

The Use of Nutraceuticals in Oncology

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Focus points

- Define 'nutraceutical'
- Common nutraceuticals recommended for the oncological patient
- Benefits of these supplements
- Concerns

Nutraceutical ... so many interpretations

- The word 'Nutraceutical' literally means pharmaceutical nourishment for the body.
- A nutraceutical product may be defined as a substance, which has physiological benefit or provides protection against chronic disease.
- Nutraceuticals are additional nourishment for our body apart from the food consumed.
- Nutraceuticals, have been called medical foods, designer foods, phytochemicals, functional foods and nutritional supplements.

What is a nutraceutical, FDA?

According to the industry, nutraceuticals are 'pharmaceutical grade' nutrients that are consumed for a health benefit.

In reality, they are vitamins, minerals, botanicals, herbs or dietary substances "for use by man to supplement the diet by increasing the total dietary intake."

According to the FDA regulations, most nutraceuticals would be categorized as "**dietary supplements**

Dietary supplements appear drug-like and can induce drug-like reactions in high enough concentrations. They are made from food, isolated nutrients or food-like substances to augment health.

DSHEA *“a product (other than tobacco) that is intended to supplement the diet, which contains one or more of the following dietary ingredients—a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients; is ingested in pill, capsule, tablet, or liquid form; is not represented for use as a conventional food or as the sole item of a meal or diet; and is labeled as a ‘dietary supplement.’”*

So, the playing field is wide for dietary supplements, which can be an isolated vitamin (like a capsule of Vitamin E), an extract (like that of the plant ginkgo biloba), or a fatty acid (like omega-3).

[Dietary Supplement Health and Education Act of 1994](#)

Nutraceutical / Dietary Supplement du *jour*

Antioxidants

Omega-3 Fatty Acids

Vitamin D

Branched-chain Amino acids (BCAA)

Antioxidants (AOX)

Reactive oxygen species (ROS) formed by incomplete reduction of molecular oxygen → oxidative stress in the organism and can often be involved in the pathogenesis of many diseases.

Two important sources of free radical formation.

1. Internal factors i.e. normal cellular metabolism like mitochondrial ETC, endoplasmic reticulum oxidation and many enzymatic activities.
2. Other exogenous factors: radiation, chemotherapy and oxygen

AOX mechanism(s) of action:

- Catalyze the breakdown of ROS ('neutralize free radicals') by:
 - chelating transition metals → which makes them non-reactive
 - chain-breaking antioxidants act by halting the cascade of free radical reactions
 - eliciting a pro-oxidant effect (less common)

Antioxidants (AOX)

In cancer chemotherapy, a mode of action of certain anti-neoplastic agents involves generation of free radicals (ROS) further leading to cellular damage and necrosis of malignant cells.

So the questions arise ...

1. Do antioxidants increase or decrease the efficacy of anticancer agent?
2. Do antioxidants protect normal tissue and ameliorate toxicity or protect cancer cells from the effect of chemotherapy?.

Antioxidants

Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity – Exploring the armoury of obscurity

Singh, Bhoori, Kasu, Bhat, and Marar 2018 Feb; 26(2): 177–19

The effect of supplementation of thirteen different antioxidants and their analogues as a single agent or in combination with chemotherapy was compiled.

The review encompasses 174 peer-reviewed original articles from 1967 till 2018 (93 clinical trials; cumulative of 18,208 patients, 56 animal studies and 35 *in vitro* studies).

Summary of study results

Vitamins	
A (β carotene)	12/21 toxicity from chemo Rx was mitigated 2/21 no difference noted
C	5/9 excellent synergistic and increased therapeutic effect
D / K	9 & 3, respectively
E	28/34 drug induced toxicity was efficiently ameliorated
Totals	36 clin trials (8047); 19 in-vitro; 28 animal
	34 chemo agents as individual or in combo 53/75 (70%) reports remarkable antioxidant mediated toxicity mitigation 27/75 suggest no changes in the data or toxicity 65% articles mentioned AOX supplementation increases therapeutic efficiency (20%) articles reports increase in survival time

Summary of study results

AOX (n=)	Article totals
GSH (23)	76% articles states AOX administration mitigates drug induced toxicity which indicate superior potential of all 3 antioxidant in clinical and <i>in vitro</i> settings.
Melatonin (12)	
NAC (11)	
	26% confirm higher therapeutic response upon antioxidant supplementation, 9% have published possible or partial usefulness of these antioxidants during chemotherapy 10% suggest no possible role of antioxidant in enhancing the therapeutic response. 6 reports reveal increased survival of subjects when provided w/ antioxidant + chemotherapy combo.

Synthesis of (PUFA) polyunsaturated FA

- ◆ Combination of chain elongation and desaturation from parent n-6 (linoleic) & n-3 (linolenic)
- ◆ Fasting state and hypo-insulinemia \Rightarrow diminish the elongation / desaturation system.

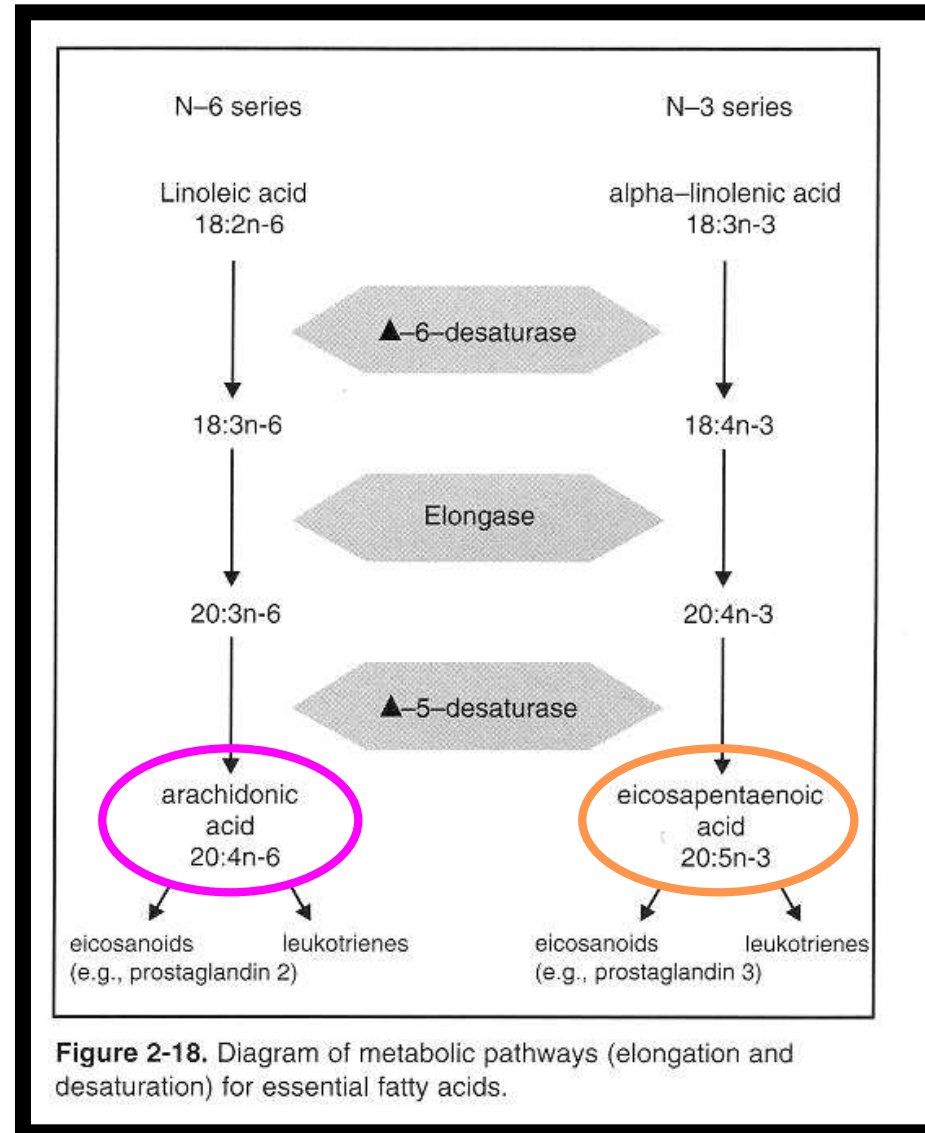


Figure 2-18. Diagram of metabolic pathways (elongation and desaturation) for essential fatty acids.

Omega-3 Fatty Acids

Omega-3

α -Linolenic Acid
(ALA)



Desaturases
Elongases

Eicosapentaenoic acid
(EPA)



Desaturases
Elongases

Docosahexaenoic acid
(DHA)

Cyclooxygenases
Lipoxygenases

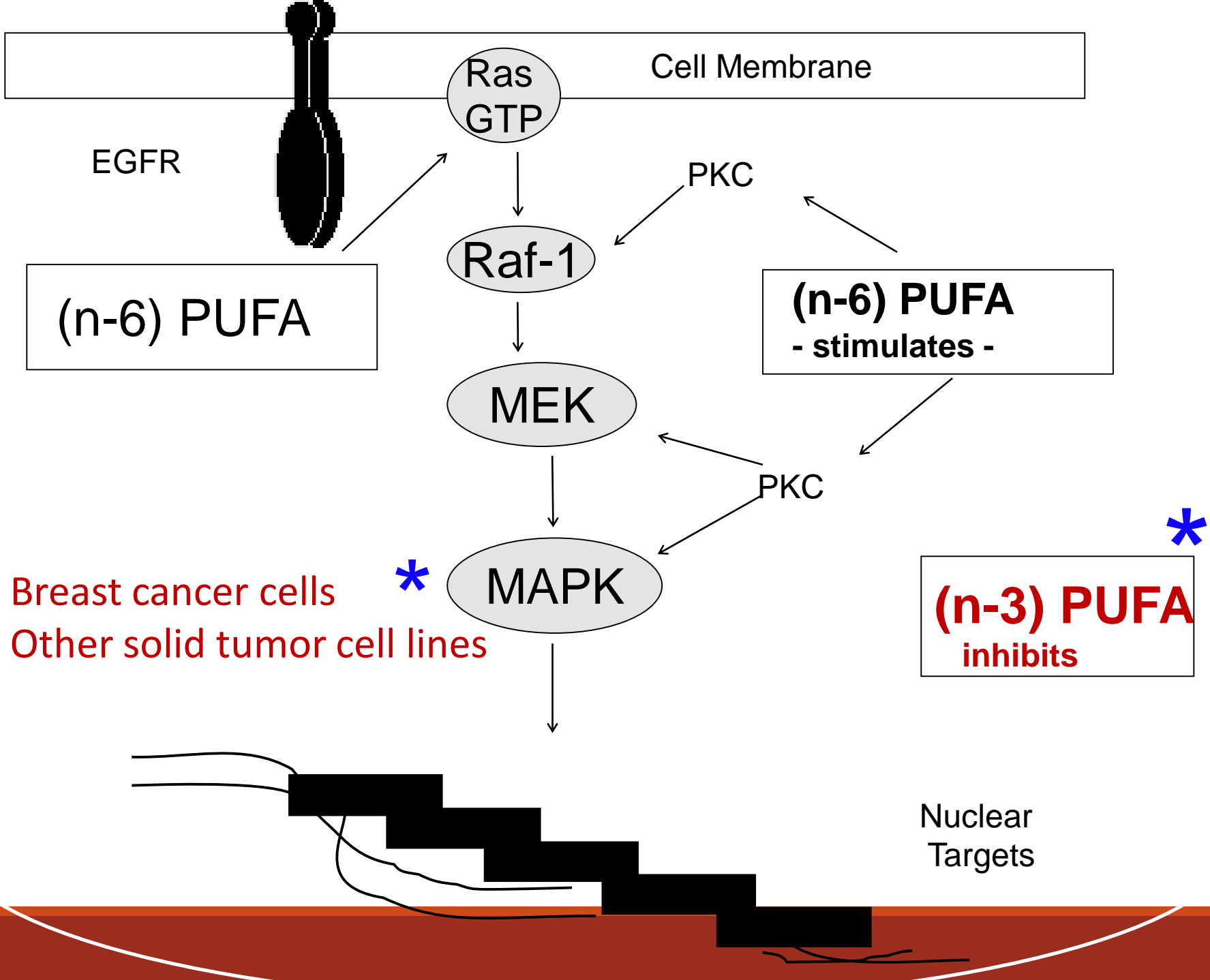


Minimally Inflammatory:
Eicosanoids
Inflammation Resolving:
Resolvins, Protectins



Enriched in EPA & DHA
(omega-3 fatty acid family)





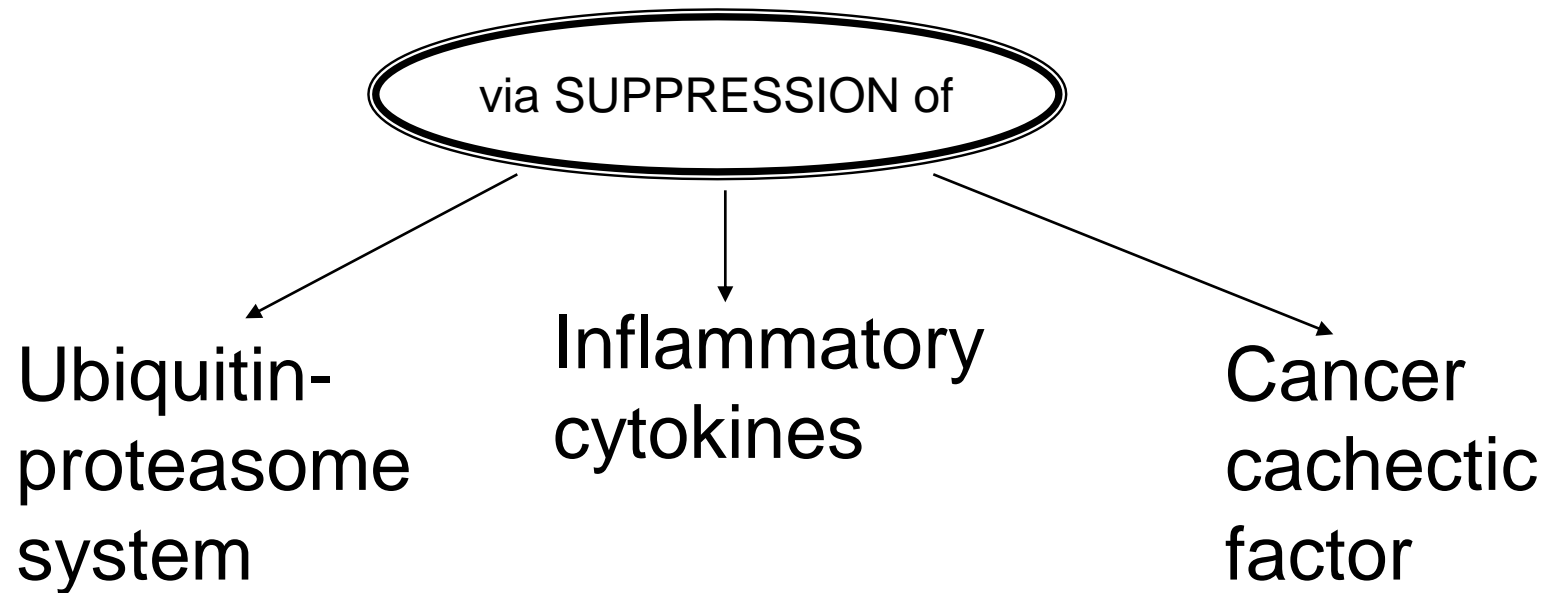
Influence Tumorigenesis

Example: PUFA –MAPK- Breast cancer

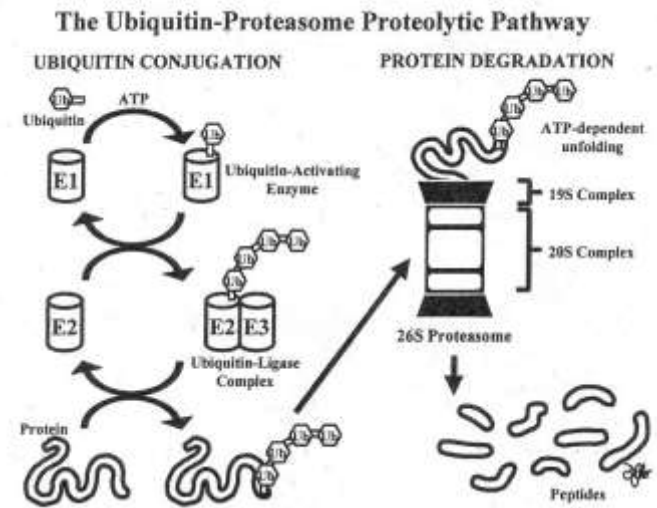
- *Human Cell Line and Rodent Studies*
 - Over-expression and increased activation in cancerous tissue vs. normal counterparts (Maemura et al., 1999; Wang et al., 1999)
 - n-6 stimulate (1979-present);
 - n-3 inhibit growth, malignancy, and metastasis (1993-present)
 - ↑ (n-3) to (n-6) PUFA ratio... ↓ cell growth (Chamras et al., 1999)



Purported Mechanism of n-3 FA in Preventing Lean Tissue Wasting in Cancer



Ubiquitin-proteasome system



- UPP responsible for > 80% lean tissue wasting in hepatocellular cancer model.
(Baracos et al., 1995; Lazarus et al., 1999)
- UPP pathway activated in muscle of gastric cancer patients (Bossola et al., 2003)

CAN ω -3 FA play a role?

- Lower rate protein breakdown in harvested muscle of EPA-fed animals → due to suppression of UPP
- EPA paralyzes the proteasome (Whitehouse et al., 2001)

Fat metabolism

1. Lipolytic factor in cachexic state → enhances fat oxidation
 2. Many solid type tumors have difficulty utilizing dietary fat as an energy source.
 - Fewer mitochondria in tumor cells for beta-oxidation of fat as energy source
-



- Patient can efficiently utilize fat calories as the **primary** energy source.
- Utilize omega-3 fatty acids (EPA& DHA) for their anti-tumorigenic and anti-cachexic activity.

Vitamin D

inhibits the growth of cancer cells by regulating several genes responsible for cell proliferation and differentiation

Effect of Vitamin D3 Supplements on Development of Advanced Cancer: A Secondary Analysis of the VITAL Randomized Clinical Trial

Chandler, Chen, Ajala, et al

JAMA Network Open. 2020;3(11):e2025850. doi:10.1001/jamanetworkopen.2020.25850

Evaluate whether vitamin D reduces incidence of advanced (metastatic or fatal) cancer and an examination possible effect modification by body mass index.

- Randomized, double-blind, placebo-controlled; 2 × 2 factorial clinical
- Vit D3 (cholecalciferol, 2000 IU/d); marine omega-3 fatty acids (1 g/d) supplements.
- 25,871 adults, randomized, ≥ 50-55 yr old adults, study duration 201-2017

Conclusions: In this RCT, supplementation with vitamin D reduced the incidence of advanced (metastatic or fatal) cancer in the overall cohort, with the normal BW

Combined Vitamin D, Omega-3 Fatty Acids, and a Simple Home Exercise Program (SHEP) May Reduce Cancer Risk Among Active Adults Aged 70 and Older: A Randomized Clinical Trial

Bischoff-Ferrari, Willett, Manson et al Front. Aging, 25 April 2022 <https://doi.org/10.3389/fragi.2022.852643>

- Three-year, multicenter, $2 \times 2 \times 2$ factorial design double-blind, RCT
- 3 yr duration (12/12 -12/17)
- Healthy community-dwelling adults ≥ 70 years were recruited (senior-geriatric).

Conclusion: Supplementation with daily high-dose vitamin D₃ (2000 IU/day), **plus** omega-3s (1 g/day of marine omega-3s), **combined** with SHEP, showed cumulative reduction in the cancer risk in generally healthy and active and largely vitamin D-replete adults ≥ 70 years.

Vitamin D - Cancer - Dogs

An in vitro study observed that oral calcitriol administration improves the effects of chemotherapy in canine MCTs.

How so?

- activation of VDR, expressed broadly in K-9 neoplastic mast cells;
- decrease in receptor tyrosine kinase activity;
- calcitriol and calcipotriol (analogue) showed cytotoxic effects on multidrug resistance protein-1 overexpressing cells
- Impaired transport function of ATP-binding cassette transporters → related to proteins involved in multidrug resistance (P-glycoprotein, MRP1 and breast cancer resistance protein) WAS also observed.
- synergistic effects of calcitriol and cisplatin on inhibition of proliferation of K-9 tumor cells.

Vitamin D- Cancer – Dogs .. cont.

Selting; Weidner studies

The vitamin D status is linked to tumors related to bone metabolism, like osteosarcoma.

Lower serum 25-OHD concentrations were found in dogs with mast cell tumors (MCT) and dogs with splenic hemangiosarcoma.

BUT ... In humans, a systematic review and meta-analysis concluded no evidence was found to support the use of vitamin D supplementation to decrease mortality in patients with cancer, or to decrease cancer incidence.

Cancer and vitamin D supplementation: a systematic review and meta-analysis.

Am J Clin Nutr. 2018; **107**: 652-663

Branched-Chain Amino Acids

What is known –

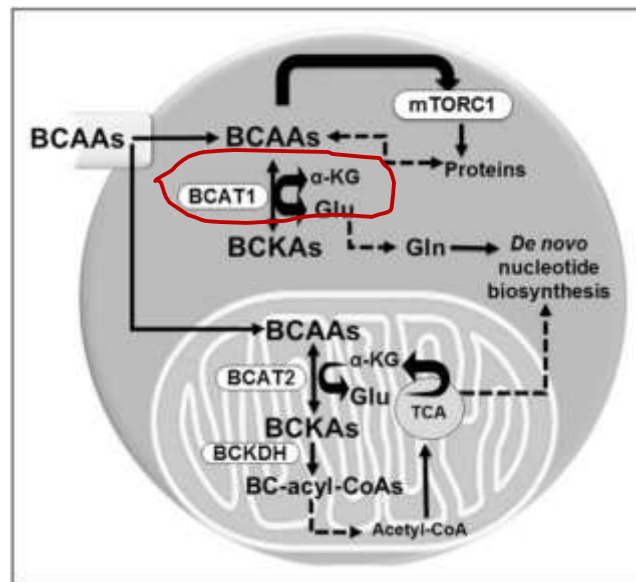
- Evidence demonstrates that BCAAs are essential nutrients for cancer growth and are used by tumors in various biosynthetic pathways and as a source of energy.
- Tumors preferentially uptake the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine.

BCAAs can be used for protein synthesis or oxidized for energy purposes by tumors.

BCAAs are essential amino acids; tumors must rely on dietary BCAA intake and their release from protein degradation.

BCAA metabolic enzymes, such as the cytosolic branched-chain aminotransferase 1 (BCAT1) and mitochondrial branched-chain aminotransferase 2, have emerged as useful prognostic cancer markers.

- BCAT1 expression commonly correlates with more aggressive cancer growth



Both oncogenic mutations and cancer tissue-of-origin influence BCAA metabolism and expression of BCAA-associated metabolic enzymes

LBM in Oncologic Patient

LBM, as skeletal muscle, is the predominate source of protein in the body.

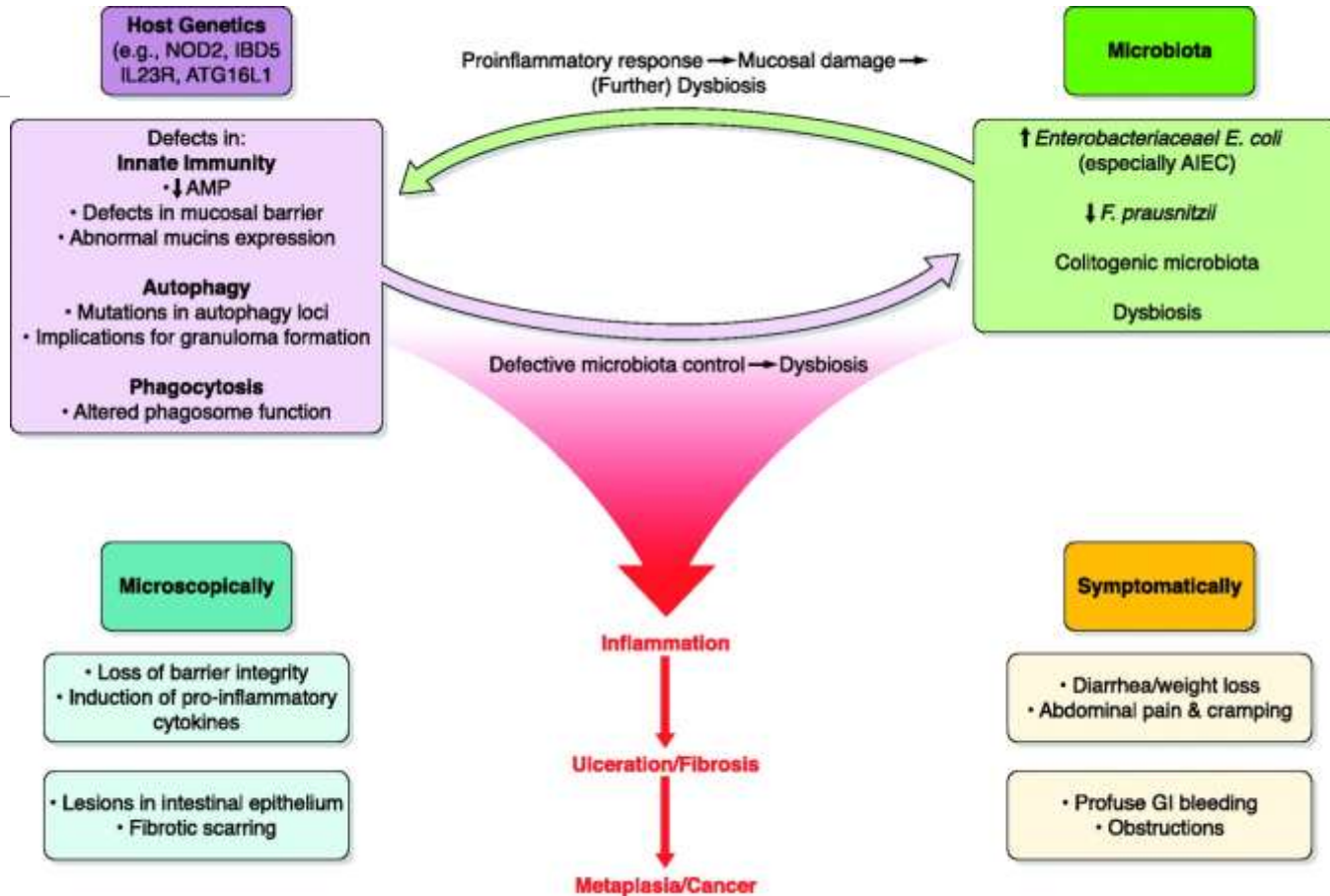
- Synthesis of contractile elements
- Antibodies
- Enzymes
- Cell signaling
- **Development of muscle mass**



Should dietary BCAA be restricted in cancer patients?

In-depth research on BCAA metabolism in cancer has provided strong evidence for the essential role of BCAAs in tumor progression and has clearly established *BCAT1* as an important prognostic cancer marker

The reliance of cancer cells on BCAAs needs to be addressed with future studies so that therapeutic approaches aiming to target BCAA metabolism in cancer can be successfully developed.



Anti-tumor regimes and probiotics

Probiotics – What’s their Magic?

“Live microorganisms”

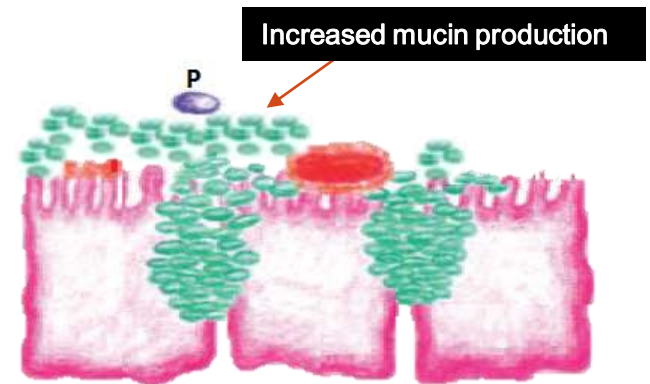
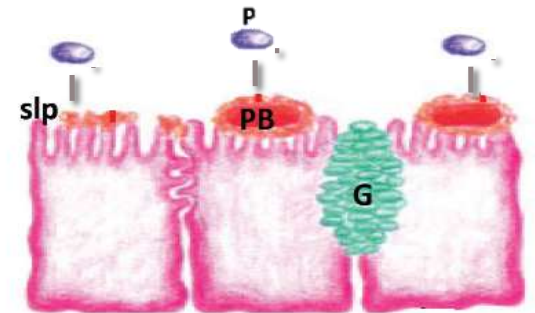
Maximize energy available to the host

Promote non-immunologic gut defense barrier

Modulate the balance between defense immunity;
pathogen-induced inflammation

Stimulate secretory IgA production within GI tract

Influence composition of the mucus layer



Sherman et al.

Gut Microbiota ↔ Antitumor Regimes

***Lactobacillus* supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study** Österlund, et al. *Br J Cancer* 2007

Lactobacillus GG supplementation well tolerated; may reduce frequency severe diarrhoea and abdominal discomfort related to 5-FU-based chemotherapy. (N=150)

- guar gum included and no *Lactobacillus*-related toxicity was detected

Nutrition Modulation of Gastrointestinal Toxicity Related to Cancer Chemotherapy: From Preclinical Findings to Clinical Strategy. Xue, et al. *JPEN* 2011

Modulation mechanisms, which combinations best, optimal trt strategies

Gut Microbiota ↔ Antitumor Regimes

Probiotic bacteria in cancer patients undergoing chemotherapy and radiation therapy.
Mego, et al. Complement Ther Med. 2013

Current evidence supporting probiotic use probiotic therapy to anticancer treatment limited, especially chemotherapy. More common with radiation Rx

The efficacy and safety of probiotics in people with cancer: a systematic review.
Redman, et al. Annals of Oncology 2014

11 studies (N = 1557) included for assessing efficacy. Primary outcomes were the reduction in duration-severity- incidence of Ab- and chemo-associated diarrhea; probiotic-associated AE's

Probiotics may be rare cause of sepsis. Further evidence needed to determine whether probiotics provide signif overall benefit for cancer patients



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NC STATE UNIVERSITY

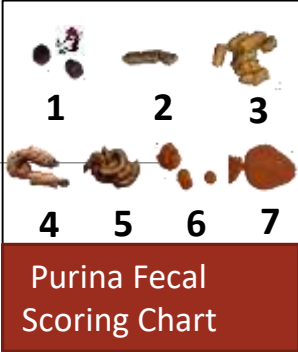


Effect of Oral Probiotic on Gastrointestinal Toxicity Among Dogs Receiving Doxorubicin Chemotherapy



Design and Methods, continued

- Sample collection & analysis
 - Fecal samples
 - Fecal inflammatory biomarkers
 - Fecal scores & Client questionnaire
- Data Analysis
 - Data averaged per period (8 days) for each patient
 - Significance at $p < 0.05$



CBC, Chem profile
Fecal-pre
Probiotic or Placebo
begins

Doxorubicin
administere
d

Fecal-post

Repeat with
Placebo or
Probiotic

2 wks

d1

d2

d3

d4

d5

d6

d7

d8

Online daily VCOG-CTCAE questionnaire & Fecal Score recorded (d1 thru d8)

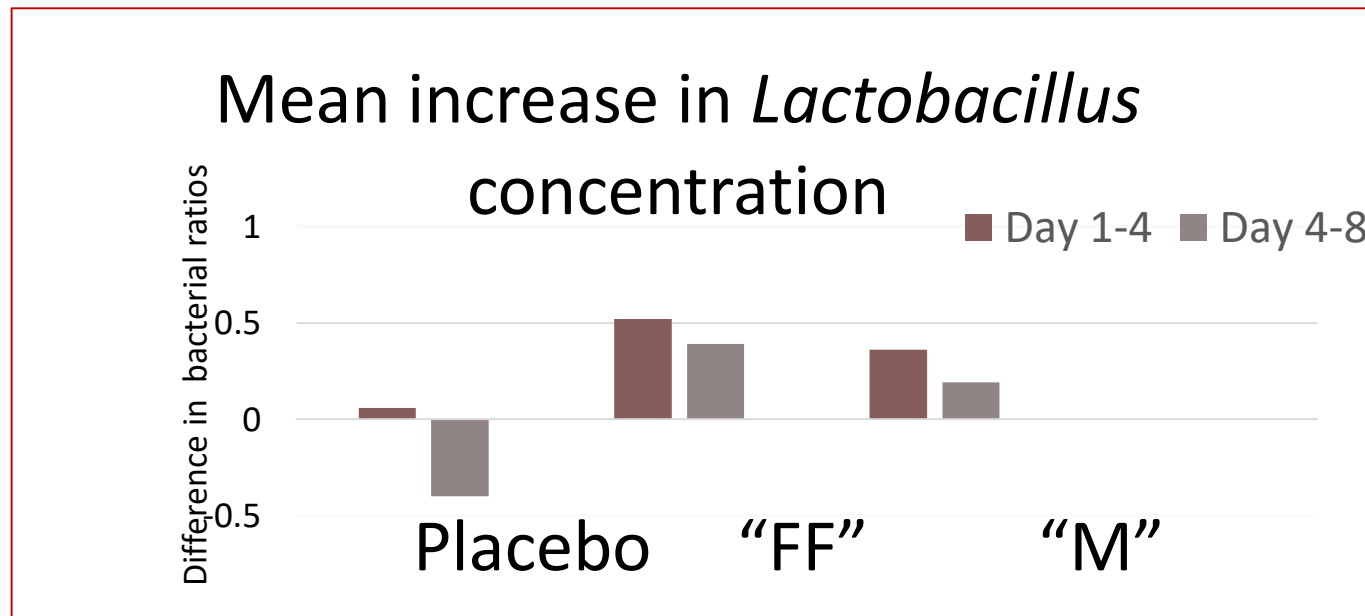
Results – Fecal Lactoferrin

Effect	DF	Wald Chi-Sq	Pr>ChiSq	Odds Ratio	95% CI	
“PROBIOTIC” vs PLACEBO						
Treatment (Pr/Pl)	1	28.892	<0.0001	16.457	5.927	45.696
Sequence (1st or 2nd)	1	0.837	0.360			

Results – Fecal RT-PCR

All trts: No increase ($p=0.0521$) in concentration *Lactobacillus* species (relative to total Eubacteria) over time.

Fecal samples from Probiotic “FF” and M” groups showed numerical increase *Lactobacillus* species between day1 and d4; d4 and d8





SUMMARY

Appeared to have more D-free days with FortiFlora® probiotic /chemo

Fecal MPO values sig. decreased with oral probiotics pre-doxo vs. placebo.

Inflammation (MPO) persists/worsens over 8-day period without probiotics

Odds ratio favored placebo treatment resulting in a lower agglutination (gut inflammation) value vs placebo.

Oral probiotic(s) increased/sustained GUT *Lactobacillus* during doxo chemotherapy regime

Study Limitations –

Anti-lactoferrin agglutination assay

- Not yet validated for canine use

Fecal scores

Subjective measure; Fecal water content (quantitate)

Pomegranate

Rich in flavanoids, bioflavones, antioxidants

Tanner AE, **Saker KE**, Ju Y, Lee YW, O'Keefe S, Robertson J, Tanko JM. Cell proliferation of feline and human breast cancer cell types is inhibited by pomegranate juice. *JAPAN* 2008; 92(2):221

Saker KE, Wilson A, Tanner AE. 2009, Feline mammary gland organ culture model for evaluation of nutritional chemopreventive agents. *Compend Contin Educ.*

Conclusions – Take Away

- AOX studies support the benefits of supplementation for decreasing risk and decreasing adverse concerns of cancer (human literature)

- EPA /DHA show documented benefit to interrupt cell-signaling MAPK pathway to tumor cell proliferation;

Re-balancing protein synthesis-degradation balance via UPP to slow muscle wasting of cachexia

- Vitamin D still varied reports

- BCAA are a double-edged sword

- Probiotics beneficial to mitigate chemo Rx GI toxicity

- Pomegranate ... in vitro benefit in mammary cell tumor model

Thank you !

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