Specific needs of patients with chronic disease

The use of dietary supplements in cancer patients

A. Kapala (PL)
The use of dietary supplements in cancer patients

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Disclosure for Aleksandra Kapała

In compliance with COI policy, ESPEN requires the following disclosures to the session audience:

<table>
<thead>
<tr>
<th>Shareholder</th>
<th>No relevant conflicts of interest to declare</th>
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<tr>
<td>Grant / Research Support</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Consultant</td>
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<td>Speaker bureau</td>
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<tr>
<td>Other</td>
<td>No relevant conflicts of interest to declare</td>
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Presentation includes discussion of the following off-label use of a drug or medical device: <N/A>
Learning objectives:

• The difference between dietary supplement and drug
• The frequency of use the dietary supplements in cancer patient
• Are there any indications to use supplements: vitamin C, melatonin, curcumin in cancer patients?
• Safety and side effects of dietary supplements in cancer patients
• Quality of scientific proofs in terms dietary supplements
• Take home messages
Difference between supplement and drug

**Supplement**
- The FDA treats supplements like food and defines supplements as “products taken orally for supplementing the diet.”
- Can include minerals, vitamins or other natural biological substances and they’re available in a variety of shapes and sizes, including concentrates, extracts, capsules, tablets, liquids and powders.
- Don’t have to be tested for safety. Self-regulated by the manufacturer, no proof is required to demonstrate their effectiveness.
- **The general rule for supplements is they’re considered safe until they’re proven unsafe.**

**Drug**
- Defined as substances intended to diagnose, treat or prevent disease.
- Must pass clinical trials before being released to the public and the tests need to prove each drug is safe, performing just as the manufacturer claims.
- **The general rule is drugs are considered unsafe until they’re proven safe.**
The frequency of dietary supplement use in cancer patients

- 26 surveys from 13 countries, including 4 studies of pediatric patients, 10,690 patients
- The use of CAM therapies in adult populations ranged from 7–64%
- The average prevalence across all adult studies was 31.4%
- Laethrile, vitamins, minerals, herbs, „detoxification”, immune stymulants

CAM = Complementary and alternative medicine is used by 25%-50% of the general population of industrialized nations. It has been described as “diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine,” - definition recently adopted by the Cochrane Field in Complementary Medicine. Some “alternative” therapies are promoted not to complement mainstream medicine, but to substitute for it. These products and regimens, unproved and deemed unpromising by oncologists, typically are invasive and costly.
The frequency of dietary supplement use in cancer patients (The USA)

• A systematic summary of studies published between 1999 and 2006, 32 in total, addressing vitamin and mineral supplement use among US adult cancer patients and survivors = estimated 10 million patients!

• Supplement use is widespread among cancer patients and longer-term survivors.

• In studies combining different cancer sites, 64% to 81% of survivors reported using any vitamin or mineral supplements and 26% to 77% reported using any multivitamins.

• Breast cancer survivors reported the highest use, whereas prostate cancer survivors reported the least.

• Higher level of education and female sex emerged as factors most consistently associated with supplement use.

• Up to 68% of physicians are unaware of supplement use among their cancer patients

The frequency of dietary supplement use in cancer patients (UK)

- N= 164 (51.6%) took herbal remedies and/or food supplements.
- 16 (9.8%) took CAM in the form of homeopathic preparations
- Patients took on average 1.8 (±2.34) supplements; 40.9% took more than one substance and three patients took 10 or more preparations, and 17 (10.4%) only took herbal remedies, 69 (42.1%) only supplements and 78 (47.6%) a combination of both.
- Among the alternative remedies, Echinacea, evening primrose oil, ginkgo, milk thistle and Essiac were most popular. Individual supplements included vitamin C, E and a combination of vitamin A, C and E (ACE), cod liver oil, selenium, beta-carotene, coenzyme Q10 and germanium

## Anticancerogenic

<table>
<thead>
<tr>
<th>Remedy</th>
<th>Approved by German regulatory authority (Commission E)</th>
<th>Selected other/unproven</th>
<th>Suggested mechanism of action</th>
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<tbody>
<tr>
<td>Coenzyme Q10 (ubiquinone)</td>
<td>—</td>
<td>Inhibition of cancer growth; prevention of cardiotoxicity associated with anthracyclins</td>
<td>Antioxidant</td>
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<tr>
<td>Beta-carotene, vitamin C and E and ACE</td>
<td>—</td>
<td>Inhibition of cancer growth; stimulation of immune system</td>
<td>Antioxidants; Vitamin c and E and ACE can neutralise carcinogenic metabolites of beta-carotene</td>
</tr>
<tr>
<td>Essiac</td>
<td>—</td>
<td>Inhibition of cancer growth; stimulation of immune system</td>
<td>Burdock root: prevention of angiogenesis and inhibition of tumour neovascularisation (also contains: sheep sorrel, rhubarb and slippery elm)</td>
</tr>
<tr>
<td>Goldenseal</td>
<td>—</td>
<td>Inhibition of cancer growth</td>
<td>Berberine: (isoquinoline alkaloid): inhibition of tumour promoters, inhibition of cancer cells; neutropenia resulting from radio- and chemotherapy; gastritis, gastric ulcers and gallbladder disease, diarrhoea</td>
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<tr>
<td>Green tea</td>
<td>—</td>
<td>Cancer prevention; inhibition of cancer growth; nausea and vomiting; diarrhoea; caries prevention</td>
<td>Polyphenols: antioxidant</td>
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<tr>
<td>Laetrile (Vitamin B17, Apricot kernels)</td>
<td>—</td>
<td>Cancer prevention</td>
<td>Amygdalin: cytostatic through cyanide release; balance of vitamin deficiency</td>
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<td>Mistletoe (Isacaorder)</td>
<td>—</td>
<td>Cancer prevention and treatment; stimulation of immune system</td>
<td>Viscotoxins and viscumin (mistletoe lectin): modification of intracellular protein syntheses, stimulation of cytokine production, inhibition of tumour colonisation, induction of cell necrosis (Ernst and Cassileth, 1999)</td>
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<tr>
<td>Selenium</td>
<td>—</td>
<td>Cancer prevention; inhibition of cancer growth</td>
<td>Antioxidant</td>
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<tr>
<td>Shark cartilage</td>
<td>—</td>
<td>Cancer prevention; inhibition of cancer growth</td>
<td>Sphymnastatin 1 and 2; prevention of angiogenesis and inhibition of tumour neovascularisation</td>
</tr>
<tr>
<td>Turmeric</td>
<td>Dyspeptic complaints; loss of appetite</td>
<td>Cancer prevention; inhibition of cancer growth</td>
<td>Curcuminoids: antioxidant, alteration of cancer cell metabolism, cytotoxicity against human chronic myeloid leukaemia</td>
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<tr>
<td>Remedy</td>
<td>Commission E approved</td>
<td>Selected unproven other</td>
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<tr>
<td>Bach Flower remedies</td>
<td>—</td>
<td>Nervousness, tension</td>
<td></td>
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<tr>
<td>Ginkgo</td>
<td>Symptomatic relief of organic brain dysfunction; intermittent claudication; vertigo and</td>
<td>Boost immune system</td>
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<tr>
<td></td>
<td>tinnitus of vascular origin</td>
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<tr>
<td>Kava Kava</td>
<td>Nervousness and insomnia</td>
<td>—</td>
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<tr>
<td>Panax Ginseng</td>
<td>Lack of stamina and fatigue</td>
<td>—</td>
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<tr>
<td>Siberian Ginseng</td>
<td>Lack of stamina; risk of infections</td>
<td>—</td>
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<tr>
<td>Passion flower</td>
<td>Nervousness and insomnia</td>
<td>—</td>
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<tr>
<td>St John's wort (Hypericum)</td>
<td>Anxiety; depressive moods; topical use; skin inflammations, blunt injuries, wounds and</td>
<td>—</td>
<td></td>
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<tr>
<td>Valerian</td>
<td>Nervousness and insomnia</td>
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Vitamin C – a „miracle pill”?

• A “miracle-pill” capable to heal a variety of illnesses. Cancer is one of the most common diseases for which a beneficial role of vitamin C has been claimed.

• Role of vitamin C: redox properties, collagen synthesis. Scurvy symptoms are associated with a defect in collagen synthesis and include failure of wounds to heal, defects in tooth formation and rupture of the capillaries leading to petechiae and ecchymoses.
Vitamin C – preclinical data

1. Many papers have described that millimolar concentrations of ascorbate have a deep inhibitory effect on the growth of several cancer cell lines in vitro
2. Cytotoxic activity of vitamin C relies on its ability to generate reactive oxygen species rather than its popular antioxidant action
3. It’s linked to the generation of hydrogen peroxide
4. The mechanisms leading to hydrogen peroxide production in vivo are unknown but likely involve protein-bound metal cations, it seems only possible in extracellular fluids
5. Hydrogen peroxide production is proposed a critical parameter for the activity of ascorbate, leading to the concept that vitamin C could act as a prodrug to deliver hydrogen peroxide into tissues - cancer cells and damage them
6. Cancer cells are more prone to toxic activity of vit.C because they readily take up ascorbate, transported by GLUTs like glucose
7. Activity of HIF-1 is mandatory for solid tumor progression, its inhibition represents a very attractive target for cancer therapy. Vit. C support an inhibitory effect on HIF-1 activity

Vitamin C and efficacy of chemotherapeutic drugs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Influence of vitamin C</th>
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<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>↑&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>↑&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>↑&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>↑&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>↑&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>↑&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Procarbazin</td>
<td>↑&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>↑&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Vinblastine</td>
<td>↑&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>↑&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>↑&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vincristin</td>
<td>↑&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>X-rays</td>
<td>↑&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trisenox</td>
<td>↑&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>↑&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>TRAIL ligand</td>
<td>↑&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>↓&lt;sup&gt;a&lt;/sup&gt;</td>
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1. The therapeutic efficacy of the widely used antineoplastic drugs doxorubicin, cisplatin, vincristine, methotrexate, and imatinib were compared in leukemia (K562) and lymphoma (RL) cell lines with and without pretreatment with dehydroascorbic acid.

2. Effect of vitamin C on viability, clonogenicity, apoptosis, P-glycoprotein, reactive oxygen species (ROS), and mitochondrial membrane potential was determined.


4. **Vitamin C supplementation during cancer treatment may detrimentally affect therapeutic response.**


Vitamin C – clinical data

- McCormick: stromal changes of scurvy are identical to the local stromal changes observed in the invading neoplastic cells. Hypothesis: cancer is a collagen disease, secondary to vitamin C deficiency
- McCormick, Pauling and Cameron proposed the use of vitamin C supplementation in large doses for the prevention and treatment of cancer. The two controlled retrospective studies published in 1976 and 1978 showed that the mean survival times were, respectively, more than four and three times as great for the ascorbate subjects as for the controls. Explaining these results, they postulated that the dangerous features of neoplastic cell (invasiveness, growth, etc.) were caused by matrix destabilization allowing the spread of cancer cells
- Pauling and collaborators were convinced that high doses of ascorbate would increase the formation of collagen, leading to tumors encapsulation


Vitamin C- clinical data

• Criticisms were raised about the design of the Pauling/Cameron studies since they were not randomized or placebo controlled

• The average time from the initial diagnosis to “untreatable” status was not the same in the two groups, leading to an earlier “untreatable” labeling for Cameron’s patients.

Comroe JJ. Experimental studies designed to evaluate the management of patients with incurable cancer. Proc Natl Acad Sci USA 1978;75:4543.

• Either duplicate or refute the amazing results obtained by Cameron and Pauling, the Mayo Clinic initiated different controlled double-blind studies. All concluded that high doses of vitamin C, when given orally, are not effective against advanced malignant disease

Vitamin C – clinical data

• Concentrations in plasma and tissue are tightly controlled as a function of oral dose - the bioavailability of vitamin C is complete for 200 mg as a single dose and decreases above 500 mg and higher, due to urinary excretion

• As a consequence, the oral administration of vitamin C cannot achieve plasma concentrations higher than 50–100 µM, but to achieve concentrations clearly cytotoxic for cancer cells in vitro 20 mM is needed = 30-60g of vitamin C = 1,5g/kg BW!

Vitamin C – Phase I trials

- Doses up to 1.5 g/kg have been injected i.v. to cancer patients
- This protocol achieved plasma ascorbic acid concentrations >10 mM for more than 4 h, which is largely sufficient to induce cancer cell death in vitro

- **Adverse effects:**
  - may trigger hemolysis in patients suffering from glucose-6-phosphate dehydrogenase deficiency
  - oxalic acid is a major end metabolite of ascorbic acid oxidation = hyperoxaluria
  - ascorbic acid lead to urine acidification that could promote precipitation of urate, cystine, oxalate stones or drugs in the urinary tract
  - may worse renal function, especialy if any renal disease was present before
  - increase bioavailability of iron, not recommended for hemochromatosis patients
  - Diarrhae after oral ingestion >2g !

- **No objective anticancer response was reported in this trial**

Vitamin C - conclusions

• Popularity relies on expensive advertising campaigns which claim unproved benefits of vitamin C-based products
• Preclinical studies suggest that ascorbic acid may have interesting anticancer properties
• Data demonstrate that oral and i.v. administration are not comparable
• Extensive literature exists on the use of vitamin C in cancer but finally no clear answer has yet been raised about its putative anticancer action in humans
• The research on mega-dose vitamin C is an excellent example of controversial studies generated by inappropriate early-phase research
• Further well-designed clinical trials should yield more information about the safety and the efficacy of high-dose i.v. ascorbic acid.
Curcumin supplementation in cancer patients

- A spice common to India and the surrounding regions, is turmeric, derived from the rhizome of Curcuma longa

- Epidemiological research has suggested the possible role of curcumin to prevent or delay the diagnosis of colorectal cancer as evidenced by ethnic groups that consume curcumin

- The low bioavailability of oral curcumin is well established

Curcumin:
- blocks bioactivation of pro-carcinogens to form mutagens (AHR – P450).
- inhibit NFκB and COX-2 expression (promote apoptosis)
- inhibit c-jun N-terminal kinase (JNK) pathway, which is a member of the mitogen activated protein kinases (MAPKs) and it’s pro-inflammatory effect
- lower EGFR expression
- Matrix metalloproteinases (MMPs) - inhibition of cell signaling associated with angiogenesis, metastasis, and migration

Curcumin: Preclinical data were promising, but...

- Pre-clinical studies in a variety of cancer cell lines have consistently shown that curcumin possesses anti-cancer activity in vitro, affect cancer cell growth, apoptosis, angiogenesis, inflammation and cancer spread.

- In vitro studies using colon, gastric, hepatic, leukemia, ovarian, pancreatic, and prostate cancer cell lines have been performed, showing that curcumin displays a potentiating effect with traditional pharmaceuticals such as 5-fluorouracil (5-FU), all-trans retinoic acid, cisplatin, celecoxib, and doxorubicin.


Pharmacokinetics of curcumin

• The low bioavailability of oral curcumin is well established
• Typically, quantifiable serum levels are not achieved until doses of up to 3600 mg are used
• **Curcumin is active only in intestinal epithelium**, is immediately glucouronidated and sulfated to form curcumin glucuronide and curcumin sulfate and rapidly excreted, **unstable in human plasma**
• Addition of piperine may enhance bioavailability of curcumin by 2000% or liposome drug delivery technology
Curcumin: clinical trials

- Phase I trial: 15 Caucasian patients with a history of colorectal cancer. Pts received a 5-FU based therapy in addition to undergoing surgery with measurable disease beyond the colon.
- Dose: 440-2200 mg curcuma extract daily, orally, 4 months; max.dose used in phase I trials: 8000mg
- Lymphocytic glutathione-s-transferase (GST) activity and M1G levels was assessed as a biomarker to curcumin activity
- Levels of curcumin and its metabolites were not observed in plasma, urine, or blood cells. This finding is not surprising as it is well established that curcumin undergoes rapid glucouronidation in the small intestine
- Minimal side effects (NCI grade I, II) nausea, diarrhea
- SD or PD

Curcumin: clinical trials

- Phase II: pancreatic cancer pts n=25, after surgery, Rth or/and gemcytabine treatment.
- Study design: Patients received 8 g curcumin by mouth daily until disease progression, with restaging every 2 months. Serum cytokine levels for interleukin (IL)-6, IL-8, IL-10, and IL-1 receptor antagonists and peripheral blood mononuclear cell expression of NF-KB and cyclooxygenase-2 were monitored.
- Result: 21 evaluable for response. Circulating curcumin was detectable as drug in glucuronide and sulfate conjugate forms, albeit at low steady-state levels, suggesting poor oral bioavailability. Two patients showed clinical biological activity. One had ongoing stable disease for > 18 months; interestingly, one additional patient had a brief, but marked, tumor regression (73%) accompanied by significant increases (4- to 35-fold) in serum cytokine levels (IL-6, IL-8, IL-10, and IL-1 receptor antagonists). No toxicities were observed.

Melatonin – promising agent?

• Melatonin is a naturally occurring derivative of the amino acid tryptophan and was first isolated from bovine pineal gland and was believed to be locally acting as a hormone regulating the circadian and circannual cycles.

• Major source of melatonin is GI tract.

• Further studies have discovered melatonin-related enzymes in various other tissues. Melatonin is involved in the protection against a spectra of diseases: diabetes, obesity, gastrointestinal disorders - IBD and IBS, immune disorders, cardiovascular diseases, neurodegenerative diseases, numerous cancers such as pancreatic, liver, breast, prostate and oral cancer and toxicant-induced disorders via its pleiotropic effects on cell functions.

Melatonin – promising agent?

• Physiologic functions of melatonin in GI include the inhibition of smooth muscle contraction, regulation of ions and water transport and secretion, mediating gastric acid neutralization by bicarbonate, controlling proliferation of cells, augmentation of the immune system and modulation of the myenteric nervous system.

• Ways of anti-cancer activity: direct and indirect antioxidant activity which limits oxidative DNA damage. Reduces carcinogenesis and antagonizes the pro-angiogenic effects of nitric oxide (NO), can block growth factor signaling in cancer cells and arrest cell cycle causing decreased proliferation.
The effects of melatonin on different aspects of cancer pathogenesis and the molecular mechanisms in gastric cancer.

<table>
<thead>
<tr>
<th>Aspect</th>
<th>In vitro/ In vivo</th>
<th>Subject</th>
<th>Effects</th>
<th>Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proliferation</strong></td>
<td>In vitro</td>
<td>SGC-7901</td>
<td>↓Viability, ↑Apoptosis</td>
<td>↑P38, ↑PI3K/Akt, ↑HSP27 (This signaling induces resistance to apoptosis)</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td>AGS</td>
<td>↓Viability, ↓Colony formation, ↑Apoptosis, ↓Migration</td>
<td>↓P65 NF-κB, ↑P38 MAPK, ↑JNK ↑Bax ↓Bcl-2, ↑Caspase-3</td>
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<tr>
<td></td>
<td>In vitro</td>
<td>SGC-7901</td>
<td>↓Viability, ↓Colony formation, ↑Apoptosis, ↓Migration</td>
<td>↑Caspase-3</td>
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<td></td>
<td>In vitro</td>
<td>SGC-7901</td>
<td>↓Viability, ↓Colony formation, ↑Apoptosis, ↓Migration</td>
<td>↑P38, ↑JNK, ↓P65 NF-κB</td>
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<td><strong>Differentiation</strong></td>
<td>In vitro</td>
<td>SGC-7901</td>
<td>↑Differentiated morphology</td>
<td>↓Endocan, ↓ALP, ↓LDH</td>
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<td></td>
<td>In vivo, In vitro</td>
<td>BALB/c nude mice, AGS, MKN-45</td>
<td>↓Tumor growth, ↓Peritoneal dissemination, ↓Metastasis, ↓EMT</td>
<td>↑ER stress, ↑Calpain, ↑p-elf2α, ↓C/EBPβ, ↓NF-κB, ↓E-cadherin, ↓Snail/Slug, ↑Wnt/β-catenin</td>
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<tr>
<td><strong>Angiogenesis</strong></td>
<td>In vitro</td>
<td>SGC-7901</td>
<td>↓VEGF expression and protein</td>
<td>↓RZR/RORγ expression, ↓SEN1, ↓HIF-1α, ↓RZR/RORγ ↓SEN1, ↓HIF-1α</td>
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<tr>
<td></td>
<td>In vitro, in vivo</td>
<td>SGC-7901</td>
<td>↓Tumor growth, ↓Tumor angiogenesis, ↓VEGF</td>
<td>↓C/EBPβ, ↓NF-κB, ↓PGE\textsubscript{2}, ↓IL-8, ↓CXCL1, ↓VEGF</td>
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<td></td>
<td>In vivo, In vitro</td>
<td>BALB/c nude mice, AGS, MKN-45</td>
<td>↓Tumor growth, ↓Proangiogenesis factors, ↓Peritoneal dissemination, ↓Metastasis, ↓EMT</td>
<td>↓MMP expression</td>
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<tr>
<td></td>
<td>In vitro</td>
<td>AGS</td>
<td>↓MMP activity</td>
<td>↑Blockade of MMP9 active site</td>
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<tr>
<td><strong>Metastasis</strong></td>
<td>In vivo, in vitro</td>
<td>BALB/c nude mice, AGS, MKN-45</td>
<td>↓Peritoneal dissemination, ↓Metastasis</td>
<td>↑E-cadherin, ↑ER stress, ↑Calpain, ↑p-elf2α, ↓C/EBPβ, ↓NF-κB, ↓Snail/Slug, ↓Wnt/β-catenin</td>
</tr>
<tr>
<td><strong>Immune system</strong></td>
<td>In vivo, in vitro</td>
<td>MFC, H-2K\textsuperscript{K} mice</td>
<td>↓Tumor weight, ↓Tumor volumes</td>
<td>↓Tregs in the tumor tissue, ↓Foxp3 expression</td>
</tr>
</tbody>
</table>

Melatonin – clinical trials

- n=14. Melatonin was given intramuscularly at a daily dose of 20 mg at 3.00 p.m., followed by a maintenance period in an oral dose of 10 mg daily in patients who had a remission, stable disease or an improvement in PS. A partial response was achieved in 1 case with cancer of the pancreas, 6 patients had stable disease, while the other 8 progressed.


- n=50, advanced solid tumors with brain metastases; supportive care alone or supportive care and melatonin. 9 of the 24 patients who received melatonin survived 1 year compared with 3 of 26 who did not receive melatonin. The mean survival time was 9.2 +/- 0.9 versus 5.5 +/- 0.7 months and the time free from brain progression was 5.9 +/- 0.8 versus 2.7 +/- 0.6 months in patients receiving melatonin.


- melatonin may down regulate the expression of estrogen receptor (ER), thus inhibiting the binding of the estradiol-ER complex to the estrogen response element. These actions might be the cause of the negative proliferative response of melatonin toward breast cancer cells, 14 metastatic breast cancer patients, unresponsive to tamoxifen alone were given 20 mg melatonin daily in the evening along with tamoxifen. A response was achieved in 28% of these patients.

The effects of concomitant MLT administration on toxicity and efficacy of several chemotherapeutic combinations

Moreover, the concomitant administration of MLT significantly reduced the frequency of thrombocytopenia, neurotoxicity, cardiotoxicity, stomatitis and asthenia.

Melatonin – clinical trials

• No typical Phase I trials to assess safety dose of melatonin, different administration ways and timing
• Phase II trials - few
• Some trials with other agents (anti-tumor cytokines IL-2, IL-12, INF-alfa)
• Despite the positive results achieved from some laboratory experiments, clinical trials did not verify those findings, and no clear benefit of melatonin for cancer treatment could be demonstrated
Review the methodologies applied in clinical trials of unconventional treatments specifically for cancer

- 14,735 articles, 198 different clinical trials included
- Twenty trials were phase I, three were phase I and II, 70 were phase II, and 105 were phase III
- Approximately half of the trials investigated fungal products, 20% investigated other botanicals, 10% investigated vitamins and supplements, and 10% investigated off-label pharmaceuticals
- Only eight of the phase I trials were dose-finding trials, and a mere 20% of phase II trials reported a statistical design! The maximum-tolerated acute dose unknown
- Of the 27 different agents tested in phase III, only one agent had a prior dose-finding trial, and only for three agents was the definitive study initiated after the publication of phase II data.
Take home messages

• In general rules is a huge difference between supplements and drugs
• The frequency of use dietary supplements in cancer patients is very common and ranges 31-94%, but 68% oncologist doesn’t know about it!
• In preclinical data (in vitro, cell lines) result are very promising in any field of term carcinogenesis (tumor growth, cell differentiation, apoptosis, neoangiogenesis, metastasis etc)
• Well designed clinical trials in humans are scarce, results inconsistent and conflicting
• The methodologies applied in clinical trials of unconventional treatments is poor, no dose-finding trials, statistical design not clear
• Future research should involve dose-finding phase I and phase II studies to determine the suitability of definitive trials
• Further clinical trials are needed to yield safety and efficacy of dietary supplements used in cancer patients