# Nutraceuticals for Cancer Prevention & Survival

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# Disclosure of Conflicts of Interest

- Lilly Oncology: Speaker’s Bureau
- Kate Farms: Speaker’s Bureau
- Digestive Care, Inc.: Speaker’s Bureau

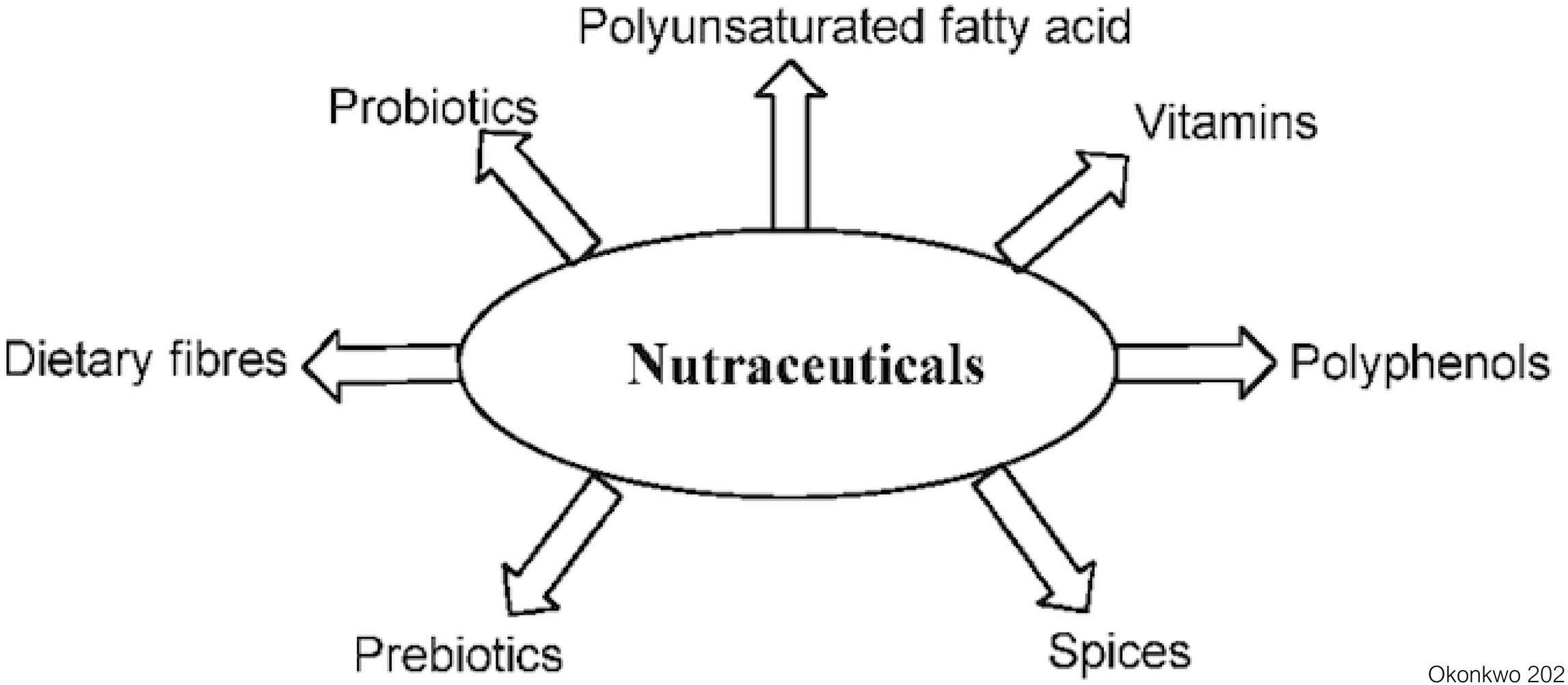
# Nutraceutical Industry

The global nutraceuticals market size was valued at $ 712.97 billion in 2023 & is expected to grow to $1, 251.07 billion in 2030.[1]

Dietary supplements are regulated in the U.S. by several federal agencies with overlapping jurisdiction - FDA and the FTC; enforced by the State AGO and DOJ; and monitored (not regulated) by the CDC.[2]

In 1994, the U.S. Congress, when passing the Dietary Supplement Health and Education Act (DSHEA), defined & established a regulatory framework for dietary supplements.[3]

It is paramount that healthcare providers openly discuss the use of dietary supplements with patients and present safe, evidence-based recommendations.




Okonkwo 2021

# Select Nutraceuticals for Cancer Prevention & Survival

- Omega-3 fatty acids – EPA/DHA
- Curcumin
- Vitamin D
- Sulforaphane
- Green Tea/EGCG

# Omega-3 Fatty Acids

# Omega-3 Fatty Acids

- Offer cardioprotective, anti-inflammatory, immunomodulatory effects, and possible anti-cancer effects[5-8]
- Potential cancer benefits: anti-inflammatory, peripheral neuropathy, mucositis, cachexia, sarcopenia[5-8]
- Reduces the incidence of postoperative infectious complications[9]
- Slows the progress of cancer growth in lung, colon, mammary & prostate, and also increases the effectiveness of cancer therapies such as chemotherapy and radiation[5-8]
- Reduces treatment side effects & may enhance clinical benefit of several treatments - Cisplatin, Paclitaxel, and Oxaliplatin + 5-FU[5-8]

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PMCID: PMC10052714
PMID: 36986040

# The Effects of Omega-3 Polyunsaturated Fatty Acids on Breast Cancer as a Preventive Measure or as an Adjunct to Conventional Treatments

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cancer in the literature, with very relevant histological and molecular similarities depending on the specific

The use of ω-3 PUFAs, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) has been shown to minimize chemotherapy side effects and improve progression-free survival as well as the overall survival of patients with breast cancer.

ω-3 PUFA supplementation is an important coadjuvant to chemotherapy or other traditional antitumor therapies and shows remarkable results in combination with these other treatments, reducing tumor growth and weight (during the first fifteen days after tumor induction) compared to the isolated use of drugs or ω-3 PUFAs alone. Furthermore, the survival rate is increased.

# Omega-3 Fatty Acids to Reduce Treatment Associated Side Effects


A review of 49 clinical studies reports that the main effect of ω-3 PUFA appears to be on cancer associated symptoms, namely cachexia, inflammation, neuropathy, post operative complications and QoL.[11]

Breast cancer patients undergoing paclitaxel therapy had a 70% lower risk of peripheral neuropathy with the use of 640 mg EPA/DHA TID.[12]

ω-3 PUFAs may reduce the severity of chemotherapy induced mucositis.[13]

Esophageal cancer patients undergoing chemotherapy experienced less stomatitis when consuming 900 mg ω-3 PUFAs daily.[14]

ω-3 PUFAs increased overall body mass & strength[15]

# Omega-3 Fatty Acids & Chemotherapy

ω-3 PUFAs strongly prevent cisplatin-induced myelosuppression.[5]

ω-3 PUFAs seem to reduce the incidence & severity of oxaliplatin-related neurotoxicity, & improve QOL.[6]

ω-3 PUFAs reduced chemotherapy-related toxicity & resulted in better radiological responses.[7]

This review finds, with low certainty, that ω-3 PUFAs attenuates sensory loss & reduces the incidence of neuropathy secondary to oxaliplatin and paclitaxel treatment.[8]

Multiple studies have reported the effectiveness of ω-3 PUFAs in reducing the incidence of postoperative infectious complications.[9]

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PMCID: PMC10997328
PMID: 38578269

# Higher ratio of plasma omega-6/omega-3 fatty acids is associated with greater risk of all-cause, cancer, and cardiovascular mortality: A population-based cohort study in UK Biobank

Yuchen Zhang,[1] Yitang Sun,[2] Qi Yu,[3] Suhang Song,[4] J Thomas Brenna,[5,6] Ye Shen,[1] and Kaixiong Ye[2,7]

Edward D Janus, Reviewing Editor and Eduardo L Franco, Senior Editor
Edward D Janus, University of Melbourne Australia ;
Contributor Information.



n January
e, cancer,

Using a population-based cohort in UK Biobank, our study revealed a strong association between the ratio of circulating omega-6/omega-3 PUFAs and the risk of all-cause, cancer, and CVD mortality.

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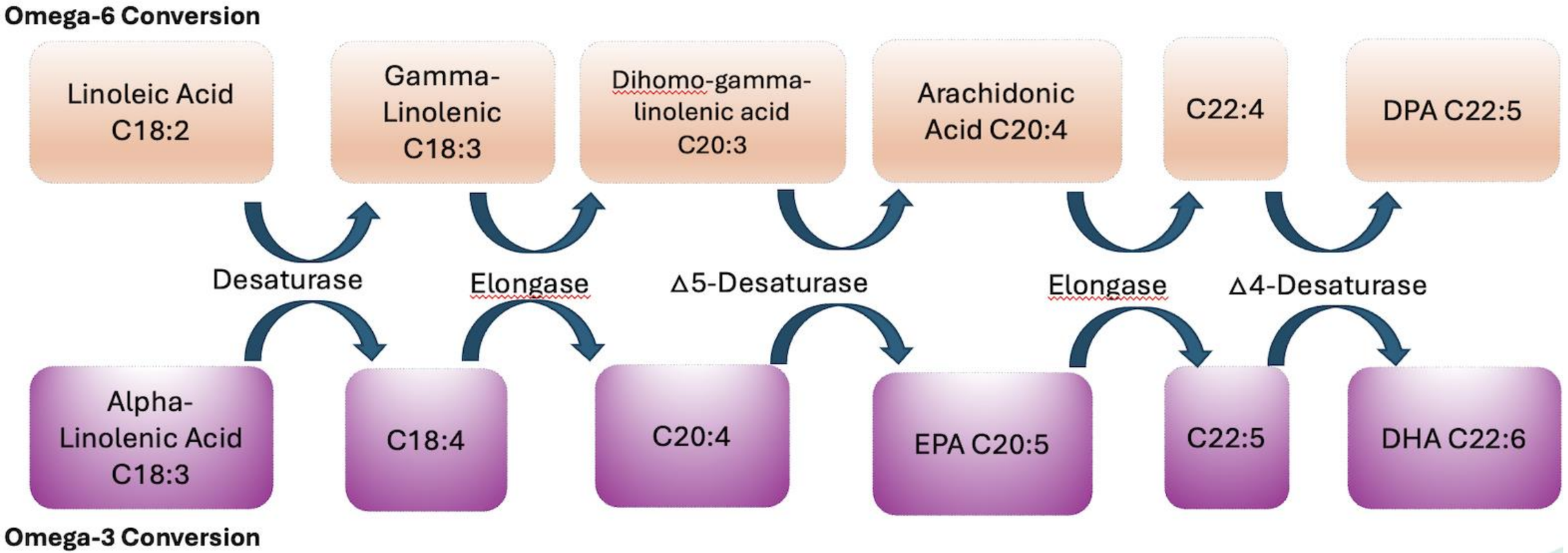
# Essential Fatty Acids




17,18

# Effects of EFA Imbalance

## Omega-6 Fats

Meats (especially grain-fed), butter, whole milk, egg yolks, sunflower oil, safflower oil, cottonseed oil, corn oil, & processed foods made with these oils

- Promote inflammation
- Foster tumor growth, progression, & angiogenesis
- Suppress immune function

## Omega-3 Fats

Cold-water fish (i.e., salmon, trout, sardines, herring, black cod), chia seeds, flaxseeds, walnuts, hemp hearts, Zen basil seeds, & sacha inchi seeds

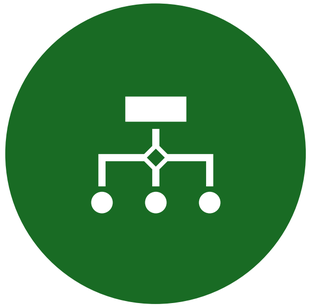
- Inhibit inflammation
- Inhibit tumor growth & angiogenesis
- Enhance immune function
- Complement chemo & XRT

# EPA/DHA Bioavailability & Dosage

- ALA → EPA/DHA
  - FADS
- Consume with a meal/snack that contains fat.
- Dosage commonly used for chronic health conditions:
  - 2-4 gm daily
  - Test Omega-3 Index
- A balanced ω-6/ω-3 FA ratio (1:1 to 2:1 is optimal) is vital for homeostasis and regular development throughout the lifespan.

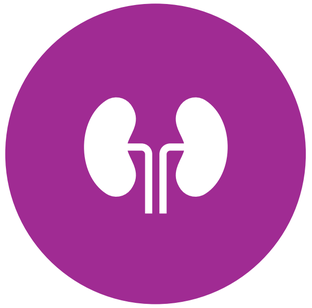
# Curcumin

the yellow-pigmented active constituent derived from turmeric with various roles, including anti-inflammatory, anti-oxidant, & anti-cancer properties



provides chemopreventive, antitumor, chemo-, & radio-sensitizing properties

downregulates COX-2 enzyme activity & NF-kB pathways, and apoptotic effects



may enhance effect of some chemotherapies, such as 5-FU, cisplatin, doxorubicin, paclitaxel, & gefitinib.

# Curcumin & Cancer

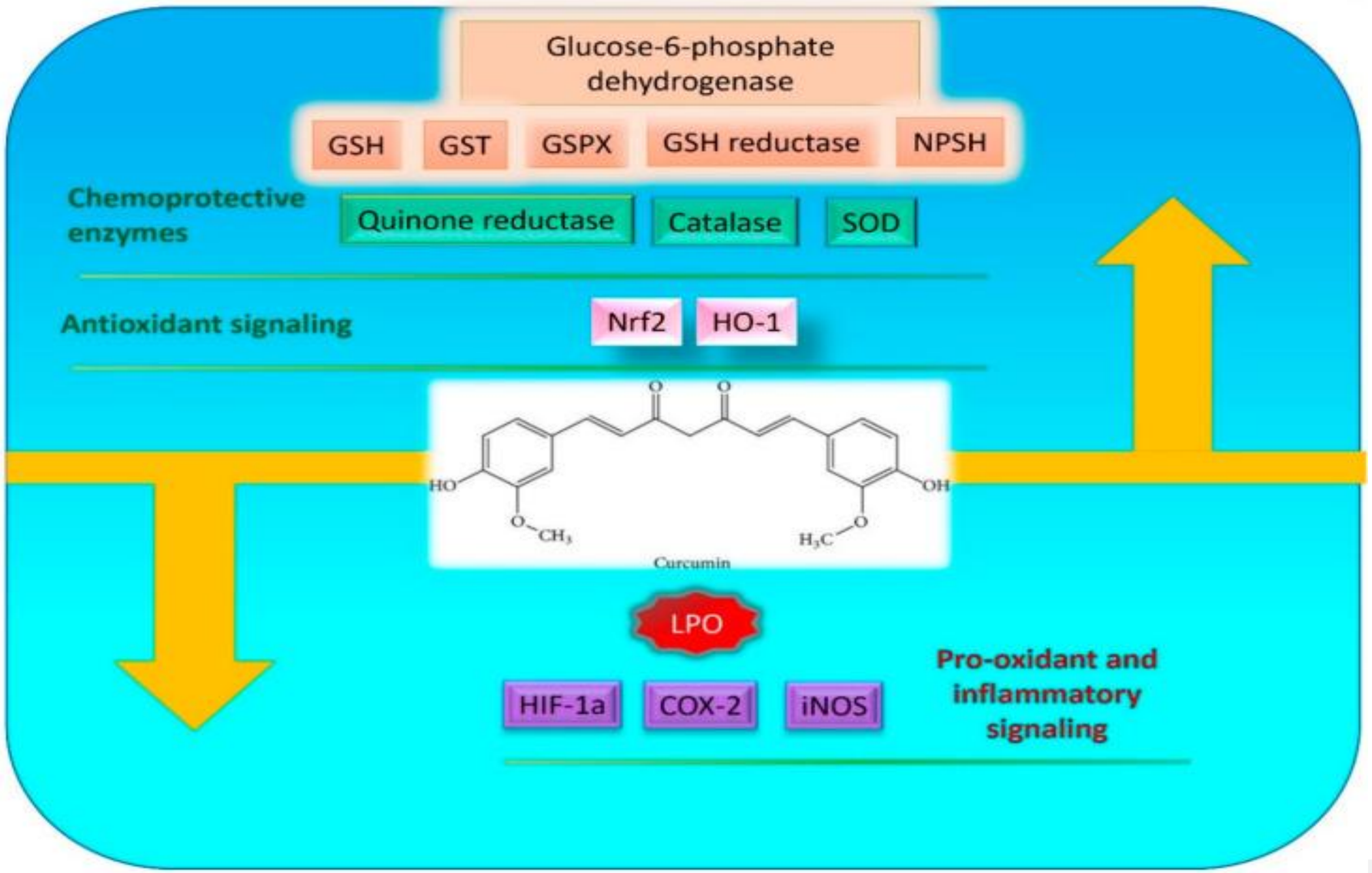
↓ proliferation of breast cancer cells[24]

enhanced autophagy and apoptosis in NSCLC cells[25] & pancreatic cancer cells[26]

reduces chemotherapy toxicities:[22,26]

- improves myelosuppression induced by carboplatin & etoposide
- may ↓ cisplatin-induced neurotoxicity
- ameliorates GI toxicity by 5-FU & methotrexate
- ↓ cardiotoxicity from doxorubicin & cisplatin
- ↓ nephrotoxicity induced by cisplatin

# Antioxidants and Cancer Treatment




Gupta 2020

Life Sciences
Volume 318, 1 April 2023, 121504

Review article

# Curcumin, calebin A and chemosensitization: How are they linked to colorectal cancer?

Aranka Brockmueller [a], Samson Mathews Samuel [b], Alena Mazurakova [c d], Dietrich Büsselberg [b], Peter Kubatka [c], Mehdi Shakibaei [a]

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Curcumin has capabilities to chemosensitize or re-sensitize CRC cells to 5-FU, oxaliplatin, cisplatin, & irinotecan; this polyphenol enhances the receptiveness of CRC cells to standard cytostatic drugs converting them from chemoresistant into non-chemoresistant CRC cells by modulating inflammation, proliferation, cell cycle, cancer stem cells, &apoptotic signaling.

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# Influence of Curcumin on Breast Cancer Cells

Turmeric
(Curcumin)

| Cell proliferation (−) | Cell migration (−) | Apoptosis (+) | Epigenetic modification (+) | Chemo-sensitization (+) |
|---|---|---|---|---|
| ↑AMPK<br>↓Akt<br>↓P65<br>↓Cyclin D1 | ↓NF-kB, STAT3<br>↓β-catenin<br>↑E-cadherin<br>↓N-cadherin<br>↓vimentin<br>↓fibronectin | ↑Caspase 3<br>↑Caspase 9<br>↑Bax<br>↓Bcl-2 | ↓Methylation of GSTP1 and RASSF1A<br>↓miR21,<br>↑miR181b | ↓Chemoresistance |

Bhattacharya 2021

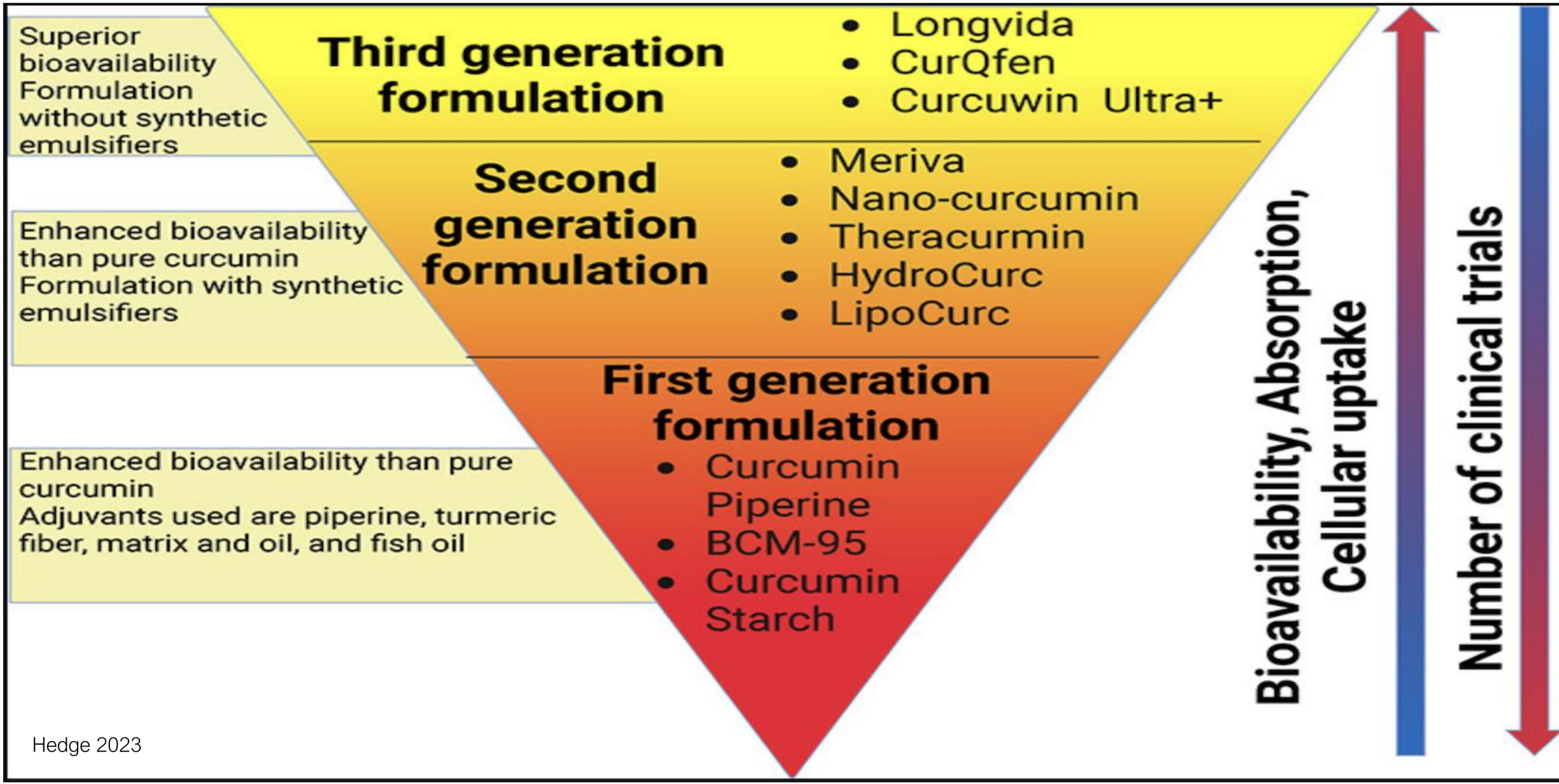
# Curcumin Bioavailability & Dosage

Well tolerated though known to have low bioavailability

Dosage used in cancer trials: 4gm-8gm curcumin daily

- 1 tsp dried turmeric = 200 mg curcumin

Safe for humans even at high doses - 12 gm daily[29]

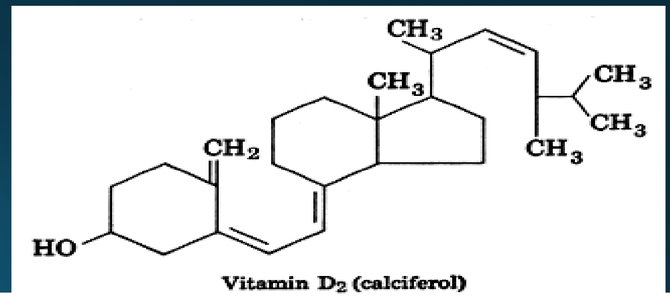

Superior bioavailability Formulation without synthetic emulsifiers
Third generation formulation
Longvida
CurQfen
Curcuwin Ultra+
Enhanced bioavailability than pure curcumin Formulation with synthetic emulsifiers
Second generation formulation
Meriva
Nano-curcumin
Theracurmin
HydroCurc
LipoCurc
Enhanced bioavailability than pure curcumin
Adjuvants used are piperine, turmeric fiber, matrix and oil, and fish oil
First generation formulation
Curcumin Piperine
BCM-95
Curcumin Starch
Bioavailability, Absorption, Cellular uptake
Number of clinical trials

Hedge 2023

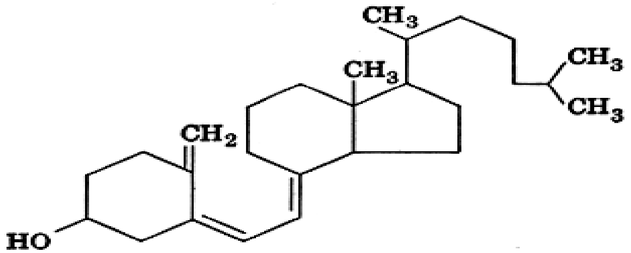
# Vitamin D

- Important for good overall health &:
  - Bone health
  - Immune system
  - Muscle function
  - Cardiovascular function
  - Respiratory system
  - Brain development
  - Anti-cancer effects

# Vitamin D & Cancer – Mechanisms of Action[31-32]



Vitamin $D_2$ (calciferol)



Vitamin $D_3$

- Induces differentiation
- Inhibits cell cycle
- Promotes apoptosis
- Inhibits invasion, angiogenesis, & metastasis in animal models
- Inhibits E2 synthesis & signaling (↓expression of aromatase, down-regulates expression of ER-α)
- Anti-inflammatory (↓COX-2 expression, ↓PGE2)
- Controls immune cell regulation and differentiation, gut barrier function and antimicrobial peptide synthesis
- Plays a role in blood sugar regulation, insulin sensitivity

# Vitamin D – Cancer Incidence

High-dose vitamin D supplementation prescribed monthly for up to 4 years without calcium may not prevent cancer[33]

Vitamin D supplementation alone → No effect on incidence of cancer or cancer mortality[34]

Updated meta-analysis of RCTs, vitamin D supplementation significantly ↓ total cancer mortality but did not reduce total cancer incidence[35]

# Vitamin D – Mortality and Cancer Survival

Evidence suggests that low circulating vitamin D levels are associated with an increased risk of cancers, whereas supplementation alone or in combination with other chemo/immunotherapeutic drugs may improve clinical outcomes even further.[36]

Low 25(OH)D associated with ↑ risk of all-cause mortality[37]

Meta-analysis of five clinical trials demonstrated that 400-4000IU D3 supplementation may modestly reduce risk for CRC-specific mortality (HR [95% CI]: 0.70 [0.48–0.93][38]

Meta-analysis of 14 RCTs yielded a statistically non-significant reduction in cancer mortality by 6%; subgroup analyses revealed a 12 % lower cancer mortality in the vitamin $D_3$ group compared with the placebo group in 10 trials with a daily dosing regimen (RR [95%CI]: 0.88 [0.78–0.98][39]

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# Higher 25(OH)D levels:

↓ cancer mortality for prostate, kidney, & melanoma, NS improved survival for head and neck, gastric, pancreatic, and liver cancers [40]

↓ lung cancer risk and mortality but not overall survival[41]

↑ overall survival in patients with breast cancer; ↓ risk of breast cancer morbidity and mortality [42]

25(OH)D levels are associated with a better prognosis of breast and colorectal cancer yet too few studies currently to draw conclusions for other cancers.[43]

82% lower risk of breast cancer for 25(OH)D concentration >60 ng/mL versus <20 ng/mL[44]

# Vitamin D & Immunotherapy

Overall survival was significantly different between VitD sufficient, insufficient, & deficient patients (log-rank P =0.01), which remained after adjustment in Cox proportional hazards regression models. Baseline 25(OH)D levels seem to be associated with ICI efficacy & prognosis, it might be helpful to assess the baseline VitD status, & supplementation with VitD might bring some benefit to enhance ICI efficacy and reduce moderate-severe irAEs.[45]

The PROVIDENCE study suggests the potential positive impact of early systematic vitamin D supplementation on outcomes of patients with advanced cancer receiving ICIs & support adequate repletion as a possible prophylaxis for thyroid irAEs.[46]

Findings highlight vitamin D levels as a potential determinant of cancer immunity & immunotherapy success.[47]

# Vitamin D Recommendations

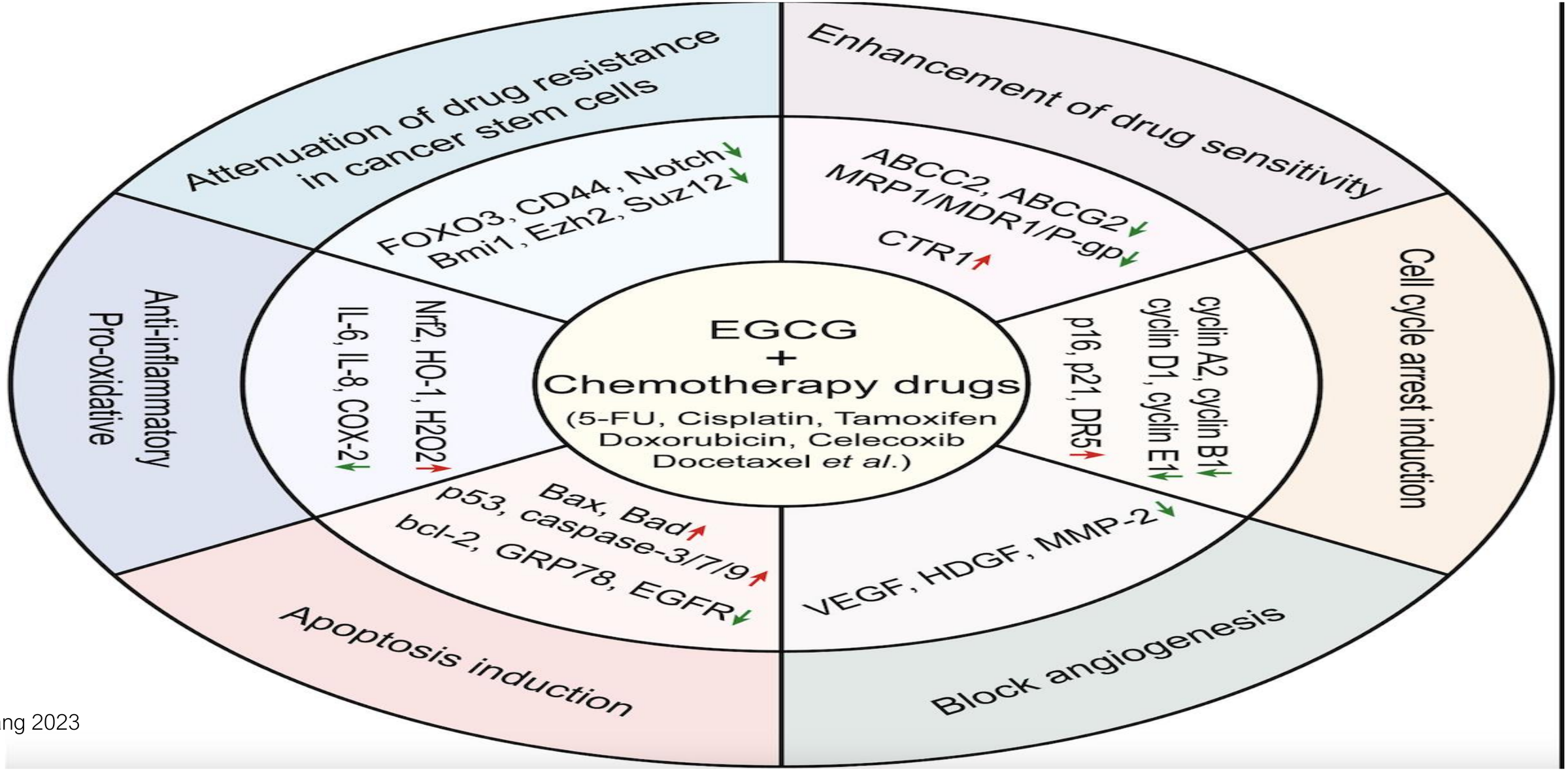
- Recommended dosage: 1,000-10,000 IU D3 daily
  - Base on serum 25(OH)-vitamin D level
  - Consider combining with K2
- Optimal serum 25(OH)-vitamin D levels have not been established though research suggests 40-80 ng/ml[48]

# Green Tea/Matcha EGCG

# EGCG (epigallocatechin gallate)

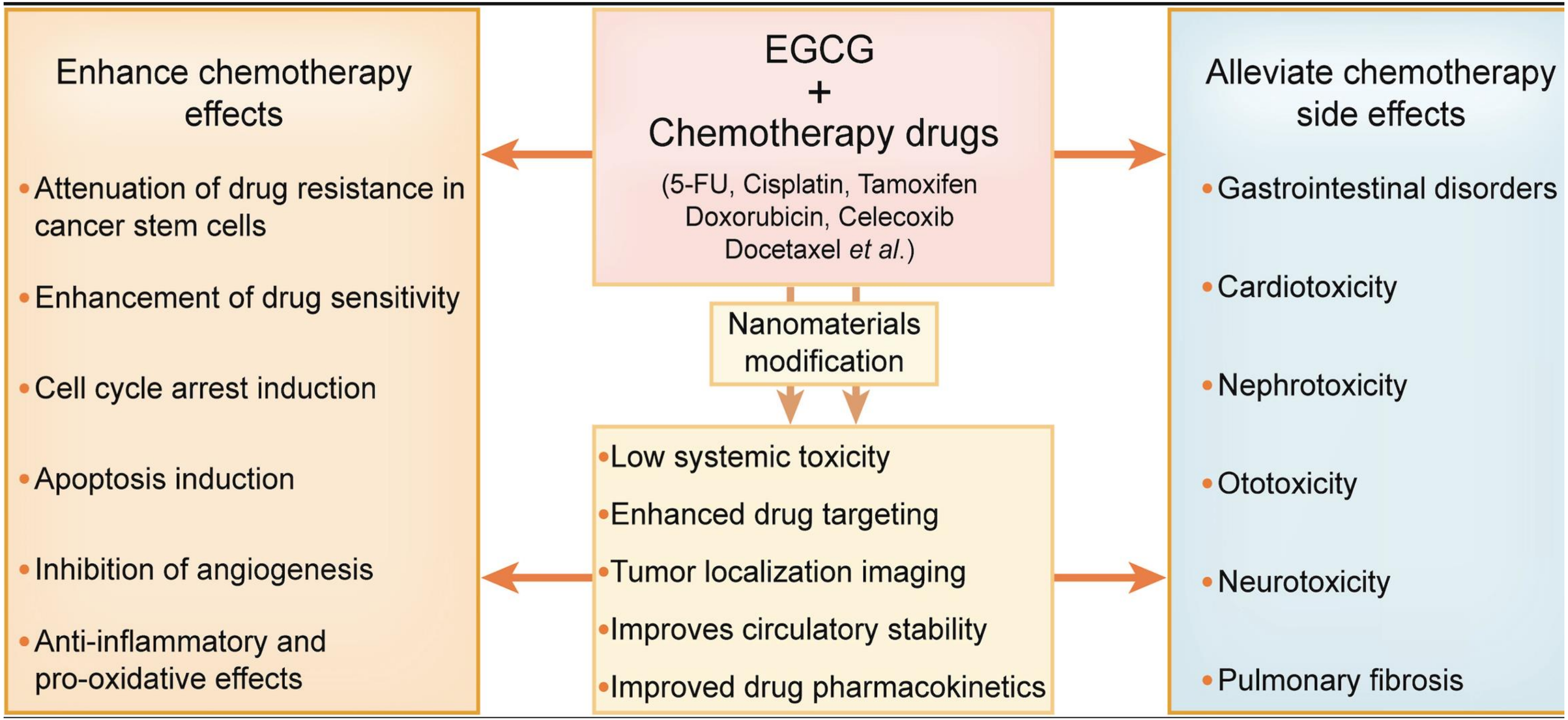
- A free radical scavenger that possesses anti-cancer, anti-obesity, anti-diabetic, anti-cardiovascular, anti-infectious & anti-neurodegenerative effects[49-50]
- 4 cups green tea daily for 4 months can reduce the amount of 8-OHDG found in the urine [Hakim],particularly for those with a GST SNP[51-52]
- EGCG is well known for its inhibitory activity at all stages of cancer initiation, promotion, and progression.[53]
- Inhibitory effects of EGCG on cancer cells has been demonstrated in 25 different cancer types[54]
- Clinical studies suggest favorable effects in breast, colon, prostate, lung and blood cancers by green tea consumption[55]

# Mechanism of EGCG combined with chemotherapeutic drugs to enhance antitumor efficacy




Wang 2023

# Advantages of EGCG in Adjuvant Chemotherapy

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# Green Tea/Matcha

- 1-4 cups daily green tea OR 1-2 cups matcha daily
- 1 cup green tea has ~40-50mg  EGCG; 1 tsp matcha has 60-200mg EGCG[57-58]
  - Many research studies use 400-800mg EGCG daily
- Brew in hot, but not boiling, water
- Add citrus

# Sulforaphane

# Sulforaphane

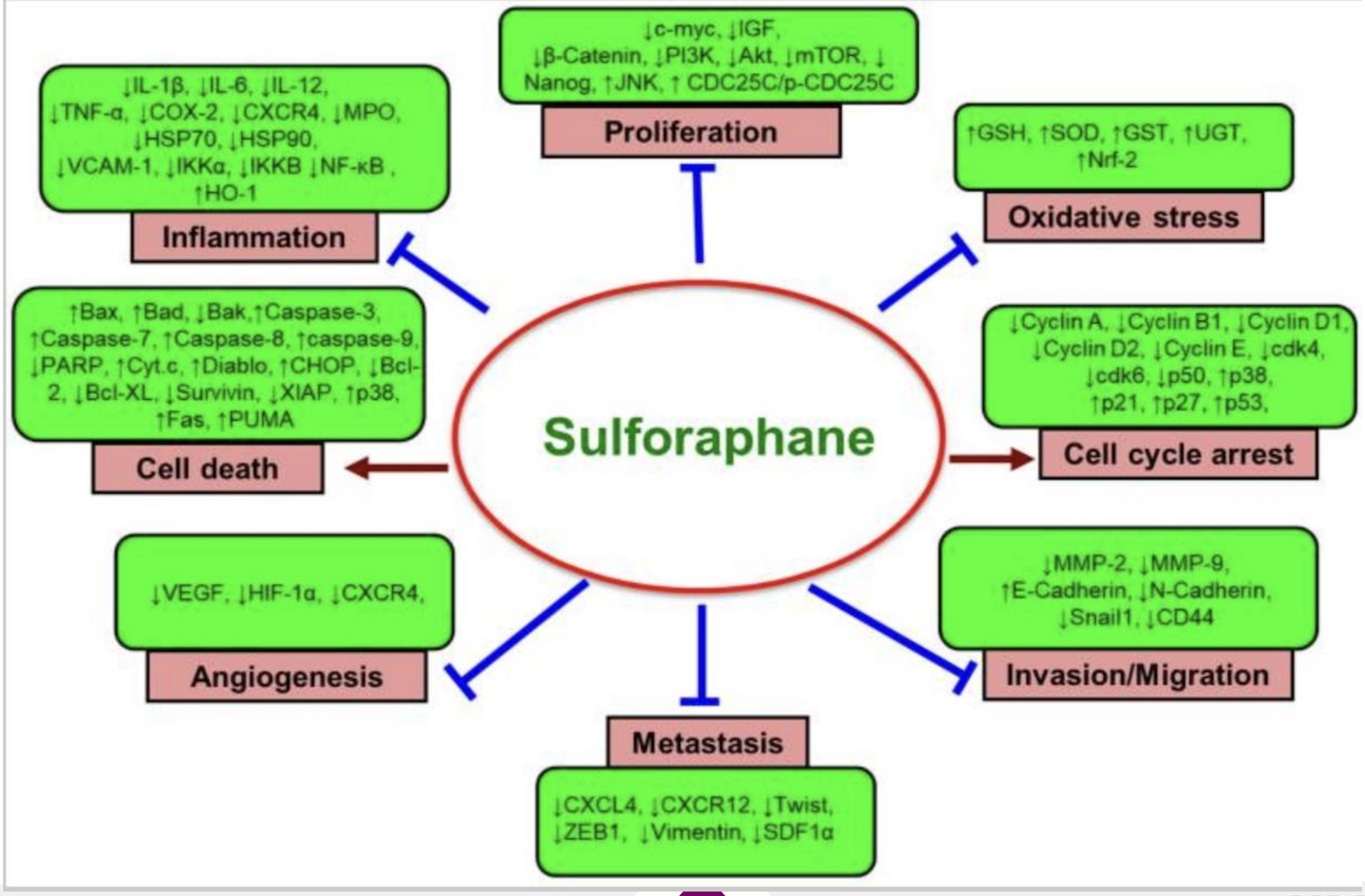
shows antioxidant & anti-inflammatory properties and targets several molecular pathways involved in the development of cancer[59-60]

exhibits neuroprotective effects and is implemented in treating conditions such as traumatic brain injury, Alzheimer's disease & Parkinson's disease

exhibit chemoprevention by various mechanisms → leukemia, prostate cancer, breast cancer, colon cancer, skin, lung, gastric, pancreatic, urinary bladder, & oral cancers

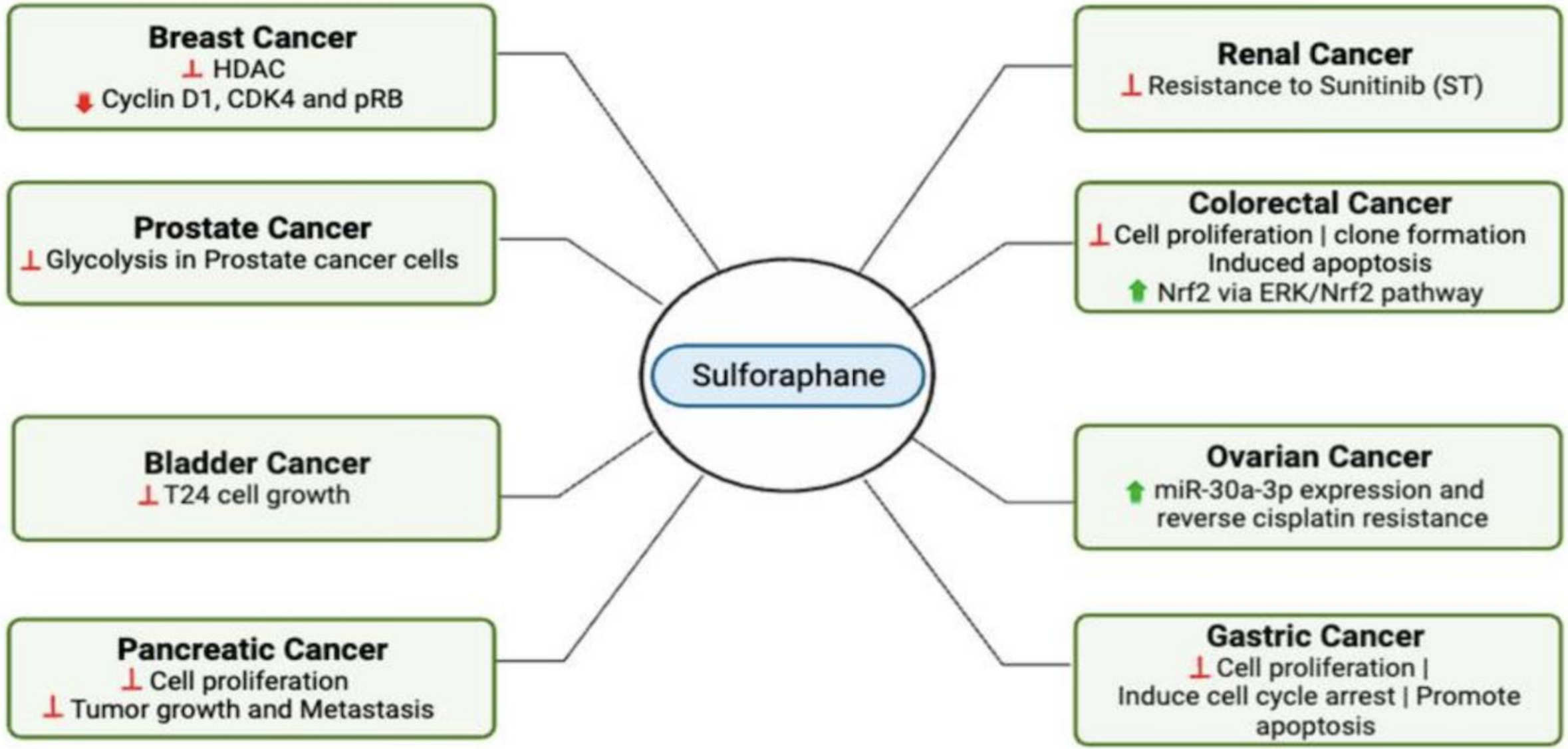
promotes apoptosis, induces cell cycle arrest, inhibits angiogenesis, reduces inflammation, alters susceptibility to carcinogens, reduces invasion and metastasis, exhibits antioxidant & anti-inflammatory properties, & sensitize cancer cells to chemotherapy

# Chemopreventive & anticancer effects of SFN




Kaiser 2021

# SFN as a Anticancer Agent

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# Sulforaphane & Cancer Treatments

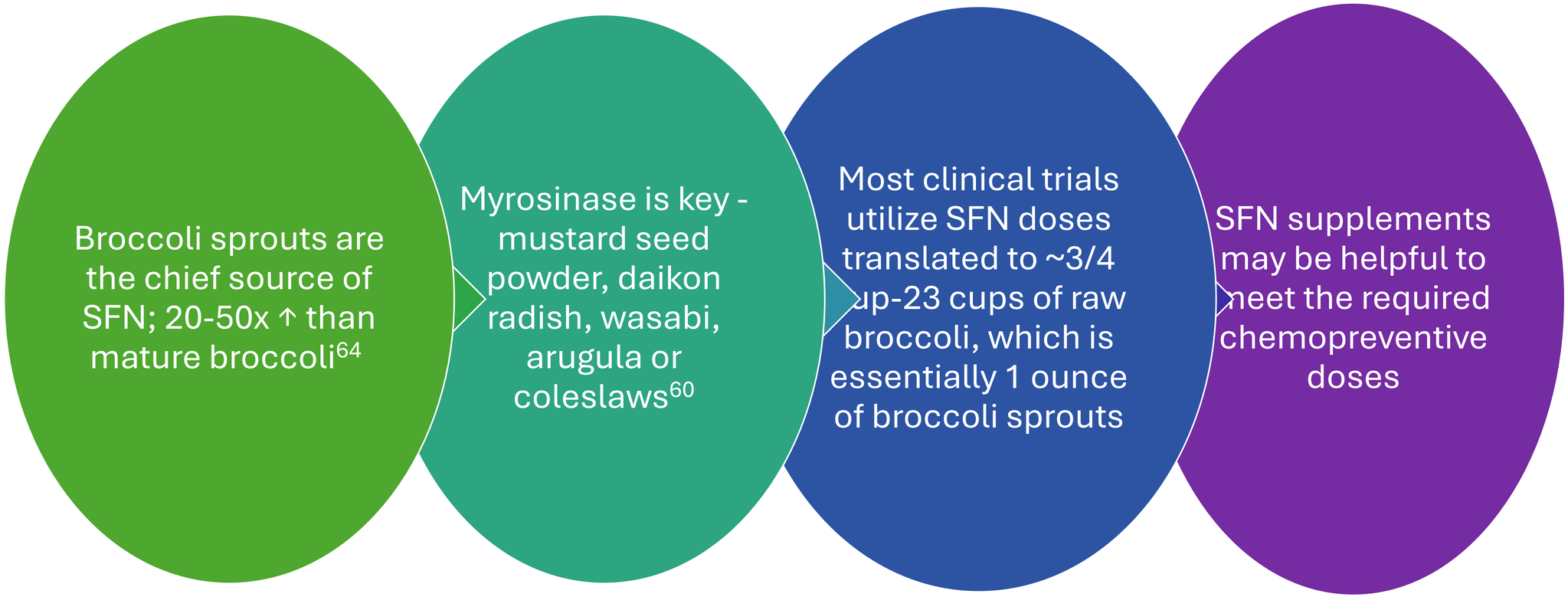
Preliminary breast ca research found SFN + 5-FU = ↑ autophagy

- resulting in ↓ cell growth & ↑ apoptosis[62]

Combination of SFN 4mg/kg + DOX showed significantly greater tumor regression & helped ↓ cardiotoxicity by enhancing mitochondrial activity[63]

Preliminary studies have suggested that SFN may help protect healthy cells and tissues from the harmful effects of radiation[61]

# Sulforaphane



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# Nutraceutical/Supplement Use by Cancer Patients

Most cancer survivors use dietary supplements, some of which may be safe and others unsafe that may interfere with cancer treatments.

Imperative that the medical team review potential effects of dietary supplements on cancer treatment & on educating cancer survivors on evidence-based and appropriate use of dietary supplements.

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