: 180-194.

44 Pariente R, Pariente JA, Rodríguez AB, Espino J (2016) Melatonin sensitizes human cervical cancer HeLa cells to cisplatin-induced cytotoxicity and apoptosis: effects on oxidative stress and DNA fragmentation. J Pineal Res 60: 55-64.

45 Zoberi I, Bradbury CM, Cury HA (2002) Radiosensitizing and antiproliferative effects of resveratrol in two human cervical cell lines. Cancer Lett 175: 65-73.

46 Díaz-Chávez J, Fonseca-Sánchez MA, Arechaga-Ocampo E, Flores-Pérez, A, Palacios-Rodríguez Y, et al. (2013) Proteomic Profiling Reveals That Resveratrol Inhibits HSP27 Expression and Sensitizes Breast Cancer Cells to Doxorubicin Therapy. Plos ONE 8: 1-12.

47 Kakar SS, Ratajczak MZ, Powell KS, Moghadamfalahi M, Miller DM, et al. (2014) Withaferin A alone and in combination with cisplatin suppresses growth and metastasis of ovarian cancer by targeting putative cancer stem cells. PLoS ONE 9: e 107596.

48 Kim SH, Singh SV (2014) Mammary cancer chemoprevention by withaferin A is accompanied by in vivo suppression of self-renewal of cancer stem cells. Cancer Prev Res 7: 738-747.

49 Fong MY, Jin S, Rane M, Singh RJK, Gupta R, et al. (2012) Withaferin A synergizes the therapeutic effect of doxorubicin through ROS-mediated autophagy in ovarian cancer. PlosONE 7: e42265.

50 Pramanik D, Campbell NR, Das S, Gupta S, Chenna V, et al. (2012) A composite polymer nanoparticle overcomes multidrug resistance and ameliorates doxorubicin-associated cardiomyopathy. Oncotarget 3: 640-650.

51 Zarogoulidis P, Tskiridis K, Karapantzou C, Lampaki S, Kioumis I, et al. (2015) Use of proteins as biomarkers and their role in carcinogenesis. J Cancer 6: 9-18.

52 Woyengo TA, Ramprasath VR, Jones PJH (2009) Anticancer effects of phytosterols. Europ J Clin Nutr 63: 813-820.

53 Bahadoran Z, Karimi Z, Houshiar-rad A, Mirzayi HR, Rashidkhani B (2013) Dietary phytochemical index and the risk of breast cancer: A case control study in a population of Iranian women. Asian Pac J Cancer 14: 2747-2751.

54 Takagi A, Kano M, Kaga C (2015) Possibility of breast cancer prevention: Use of soy isoflavones and fermented soy beverage produced using probiotics. Int J Mol Sci 16: 10907-10920.

55 McCann SE, Freudenheim JL, Marshall JR, Graham S (2003) Risk of human ovarian cancer is related to dietary intake of selected nutrient, phytochemicals and food groups. J Nutr 133: 1937-1942.

56 Filomeno M, Bosetti C, Bidoli E, Levi F, Serraino D, et al. (2015) Mediterranean diet and risk of endometrial cancer: a pooled analysis of three Italian case-control studies. Brit J Cancer 112: 1816-1821.

57 Kabat GC, Park Y, Hollenbeck AR, Schatzkin A, Rohan TE (2010) Intake of fruits and vegetables, and risk of endometrial cancer in the NIH-AARP Diet and Health Study. Cancer Epidemiol 34: 568-573.

58 Sayeed MA, Bracci M, Lazzarini R, Tomasetti M, Amati M, et al. (2017) Use of potential dietary phytochemicals to target miRNA: Promising option for breast cancer prevention and treatment? J Funct Food 28: 177-193.

59 Oprean C, Mioc M, Csányi E, Ambrus R, Bojin F, et al. (2016) Improvement of ursolic and oleanolic acids' antitumor activity by complexation with hydrophilic cyclodextrins. Biomed and Pharmacother 83: 1095-104.

60 Block KI, Gyllenhaal C, Lowe L, Amedei A, Amin AR, et al. (2015) Designing a broad-spectrum integrative approach for cancer prevention and treatment. Semin Cancer Biol 35: S276-S304.

61 Harrison AM, Heritier F, Childs BG, Bostwick JM, Dziadzko MA (2015) Systematic review of the use of phytochemicals for management of pain in cancer therapy. BioMed Research International 2015: Article ID 506327.

62 Friedel WE, Matthes H, Bock PR, Zänker KS (2009) Systematic evaluation of the clinical effects of supportive mistletoe treatment within chemo- and/or radiotherapy protocols and long-term mistletoe application in nonmetastatic colorectal carcinoma: multicenter, controlled, observational cohort study. Journal of the Society for Integrative Oncology 7: 137-145.

63 Kienle GS, Mussler M, Fuchs D, Kiene H (2016) Intravenous Mistletoe Treatment in Integrative Cancer Care: A Qualitative Study Exploring the Procedures, Concepts, and Observations of Expert Doctors. Evid-Based Compl Alt 2016: Article ID 4628287.

64 Shneerson C, Taskila T, Gale N, Greenfield S, Chen YF (2013) The effect of complementary and alternative medicine on the quality of life of cancer survivors: A systematic review and meta-analyses. Complement Ther Med 21: 418-429.

65 McLay JS, Stewart D, George J, Rore C, Heys SD (2012) Complementary and alternative medicines use by Scottish women with breast cancer. What, why and the potential for drug interactions? Eur J Clin Pharmacol 68: 811-819.

66 Yasueda A, Urushima H, Ito T (2016) Efficacy and interaction of antioxidant supplements as adjuvant therapy in cancer treatment: A systematic review. Integr Cancer Ther 15: 17-39.

67 Rice HB, Bernasconi A, Maki KC, Harris WS, von Schacky C, et al. (2016) Conducting omega-3 clinical trials with cardiovascular outcomes: Proceedings of a workshop held at ISSFAL 2014 Prostaglandins, leukotrienes and essential fatty acids 107: 30-42.

68 Thomasset SC, Berry DP, Garcea G, Marczylo T, Steward WP, et al. (2006) Dietary polyphenolic phytochemicals—Promising cancer chemopreventive agents in humans? A review of their clinical properties. Int J Cancer 120: 451-458.

69 Rais J, Jafri A, Siddiqui S, Tripathi M, Arshad M (2017) Phytochemicals in the treatment of ovarian cancer. Frontiers in Bioscience, Elite 9: 67-75.

70 Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, et al. (2015) Immune evasion in cancer: Mechanistic basis and therapeutic strategies. Semin Cancer Biol 35: S185-S198.

71 Lesinski GB (n.d.). Modulation of antitumor immunity by dietary soy and its isoflavone constituents. United States Department of Health and Human Services.

72 Wargovich M. Tea modulation of colon carcinogenesis. United States Department of Health and Human Services.

73 Caligiuri MA. Enhancing NK cell activity by dietary diphyllin lignans for cancer prevention. United States Department of Health and Human Services.

74 Kassie F (n.d.). Chemoprevention of inflammation-driven lung cancer. United States Department of Health and Human Services.

75 Howe LR (n.d.). Isothiocyanate-mediated breast cancer prevention. United States Department of Health and Human Services.

76 Singh S (n.d.). Breast cancer prevention by dietary phytochemicals. United States Department of Health and Human Services.

77 Weghorst CM (n.d.). Interactive omics: Black raspberry metabolites and the oral microbiome in smokers. United States Department of Health and Human Services.

78 Kong ANT (n.d). Prevention of skin cancer by phytochemicals via Nrf2 and epigenetics. United States Department of Health and Human Services