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INTEGRATIVE CANCER THERAPIES

- Cancer therapies can be integrated very successfully with conventional intervention therapies.
- Namely chemotherapy, radiation therapy, and surgery.
- The goal of integrating strategies is not to replace conventional therapies or interfere with their effectiveness.
- Rather to enhance efficacy and decrease side effects.
INTEGRATIVE CANCER THERAPIES

- Keep in mind that in doing so we may decrease the effectiveness of conventional therapies by manipulating
  - the Cytochrome P450 interactions
  - P-Glycoprotein interactions
  - or any other number of mechanisms of action.
- In the attempt to decrease side effects, choose a therapy that does not have these interactions
Most known drug interactions are due to changes in the metabolic rate of clearance and the routes related to an altered expression of the functional CYP450 isozymes. Interactions can also take place by the P-glycoprotein which plays a role in mediating transmembrane transport of chemotherapy.
COMMON CHEMOTHERAPEUTICS ARE METABOLIZED BY THE CYP3A4:

- Ifosfamide, Paclitaxel, Docetaxel, Abraxane, Vinblastine,
- Vincristine, Navelbine, Irinotecan, Topotecan,
- Etoposide, Tamoxifen, Arimidex, Aromasin, Femara,
- EGFR-TK inhibitors, Iressa, and Tarceva.
CHEMOTHERAPEUTICS ARE METABOLIZED THROUGH CYP2C19:

- Cytoxan and Aromatase inhibitors
Several medicinal herbs interfere with CYP3A4:

- Hypericum perforatum (which should be avoided in all chemotherapies because it interferes with CYP2B6, CYP2C9, CYP2C19, CYP2E1, CYP3A4 and P-glycoprotein induction)
- Piper methysticum, Hydrastis Canadensis, Uncaria tomentosa, Trifolium pratense, Matricaria recutita, Glycyrrhiza glabra, and grape seed extracts
OTHER HERBS THAT INTERFERE WITH CYP3A4 AND CYP2C19:

- For CYP3A4: *Echinacea* sp., *Ginseng* sp., *Ginkgo biloba*, *Silymarin* (also *P*-glycoprotein) and *Quercitin*.
- For CYP2C19: *Ginkgo* and *Valeriana*
Curcumin, a bioflavonoid found in turmeric, has specific indications for many cancer types, but has been
Contraindicated for Adriamycin and Cytoxan integrative use due to its ability to
inhibit chemotherapy-induced apoptosis in human breast cancer cells in conjunction with these chemotherapeutics
First, determine the metabolism of the drug: is it metabolized through CYP450 isoenzymes or through P-glycoprotein?

If there is a ‘yes’ to this question, how does the botanical influence the pathway?

Here the integrative strategist can determine if it is a caution or a strict avoidance that must be adhered to, and if it is a caution, then at least the half-life interaction with the chemotherapy must be avoided with the administration of the botanical.
CLASSES OF CHEMOTHERAPY DRUGS

- Alkylating agents
- Platinum compounds
- Antitumor Antibiotics
- Antimetabolites
- Topoisomerase Inhibitors
- Microtubule Inhibitors
- Monoclonal Antibodies
- Biological Response Modifiers
- Colony Stimulating Factors
ALKYLATING CHEMOTHERAPEUTICS

- Altretamine, BCNU, Busulfan, CCNU, Chlorambucil, Cyclophosphamide, Fotumestine, Ifosfamide, Melphalan, Nitrogen Mustard, Pipobroman, Procarbozine, Streptozotocin, Temozolide, Thiotepa, Triethylenemelamine
Alykylating agents affect the alkylate nucleic acids (DNA and RNA) and will break the DNA helix strand, thus interfering with DNA cancer cell replication. Alkylating agents are cell cycle specific, but not phase specific, and can inflict injury on any part of cell cycle replication. Tumor resistance appears to be related to the capacity of the cells to repair nucleic acid damage and to inactivate the drugs by conjugation with GSH.
COMBINATION THERAPIES

- Most of the regimens that include alkylating agents do so in combination with other chemotherapeutics with a cancer specific indication:
  - Cyclophosphamide (Cytoxan) in combination with Adriamycin (AC) in breast cancer
  - Cytoxan with AC, Vincristine, and Prednisone in non Hodgkin’s lymphoma (CHOP)
  - Ifosfamide (Ifex) with Carboplatin and Etoposide in NSCLC and metastatic breast cancer (mini ICE)
TOXICITY AND SIDE EFFECTS

- Myelosuppression in a dose-dependent manner with clinical presentations of fatigue
- = Secondary co-infections like candidiasis and slow overall wound healing
- = Hemorrhagic cystitis associated with Cytoxan+Ifex
- = Pan alopecia, mucositis/stomatitis, nausea, and vomiting, neutropenia, and chronic anemia
These chemotherapies cause multiple side effects, including peripheral neuropathy and neutropenia, and hand and foot syndrome (otherwise known as Palmer plantar erythematosis or PPE).

For prevention and treatment of peripheral neuropathy and PPE, apply hexane-free castor oil topically to palms of the hands and soles of the feet one to two times per day.
Also associated with these chemotherapies is mucositis, manifesting as nausea, vomiting, diarrhea, and stomatitis, all leading to cachexia.

Use L-glutamine as a preventive and as a treatment for mucositis and stomatitis as well as diarrhea and malabsorption.
INTEGRATIVE COMPLEMENT

- Catnep tea is very effective for nausea and vomiting, especially before meals.
- Drink at room temperature (also serve foods warm) with severe mucositis.
- Use 1 tablespoon of dried herb to one cup of water, cover and steep for 10 minutes. Use with honey if needed to flavor and drink prn.
Cannabis is also a great antiemetic and appetite stimulator that can also effect the anxiety associated with cancer diagnosis and treatment.

Patients report that the best use of cannabis is for nausea and vomiting.

It is also an appetite stimulant if administered by combustion or ingestion.

Instead of smoking the herb, a vaporizer can be used, which has a mechanism that burns the cannabis without smoking it and captures the smoke and THC for the patient to inhale.
PLATINUM COMPOUNDS

- Cisplatin (CDDP, Platinol)
- Carboplatin (Paraplatin),
- Oxaliplatin (Eloxatin)
Platinum compounds are an active heavy metal alkylator of DNA, which covalently binds to proteins, RNA, and especially DNA, forming DNA crosslinking.
**COMBINATION THERAPIES**

- Cisplatin in combination with Fluorouracil (5-FU) in squamous cell carcinoma of the head and neck
  - = Cisplatin, Methotrexate, Vinblastine, Doxorubicin in carcinoma of the bladder (MVAC)
  - = Cisplatin, Mitomycin-C in an intra-arterial infusion
  - = Carboplatin with Taxol in NSCLC and ovarian cancer
TOXICITIES AND SIDE EFFECTS

- Myelosuppression
- Peripheral sensory neuropathy,
- Pan alopecia
- In Cisplatin, there is a cumulative renal insufficiency, severe mucositis/stomatitis, nausea and vomiting, as well as associated ototoxicity
- = Carboplatin has a lower toxic side effects associated with its use
Platinum compounds are very toxic with side effects, including peripheral neuropathy.

What would you use?
ANTITUMOR ANTIBIOTICS

- Actinomycin D
- Bleomycin
- Danorubicin
- Doxorubicin (Adriamycin)
- Doxil (liposomal doxorubicin),
- Epirubicin
- Idarubicin
- Mitomycin C
- Mitramycin.
Antitumor antibiotics include the related antimicrobial compounds that produce *Streptomyces spp.* in culture and bind with DNA, thus inhibiting DNA and RNA synthesis. This strategy is cell cycle non specific and is only useful in slow growing tumors.
COMBINATION THERAPIES

- Adriamycin in combination with Cytoxan in breast cancer (AC)
- Mitomycin C with Leucovorin (a folinic acid) and 5-FU with Floxuridine (FUDR) in metastatic colon cancer
- Liposomal Adriamycin (Doxil) used as a single agent in ovarian cancer
TOXICITIES AND SIDE EFFECTS

- Myelosuppression, pan alopecia, mucostitis/stomatitis, nausea/vomiting, radiation recall, cardiotoxicity, associated especially with Adriamycin
- = Hand/Foot syndrome (PPE) associated especially with Doxil
- = Renal and pulmonary toxicity associated especially with Mitomycin
ANTIMETABOLITES

- Asparaginase
- Chlorodeoxyadenosine
- Cytosine arabinoside,
- Deoxycoformycin
- Floxuridine (FUDR),
- Fludarabine phosphate
- Capecitabine (Xeloda)
- Fluorouracil (5-FU)
- Gemcitabine (Gemzar)
- Hydroxyurea,
- Mercaptopurine
- Methotrexate
- Thioguanin.
Antimetabolites are the structural analogues of normal molecules that are essential for cell growth and replication. They inhibit enzyme production for DNA synthesis, leading to strand breaks and premature chain termination that act in S phase cell cycle and are most effective when cell proliferation is rapid.
5-FU with Leucovorin in colon cancer and with Methotrexate
- = Cytoxan in breast cancer (CMF)
- = Xeloda as a single agent in metastatic breast cancer resistant to anthracyclines and taxanes
- = Gemzar as a single agent in pancreatic cancer and metastatic ovarian cancer.
TOXICITIES AND SIDE EFFECTS

- Myelosuppression, mucositis/stomatitis, nausea and vomiting, diarrhea
- = Hand/foot syndrome (PPE) especially associated with Xeloda
- Photosensitivity especially associated with 5-FU and Methotrexate
- = Pan alopecia especially with 5-FU
Myelosuppression is one of the greatest concerns in all patients receiving chemotherapy. This side effect ranges from frank leucopenia to anemias that will interrupt chemotherapy treatment sequences. If the red blood cell or white blood cell counts go to a dangerously low level, treatments will not be administered. This interruption decreases the chemotherapeutic effect and creates the potential for chemoresistance.
Use these two medicinal mushrooms:

- = Fungiperfecti from Stametes. The Stametes mushroom products are all mycelium instead of mushroom and have an increased biological activity.
- Stametes 7 is a seven mushroom blend of Royal sun blazeii, cordyceps, reishi, maitake, chaga, lion's mane, and mesima.
- Each cap is 500 mg of certified organic freeze dried mushroom mycelium.
- Take 1-2 caps up to t.i.d.
Trametes versicolor (Turkey tails). Each capsule 500 mg or organic freeze dried mycelium 1-2 caps up to t.i.d.

= If these mushroom blends do not increase the WBC count as desired, add to the mushroom mix

Ashwagandha (Withania) organic only, 500 mg-1000 mg up to t.i.d.

= Also note that glutamine will also treat and prevent neuropathy but should have been already in use prior to the start of chemotherapy to prevent mu
Bone Marrow Soup

- Organic only large animal long bones are the best
- Use apple cider vinegar and salt or pre-roast the bones
- Cover in water and add Super Foods:
  - Garlic, onions, rosemary, thyme, squashes, mushrooms, astragulus and ashwaghanda roots, etc.

Cook for 24-48 hours in slow cooker ceramic only until “mush”, make sure NOT to strain off any “fat”

Strain out materials and freeze in individual portions to be used 4-6 oz 1-2x a day
TOPOISOMERASE INHIBITORS

- Etoposide (VP-16)
- Teniposide
- Irinotecan (CPT-11, Camptosar)
- Topotecan (Hycamtn).
Topoisomerase inhibitors are cell cycle inhibitors. Etoposide and Teniposide are podophyllin derivatives from may apple (*Podophyllum spp.*).

*This action* induces an irreversible blockade of cells in premitotic phases of the cell cycle, late G2 and S phases, while also interfering with topoisomerase II function.

Camptosar and Topotecan act in S phase by inhibiting topoisomerase and causing double stranded DNA changes.

Topotecan can be used as a single agent in metastatic ovarian cancer.
COMBINATION THERAPIES

- Topoisomerase inhibitors with other chemotherapies such as: VP-16 with Ifosfamide, Carboplatin (ICE) in high dose chemotherapy applications with stem cell transplantation
- = VP-16, Ifosfamide, Carboplatin in NSCLC and metastatic breast cancer (mini ICE)
- = CPT-11 in combination with Leucovorin, 5-FU in metastatic colon cancer
TOXICITIES AND SIDE EFFECTS

- These are dose dependent, and some of the individual drugs have fewer side effects than others.
- Diarrhea associated mucositis, nausea and vomiting, myelosuppression, pan alopecia, and hypotension associated especially with rapid infusion rates of Etoposide and Teniposide.
INTEGRATIVE COMPLEMENT

- Glutamine
- Catnip
- rhizante lozenges
- Cannabis

- What would you do?
MICROTUBULE INHIBITORS

- Docetaxel (Taxotere)
- Paclitaxel (Taxol)
- Vinorelbine (Navelbine)
- Vinblastine sulfate (Velban)
- Vincristine sulfate (Oncovin)
Microtubule inhibitors are derived from the vinca alkaloids in periwinkle (*Vinca spp.*).

The alkaloids Vincristine and Vinblastine act in G1 and S phase by inhibiting microtubule formation while also inhibiting DNA and RNA formation.

The Taxanes (Taxol and Taxotere) are derived from the Pacific Yew tree (*Taxus spp.*) and act in the G2 and M phase to stabilize the microtubule and thus, inhibit cellular division.
Combination Therapies

- Taxol and Carboplatin in ovarian and NSCLC
- = Taxotere and Navelbine in metastatic breast cancer
- or as a single agent in metastatic breast cancer
Microtubule inhibitors create peripheral neuropathy, which is usually dose limiting

- Transient arthralgia and myalgia, especially with Taxol

- Myelosuppression, pan alopecia, nausea/vomiting and constipation
INTEGRATIVE COMPLEMENT

- Mucositis induced constipation or constipation associated with opioids and other narcotic medications used for pain can be very uncomfortable and chronic.
- Cherry juice protocol: Use concentrated cherry juice only (no sweeteners or other juices added) to create a peristaltic reflex stimulus. 4-6 oz of cherry juice 3-6 times daily.
- Use the cherry juice as a bowel training mechanism – 4-6 oz to induce a bowel movement within a few hours – if no bowel movement repeat dose.
INTEGRATIVE COMPLEMENT

- Try to have the patient train the bowels to move the same time each day. It is usually easier to stimulate after a meal because the act of chewing and swallowing initiates peristalsis.
- Cherry juice is a low glycemic index, high antioxidant, high pycnogenol initiator of peristalsis.
- Also use EPA 2-3 g q.d., glutamine, medicinal mushrooms, ashwagandha, cannabis.
MONOCLONAL ANTIBODIES

- Rituximab (Rituxan)
- Trastuzumab (Herceptin)
Monoclonal antibodies are specific. Rituxan is a genetically engineered chimeric (murine and human) monoclonal antibody that is directed against the CD20 antigen on malignant B lymphocytes.

Herceptin is a recombinant humanized monoclonal antibody that targets HER2 receptors on some cancer cells especially indicated for breast cancer +HER2/neu
Chemotherapeutic strategies include the use of Herceptin in metastatic breast cancer that has overexpressed the HER2 protein and can be used in previously treated cases with one or more chemotherapies.

Rituxan targets CD20+ B cell non Hodgkin’s lymphoma
TOXICITIES AND SIDE EFFECTS

- The toxicities are also drug specific. Rituxan has hypersensitivity reactions, serious cardiac arrhythmias with global clinical manifestations that include fever with chills, hypotension, bronchospasm with dyspnea, angioedema, headache, nausea and vomiting.

- Herceptin has dose-limiting cardiomyopathy, fever and chills, nausea, vomiting and diarrhea.
For cardiomyopathy,
- CoQ10, L-carnitine,
- Hawthorn berry solid extract 1/4-1/2 tsp q.d. to t.i.d.: caution it will lower blood pressure!
BIOLOGICAL RESPONSE MODIFIERS

- Interferon
- Bacillus Calmette-Guerin
- Erythropoetin,
- G-SCF
- GM-SCF
- Interleukin-2
The pharmacology of the biological response modifiers is drug specific:

- **Erythropoetin (Procrit, Epogen, Aranesp, EPO)** stimulates the division and differentiation of committed erythroid progenitor cells.
- **G-SCF (Neupagen and Neulasta)** do the same thing but stimulate the white blood cell line.
- **GM-SCF (Leukine and Prokine)** promote growth and differentiation of myeloid progenitor cells and promote the survival of granulocytes, eosinophils, monocytes and macrophages and induces IL-1 and TNF.
These drugs are used as interventions for chemotherapy induced side effects:

- Procrit for chemotherapy-induced anemia indicated especially in nonmyeloid malignancies;
- Neupagen/Neulasta and Leukine for granulocytopenia secondary to chemotherapy or from primary bone marrow cancers/metastatic disease.
TOXICITIES AND SIDE EFFECTS

- Procrit causes associated edema, diarrhea, and hypertension
- Neupogen/Neulasta and Luekine cause long bone pain, musculoskeletal leg cramping, and back pain, as well as general flu-like symptoms
Radiation therapy involves the treatment of cancer cells with ionizing radiation.

The aim is to damage the cancerous cells in the target tissue area being treated, while trying to avoid healthy tissue.

Although this application damages both cancerous and normal cells, the normal cells have the ability to repair themselves more quickly than the cancer cells.
RADIATION TREATMENTS

- External Beam
- = Chemosensitizing
- = Intensity Modulated Radiation Therapy (IMRT)
- = Tomotherapy
- = High Dose Rate (HDR) Brachytherapy
- = Mammosite
This is one of the most common forms of radiation treatment (XRT).

External beam XRT uses a linear accelerator to direct radiation into the tumor and tumor bed. This procedure lasts for minutes and is repeated usually 5 days in a row out of a 7 day week over a course of 6 to 8 weeks.

It may be used in conjunction with surgery and chemotherapy.
This XRT combines the external beam with low doses of chemotherapy.

This strategy is to chemosensitize the tumor cells to the radiation treatment.

Side effects tend to be low due to the low doses of chemotherapy used.
INTENSITY MODULATED RADIATION THERAPY

- This procedure changes the size, shape, and intensity of the external beam XRT to coordinate to the size, shape and location of the tumor.
- A linear accelerator (linac) is a device that uses a number of chambers, each of which adds energy to the electrons, thus accelerating them to higher energies in the megavoltage range.
- A multileaf collimator (MLC) opens and closes individual leaves to regulate the amount of radiation passing through the patient.
- IMRT is usually delivered from several different directions (5-13 pinpoint locations).
- The greater the number of pinpoint locations of the beam, the higher the dose that will be confined to the tumor, thus reducing the risk of side effects.
Conventional IMRT requires a lengthy and complicated set up process for each treatment fraction and often the aid of ‘tattooing’ these locations

or creating wire mesh molds to hold the area still are used.

The more beam directions required for the treatment, the more time for each treatment fraction is required.
Tomotherapy

- This XRT combines in one system treatment planning, patient positioning, and treatment delivery.
- This allows a precise treatment delivery and the ability to use doses without increasing radiation exposure to healthy tissues.
- A CT and planning software are used to establish the precise 3D contours for each tumor area and any regions of risk including organs or surrounding structures.
TOMOTHERAPY

- The radiation dose as well as acceptable levels of radiation for these surrounding structures is calculated by the radiation oncologist and a physicist.
- The planning software calculates the appropriate pattern, position, and intensity of the radiation beam to be delivered in a 360° fashion.
- The CT scan is done prior to each treatment to verify the position of the tumor and to adjust for changes in the patient’s positioning for treatment.
- The treatment delivery combines IMRT with a helical delivery pattern.
TOMOTHERAPY

- The radiation produced by a linear accelerator travels in multiple circles around the gantry ring.
- The linac moves in unison with a multileaf collimator, which has two sets of interlaced leaves that move quickly to constantly modulate the radiation as it leaves the accelerator.
- The couch is also moving, guiding the patient slowly through the center of the gantry ring so that each time the linac comes around, it is directing the beam at the target tissue site at a slightly different plane giving a surrounding 3D treatment effect.
BRACHYTHERAPY

- This procedure uses multiple catheters (up to 30) that are implanted in the tumor and surrounding treatment area. It is used in breast, prostate, and lung cancers.
- After placement of the catheters, radioactive seeds are delivered into each catheter to treat the target area.
- A seed is delivered into each catheter twice a day for up to 5 days.
- The total treatment for each session is approximately 20 minutes, and the catheters are removed after each treatment is completed.
MAMMOSITE

- A small balloon attached to a thin catheter is placed in the lumpectomy cavity.
- A radioactive seed is placed within the balloon by a computer controlled machine.
- Radiation is delivered to a depth of approximately 2 mm.
- When mammosite XRT is used as a primary treatment, the seed placement is delivered twice a day for up to 5 days.
- When it is used as a boost therapy and is combined with external beam XRT, it is delivered over 1 to 2 days.
Radiation side effects are dependent on the type, amount, and location of the treatment.

Radiation-induced fatigue is the most commonly seen side effect regardless of the type of radiation. There is an increased risk in patients who have advanced stage disease, are treated with large radiotherapy fields, have a low pre-radiotherapy hemoglobin level, or poor nutritional status and whose lymphocyte counts are not correlating with the fatigue.
Mucositis, stomatitis, and xerostomia are often common and can lead to a poor nutritional status and secondary co-infections, such as candidiasis.
Acute diarrhea is not only associated with mucositis reactions but in radiotherapy directed to the pelvis for prostate or gynecological cancers, it has an increased incidence.
COMMON RADIATION SIDE EFFECTS

- Chronic proctitis and dermatitis can be associated with the positioning of the beam application.
- Radiation-induced cognitive dysfunction
Radiation-induced fatigue

**Exercise** It has been shown improving physical function helps combat radiation induced fatigue.

Exercise in a randomized controlled breast cancer study showed exercise may mitigate fatigue in breast cancer patients receiving radiation therapy.

30 minutes per day for 3-6 days
**L-Carnitine**

- This amino acid has been shown to reduce cancer-related fatigue, not specifically to XRT, with responding clinical improvement.
- Divided doses up to 4-6 g q.d.
Radiation-induced mucositis

L-Glutamine

This side effect can be treated or prevented with the use of the amino acid L-Glutamine.

Glutamine has also been shown to treat radiation-induced hyperpermeability and to protect lymphocytes.

It attenuates gut permeability in patients during chemoradiotherapies.

Dose: 10 g, t.i.d., swish and swallow
Honey

The use of honey showed a significant reduction in the symptomatic grade 3/4 mucositis in patients treated with honey post radiotherapy, and 55% of the patients treated with topical honey also showed a positive gain in body weight.

Radiation-induced xerostomia showed improvements with just a teaspoon of honey daily.

The natural bacterial content of honey has shown to decrease *Streptococcus mutans* colonies that are opportunistic in radiation-induced xerostomia patients.

Dose: 1 tsp gd-prn.
**Vitamin E**

Radiation-induced mucositis treated with natural vitamin E (alpha-tocopherol) as a topical oral rinse before and after radiation treatment showed a reduced risk of acquiring mucositis and also significantly decreased oral pain.

- **Dose:** 200-1000 IU
Radiation-induced diarrhea

*L-Glutamine*

This side effect can be prevented and treated with glutamine.

Dose: 10 g t.i.d., swish and swallow, away from food
**Probiotics and Prebiotics**

Using probiotics aids prebiotic implantation in the treatment of radiation-induced diarrhea and has shown to preserve intestinal integrity and prevent radiation-induced diarrhea.

- **Dose:** 50 billion CFU, b.i.d.
INTEGRATIVE COMPLEMENT

- Radiation-induced proctitis
- *Vitamin C and E*
- This side effect was significantly improved with the use of vitamin E and C; improving symptoms of bleeding, diarrhea and fecal urgency all sustainable in a one year follow up period.
- Dose: Vitamin C: TBT, Vitamin E: 400-1200 IU.
INTEGRATIVE COMPLEMENT

- Radiation-induced dermatitis
- *Calendula*
  - This side effect was shown to be reduced with *Calendula officinalis succus*. This medicinal herb is highly effective for the prevention of acute radiation induced dermatitis of grade 2 or higher.
- Dose: Topical gel
INTEGRATIVE COMPLEMENT

- Radiation-induced cognitive dysfunction
- *Vitamin E*
  - This side effect was shown to be significantly improved with the use of vitamin E (alpha-tocopherol) orally in patients with temporal lobe radionecrosis. Vitamin E at 2000 IU daily for one year resulted in significant improvements in global cognitive ability, memory, verbal and visual skill, but no difference was noted in language or attention.
- Dose: 2000 IU q.d
Melatonin

Melatonin is effective for chemotherapy and radiotherapy co-management use.

Oral melatonin is considered at therapeutic dosing at 20 mg nightly.

Melatonin has shown to decrease XRT related toxicities with better associated survival curves over a one year period.
Antioxidants are generally recommended if the antioxidants are of an exogenous nature.

Endogenous antioxidants are those that are formed naturally in the body’s systems, while exogenous are antioxidants that cannot be formed by the body itself.

Antioxidants and radiation therapies have shown promise in early clinical trials using green tea (ECGC) and radiation therapies on different cancer cell lines.
Integrative therapies can also play a complementary role in surgical treatments for cancer.

Surgery precautions include preventive strategies to control bleeding and manage anesthesia effects.

There are many foods and herbs that can affect coagulation adversely and should be avoided prior to surgery.

Following surgery, anticoagulant effects and clearance of anesthesia are primary concerns.

Likewise, there are foods and herbs that can promote coagulation of the blood and detoxification of anesthesia.
Pre- and post surgery protocols have been designed to prevent the spread of the micrometastatic cells of the cancerous tumor, to speed healing and recovery from surgery, and to reduce infections by immunonutaceuticals.

Surgery has the potential to misplace cancerous cells via biopsy or other surgical procedures.
Up to 85% of cancer cell types have a galectin-3 receptor, which plays an active role in cancer cell adhesion and metastasis.

Modified citrus pectin has been shown to interfere with cell-to-cell interactions mediated by cell surface carbohydrate binding galectin-3 molecules, thus helping to prevent metastatic disease.

Pectasol-C (Econeugenics), 1 scoop, b.i.d.
IMMUNOMODULATION

- Immunomodulation has been studied mostly in post operative probands with most of the research focused on gastrointestinal tract cancers.
- The most widely studied substances are glutamine, arginine, EFAs (omega-3, DHA/EPA), and RNA influencing factors.
Two 1999 studies show supplementation with all three natural strategies made a significant decrease in prealbumin and retinol-binding protein, and fewer post operative complications with lowered sepsis scores and a shortened length of hospital stay.
In 2001, these three naturopathic interventions were used again and a lowering of CRP was noted with higher nitric oxide, total lymphocytes (T lymphs, T helper and NK cells), and lower postoperative levels of IL6 and TNF-a.
In 2002, it was shown that preoperatively these strategies lowered infection rate and improved significantly gut microperfusion, immune response, and gut oxygenation.

Immunonutrients were shown to affect weight loss, postoperative infection rate, and length of hospital stay in another 2002 study.
In 2004, further study into the integrative strategy of immunonutrition with omega-3 supplementation alone revealed significantly increased serum protein with active lymphocyte proliferation, and with a relative relation between fat mass and omega-3 to omega-6 ratios.
Several medicinal herbal interactions will actually strengthen the action of anticoagulant therapy by a heterogenous mechanism of action.
MEDI CINAL HERB (ANTI-COAGULANT)

- Danshen (*Salvia miltiorrhiza*)
- Dong quai (*Angelica sinensis*)
- Garlic (*Allium sativum*)
- Ginger (*Zingiber officinalis*)
- Ginkgo (*Ginkgo biloba*)
- Ginseng (*Panax ginseng*)
- Horse Chestnut (*Aesculus hippocastanum*)
- Red Clover (*Trifolium pratense*)
- St John’s wort (*Hypericum perforatum*)
The biology of proliferating cancer cells causes cytokines that stimulate increase endothelial cells, which then increases vascular supply to the tumor.

Antioxidants inhibit these cytokines: IL-1, IL-8, bFGF (basic fibroblast growth factor), TGF (transforming growth factor, both alpha and beta), PD-EGF (platelet permeability factor), VPF (vascular permeability factor), TNF (tumor necrosis factor).
ANGIOGENESIS INHIBITION

- Vitamin E reduces IL-8 production and angiogenesis; and appears to prevent tumor formation by stimulating a potent immune response to selectively destroy tumor cells.
- Epigallocatechin (green tea) is most effective in reducing IL-8 production and angiogenesis.
- Consumption of green tea catechins or supplemental vitamin E has preventative effects on tumor development.
CELLULAR MEMBRANE INTEGRITY

- Studies show that lipid peroxidation/protein oxidation in membranes can be prevented by endogenous natural antioxidants.
- Lycopene could play a role in the recovery of the integrity of biological membranes of the liver after radiation injury.
- Omega-3 rich diets have beneficial anticancer effects when adding antioxidants such as vitamins E and C.
P53 is one of the genetic mediators of apoptosis, and 50% of cancers have abnormal P53 activity.

P53 gene mutation was an independent prognostic marker of early relapse and death in breast cancer.

A measurement of P53 mutations helps to treat the cancer more effectively.
Vitamins can induce differentiation and apoptosis in cancer cells. A mixture of antioxidants and vitamins is more effective than individual vitamins.

In contrast to cancer cells, normal cells never undergo apoptosis after conventional tx with vitamins (except retinoids).
APOPTOSIS

- N-acetyl-cysteine elevates p53 activity and apoptosis in cancer cells but not in healthy cells
- Curcumin induces apoptosis in sarcoma, colon, kidney and hepatocellular cancers but not in normal cells
- A recent study demonstrated that bladder transitional cancer cell lines treated with silybinin experienced significant growth inhibition and apoptosis. These effects were due to activation of caspase-3 and modulation of cyclin cascade.
Astragalus increases the activity of Ag-presenting macrophages and of CD4 T cell activity; theoretically, this could lead to increased ADCC with subsequent tumor cell death.

Polysaccharide (PSP) from *Trametes (Coriolus) versicolor* mushroom activates macrophages and stimulates TNF. However, a cytotoxic effect on tumor cell lines is not observed.
Curcumin induces apoptosis in a p53-independent manner, and at the higher concentrations, induces capase gene expression.

EGCG from *Camellia sinensis*, *baicalein* from *Scutellaria baicalensis*, and *Cimicifuga racemosa* extracts each increase apoptosis in CLL cells; interrupt VEGF survival signals resulting in capase activation and subsequent cell death.

*Cimicifuga* induces capases in MCF-7 cells.

Quercetin blocks epidermal growth factor receptor-signaling pathways, leading to induction of apoptosis.
GENERAL RADIOPROTECTION NUTRIENTS

- Antioxidants
- Vitamin E
- Zinc
- Selenium
- Ginkgo biloba
- Curcuma longa
- Lentinan
- Adaptogens
NATURAL VITAMIN E (D-ALPHA-TOCOPHEROL)

- Vitamin E induces cell differentiation in cancer cells, inhibits their growth, and causes cell death.
- Selective inhibition of cancer cell growth is shown with the inhibition of protein kinase C and expression of oncogenes.
- Vitamin E also inhibits phosphorylation and transactivation of the cancer cell, which is important in cell proliferation of healthy cells.
- Epidemiological studies link vitamin E use with lower risk of prostate cancer. Long-term supplementation with alpha-tocopherol substantially reduced prostate cancer incidence (32%) and mortality from prostate cancer (41%) in Finnish male smokers.
Toenail and serum samples from male study subjects showed a fivefold reduction in risk of developing prostate cancer in those with highest levels of gamma-tocopherol compared to those with lowest.

Pumpkin seeds (*Curcubita pepo*) are a good source of gamma-tocopherol.

Vitamin E has been shown to induce apoptosis and suppress tumor growth by 80%.

It inhibits gastric carcinoma cell growth *in vitro* in a dose- and time dependent fashion.
NATURAL VITAMIN E (D-ALPHA-TOCOPHEROL)

- It scavenges ROS tocopherol and ascorbate (vitamin C). a-tocopherol and ascorbate, independently and in combination, decrease the production of reactive oxygen species in human spermatocytes exposed to H2O2.
- The pretreatment of hepatocytes with tocopherol succinate (TS) dramatically enriched cells and mitochondria with alpha-tocopherol and provided these membranes with complete protection against ethyl methanesulfonate (EMS)-induced oxidative damage. TS pretreatment suppressed EMS-induced cellular ROS production, generated from mitochondrial complex I and III sites.
NATURAL VITAMIN E (D-ALPHA-TOCOPHEROL)

- Vitamin C supplementation in chronic hemodialysis patients can reduce the lymphocyte intracellular ROS production, as well as up-regulate hOGG1 gene expression for repair

- Vitamin E and ECGC
  - One study looked at vitamin E and EGCG with the hypothesis that these antioxidants may be antagonistic during radiation treatment
Tumor growth was 10% slower in EGCG fed mice and 3% slower in vitamin E fed mice.

EGCG and vitamin E protected normal tissues from severe XRT related soft tissue reactions.

Intramural apoptosis in the EGCG and vitamin E concentrations were 8.3 fold and 1.3 fold increase as compared to control. Tumor cell invasiveness was decreased by 25% with EGCG and vitamin E compared to control.
Vitamin E and EGCG appear to concentrate in tumors, though the mechanism and significance of this is unknown. EGCG (in vivo) and vitamin E (in vitro) significantly slow tumor growth, which is likely due to increased apoptosis and decreased cell proliferation.

Anti-angiogenic RNA expression in the EGCG tumors may explain the slower tumor growth. Vitamin E and EGCG did not reach statistical significance in increasing radiation resistance in implanted tumors.

Vitamin E and EGCG significantly decrease radiation reactions in normal tissues.
The orange to red pigments found naturally in fruits and vegetables have been shown to control cancer cell growth, repair precancerous lesions, induce cell differentiation, prevent metastasis, prevent formation of a secondary carcinogenesis, control angiogenesis, and be immunostimulating.
Carotenoids induce cellular differentiation, inhibit growth of human melanoma cells, stimulate the level of cAMP induced differentiation and betacarotene in particular, and increase expression of the connexin gene, which functions to hold normal cells together with each other coding for gap junction in genetic code.

The best activity of retinoids is in squamous cell, cervical, renal cell cancers. They are selective for cancer cells.

Organ development is not affected.
RETINOIDS

- Retinoid therapeutic actions
  - Inhibit growth of protein kinase-C
  - Reduce oncogene expression
  - Reduce transplanted tumor growth
  - Reduce tumor size
LYCOPENE

- Lycopene is the primary red carotenoid found in tomatoes and watermelons. There is an inverse relationship between dietary intake of lycopene and the risk of developing prostate cancer.

- The data shows that lycopene supplementation in men before radical prostatectomy, pathology results compared to control subjects:
  - = 73% vs. 18% had no involvement of surgical margins and/or extra-prostatic tissues
  - = 84% vs. 45% had tumors <4 ml in size
  - = PSA levels decreased by 18%
The essential trace mineral selenium (Se) has been shown to inhibit intestinal, prostate, lung, and liver tumor development and has been associated with mortality in both experimental animals and humans.

Although Se is likely to be one of the most powerful cancer chemopreventive agents in the human diet, its mechanism of action is still under investigation. Low Se status results in a decrease in the expression of genes involved in detoxification, thus reducing the amounts of activated carcinogens.
Melatonin has been studied extensively for chemotherapy and radiotherapy co-management use.

Oral melatonin is considered therapeutic at a dosing at 20 mg nightly.

Melatonin acts as a powerful antioxidant, especially in combination with classic antioxidants, such as vitamin E and A.

The free radical induced oxidative stress caused by radiation can be exacerbated by the decreased efficiency of antioxidant mechanisms.
This enzyme is used with vitamin E to protect patients from chemotherapy-induced cardiomyopathies.

CoQ10 is nontoxic, even at high dosages, and has been shown to prevent liver damage from the drugs Mitomycin C and 5-FU.

Adriamycin-induced cardiomyopathies have been prevented by concomitant supplementation with CoQ10.
It also reduces free radical formation induced by doxorubicin. Research studies with both animals and humans have found that pretreating with coenzyme Q10, at levels of 100 mg per day, reduces cardiac toxicity caused by doxorubicin.
COX-2 INHIBITION

- Cox-2 substances can inhibit angiogenesis, inhibit cell growth and invasion, inhibit tumor associated inflammation, increase pro-apoptotic effects, and inhibit of Prostaglandin 2 (PGE2) associated aromatase induction.
**HERBAL COX-2 INHIBITORS**

- *Glycyrrhiza uralensis*: Isoliquiritigenin decreases COX-2 expression, resulting in decreased PEG-2 and nitric oxide in mouse and human colon carcinoma cells.

- *Phyllanthus amarus* (used to treat viral hepatitis): In-vitro application of extract inhibits induction of iNOS, COX-2, and TNF-a
**HERBAL COX-2 INHIBITORS**

- *Zingiber officinalis:* Traditionally used for pelvic inflammation and congestion. *In-vitro* human synoviocytes obtained during primary knee replacement from OA patients incubated with ginger extract demonstrated significantly suppressed production of TNF-alpha COX-2 expression.
- NF-kappaB was also suppressed, suggesting that ginger blocks transcription of COX-2.
Scutellaria baicalensis: Traditionally used in traditional Chinese medicine for inflammatory and cancerous conditions.

COX-2 is highly expressed in head and neck squamous cell carcinoma cells. Oral administration of Scutellaria baicalensis to mice inoculated with these cells caused inhibition of COX-2 expression, whereas celecoxib inhibited COX-2 activity directly. No inhibition was seen in mice inoculated with a nontumorigenic cell line, indicating a selective inhibition of COX-2 in tumor cells. A 66% reduction in tumor mass was also observed in these mice.
Zyflamend™: Natural Cox-2 inhibition in prostate cancer. Cox-1 and Cox-2 enzyme activities decreased with

Zyflamend, respectively, at 45% and 80%. PGE2 production decreased by 91%. Apoptosis was induced in cell lines after a 72-hour treatment period. Suppressed cell line growth occurred after a 72-hour treatment.

Activity directly inhibited Cox-2 enzyme activity and decreased signaling through PKC delta and STAT3. It is potentially a chemopreventative agent and is currently in clinical trial with prostatic intraepithelial neoplasia (PIN)