

Herbs and Natural Substances Synergies with Taxanes (Taxol, Paclitaxel, Docetaxel, Taxotere), Vinorelbine, Enhertu, and Kadcyła

Synergistic Substances with Chemotherapy

Safe to use the following during chemotherapy cycle to increase effectiveness, support immune system, and reduce side effects:

- Curcumin (Start at a low dose and work up. No effect on CYP3A4 in human studies)
- Medicinal mushrooms: Turkey tail (*Coriolis versicolor*), Reishi, Chaga, Cordyceps, Poria Cocos, Maitake, Shitake
- Beta-glucans
- AHCC (derived from Shitake mushroom)
- Melatonin (20 mg+)
- Astragalus
- Ginger
- Echinacea
- Milk thistle
- Resveratrol (low dose of 200 mg trans-resveratrol or less per day)
- GLA from borage or black current oil (not Evening Primrose Oil)
- EPA/DHA from fish oil or algae oil (best taken with tocotrienols)
- Tocotrienols (not tocopherols)
- Artemisinin (IV given day before chemo, or oral timed 4 days leading up to chemo)
- L-glutamine on chemo days 1-3 for Taxanes, 1-4 for Kadcyła, and 1-6 for Enhertu to protect gut and avoid nerve damage.
 - Dr. Alschuler states l-glutamine enhances Taxane chemotherapy.
 - Don't panic about l-glutamine "feeding" the cancer while the chemo is active. Neuropathy is forever!
 - Methylated B12 may be needed throughout treatment if you have a deficiency but this is best discussed with an integrative doctor.
 - Benfotiamine form of B1, B6, omega-3 EPA/DHA, and R-alpha lipoic acid to reduce risk of or treat neuropathy.

Cycle Recommendations for Chemotherapy

Many herbs and natural substances synergize with Taxanes (and likely Vinorelbine, Enhertu, and Kadcyła as they are microtubule disrupters as well) based on in vitro and animal studies. *However, because of potential or unknown interactions in humans that could cause the drug to be less effective or cause severe side effects, some supplements (not including safe ones listed above) should be stopped during the active days of the infusion, unless otherwise instructed by an integrative cancer practitioner.*

Guidelines for timing supplements with potential interactions during infusion cycles:

- **Taxanes** (Taxol, Paclitaxel, Docetaxel, Taxotere) and **Vinorelbine 3-week cycle: stop the day before and days 1-3**
- **Taxol or Vinorelbine** (reduced dose) **1-week cycle: stop the day before and the day of**
- **Kadcyła** (TDM-1) 3-week cycle: **stop the day before and days 1-5**
- **Enhertu** (Trastuzumab derexatecan) 3-week cycle: **stop day before and days 1-7**

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Potentially Synergistic but Possibly Should be Stopped on Active Chemo Days to Avoid Interactions

Some substances may be used during chemotherapy to help reduce drug resistance and help the drug work better but possibly should be avoided on active chemo days per the guidelines above. In some cases, in vitro or animal research suggests synergy between these substances and the drugs, but caution is needed because of the potential for serious side effects or reduced drug potency. *Use of these during the active days of chemo cycles should be done ONLY under the guidance of an experienced integrative practitioner):*

- Hydroxytyrosol or Oleuropein
- Black seed oil (thymoquinone)
- Feverfew
- Ashwagandha
- Panax ginseng
- Magnolia (Honokiol)
- EGCG
- Propolis
- PEITC (isothiocyanate from watercress, turnip, cabbage)
- Resveratrol
- Baicalein
- Betulinic acid
- Quercetin
- Apigenin
- Artemisinin (consider IV artesunate day before or oral 4 days leading up to infusion including day before. Ideal dosing is 4-7 days on, 4-7 days off, so continue through cycle to time appropriately.)

With any herb or supplement, add slowly, one new herb at a time, and at lower dose to start. That way you know if a particular supplement is causing any side effects that you experience.

Use with Herceptin or with Chemotherapy Protocols that Include Herceptin (also Kadyla and Enhertu)

Herceptin carries a risk of sometimes irreversible damage to the heart muscle. Certain herbs and natural substances should be taken throughout treatment to reduce this risk. Consult integrative practitioner about whether to stop these antioxidants on active chemo days—not all agree that this is necessary or even wise:

- CoQ10
- Hawthorn leaf and flower
- Selenium
- Resveratrol
- Statin drug (according to recent clinical trials, but with CoQ10 separated by 12 hours)

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Use with Chemotherapy under Guidance of Integrative Doctor

Integrative doctors may use certain treatments to enhance the effectiveness of chemotherapy. *These should be timed, dosed, and administered by a medical professional:*

- Mistletoe
- Ivermectin
- Low-Dose Naltrexone
- IV alpha lipoic acid
- IV Vitamin C
- IV Artusenate
- Other off-label drugs (COC drugs etc.) and IV treatments

References

Books and presentations:

“Introduction to the Eclectic Triphasic Medical System (ETMS)” presentation by Donnie Yance, Master Herbalist and cancer specialist

Naturopathic Oncology by Dr. Neil McKinney, ND

The Definitive Guide to Cancer by Lise Alschuler, ND

Functional Herbal Therapy in Cancer, course by Kerry Bone, Master Herbalist and cancer specialist

Scientific research:

Black seed oil improves effectiveness of Paclitaxel in breast cancer

https://www.mdpi.com/1420-3049/25/2/426?fbclid=IwAR2mVLZvLwzOjy_KasZIFgKfl_ytaD-uBF7i-bljUa7pqri8RPGjKn1ys

The combination of thymoquinone and paclitaxel shows anti-tumor activity through the interplay with apoptosis network in triple-negative breast cancer

https://www.researchgate.net/publication/283260823_The_combination_of_thymoquinone_and_paclitaxel_shows_anti-tumor_activity_through_the_interplay_with_apoptosis_network_in_triple-negative_breast_cancer

Modulation by hydroxytyrosol of oxidative stress and antitumor activities of paclitaxel in breast cancer

Hydroxytyrosol (olive polyphenol available in supplement) improves effectiveness and reduces oxidative stress (damage to normal tissues):

<https://pubmed.ncbi.nlm.nih.gov/29468462/>

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Anti-breast Cancer Enhancement of a Polysaccharide from Spore of *Ganoderma lucidum* With Paclitaxel: Suppression on Tumor Metabolism With Gut Reshaping

Mouse model showing that Reishi mushroom improves efficacy of Taxane chemotherapy while reducing drug resistance and side effects. The mechanism appears to be by reducing the disk biases that happens in the gut during chemotherapy.

<https://www.frontiersin.org/articles/10.3389/fmicb.2018.03099/full>

Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer

Clinical trial showing increased effectiveness when oral curcumin 6000 mg per day split into 3 doses is given with Docetaxel..

<https://www.sciencedirect.com/science/article/pii/S0944711320300507?via%3Dihub&fbclid=IwAR2nd5zAc1L5yW3A4oQXYEiUmif3ObdEuiYbS9ibNkFoKA2T6Ii-v7LljCY>

Efficacy and safety of curcumin in combination with paclitaxel in patients with advanced, metastatic breast cancer: A comparative, randomized, double-blind, placebo-controlled clinical trial

Clinical trial showing that IV curcumin increased the tolerability of paclitaxel treatment.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3769673/?report=reader>

The Effect of *Echinacea Purpurea* on the Pharmacokinetics of Docetaxel

Human study showing that echinacea supplementation doesn't impact docetaxel pharmacokinetics and has a moderate impact on reducing drug side effects.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3769673/?report=reader>

Improving outcome of chemotherapy of metastatic breast cancer by docosaheptaenoic acid: a phase II trial. Clinical trial where all metastatic breast cancer patients received 1.2 g DHA per day throughout the course of chemo. Patients who achieved the highest blood levels of DHA had significantly longer time to progression and overall survival than those at the lower end.

<https://pubmed.ncbi.nlm.nih.gov/19920822/>

Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: a randomized double-blind placebo controlled trial

Clinical trial showing omega-3 supplementation reduces peripheral neuropathy. (Long-term clinical outcomes weren't measured.)

<https://pubmed.ncbi.nlm.nih.gov/22894640/>

Omega-3 supplements for patients in chemotherapy and/or radiotherapy: A systematic review

For high quality methodology studies only, the combination of omega-3 fatty acids supplements with conventional chemotherapy was beneficial. None of the studies reported a worse outcome for the supplement patients.

<https://pubmed.ncbi.nlm.nih.gov/25907586/>

The Anticancer Activity of Sea Buckthorn

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5861756/>

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Role of docosahexaenoic acid in enhancement of docetaxel action in patient-derived breast cancer xenografts

This work is the first to confirm that DHA supplementation during chemotherapy treatment improves TXT action in two PDX models of TNBC. The results suggest that decreases in tumor size occurred via changes in apoptosis, cell proliferation, and cell cycle pathways.

<https://pubmed.ncbi.nlm.nih.gov/31236812/>

These researchers are also currently conducting a clinical trial on using DHA with neoadjuvant chemotherapy, looking at improvement and outcomes along with other measures.

<https://pubmed.ncbi.nlm.nih.gov/31530611/#affiliation-1>

Phenethyl isothiocyanate (PEITC) and paclitaxel synergistically enhanced apoptosis and alpha-tubulin hyperacetylation in breast cancer cells

This is an in vitro study on ER+HER2- and TNBC cell lines but no follow-up animal study has been done.

<https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC3927854/>

Combination of Baicalein and Docetaxel Additively Inhibits the Growth of Non-small Cell Lung Cancer *In Vivo*

<https://www.worldscientific.com/doi/10.1142/S2575900018500131>

A Novel Paclitaxel Conjugate with Higher Efficiency and Lower Toxicity: A New Drug Candidate for Cancer Treatment

<https://pubmed.ncbi.nlm.nih.gov/31597361/>

IV alpha lipoic acid added to Paclitaxel in a mouse study decreased tumor volume and increased survival times. Note that IV not oral form was used.

DHA (Dihydro-artemisinin) Affects Microtubule Dynamics Through Reduction of Phospho-TCTP Levels and Enhances the Antiproliferative Effect of T-DM1 in Trastuzumab-Resistant HER2-Positive Breast Cancer Cell Lines

<https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7290969/>

Artemisinin added to TDM-1 (Kadcyla) in both cell lines and animal models showed improved response over TDM-1 alone. (Note that this should be done under supervision of medical professional as artemisinin may increase drug side effects.)

Echinacea Angustifolia DC Extract Induces Apoptosis and Cell Cycle Arrest and Synergizes with Paclitaxel in the MDA-MB-231 and MCF-7 Human Breast Cancer Cell Lines

<https://pubmed.ncbi.nlm.nih.gov/32959676/>

A Combination Therapy with Baicalein and Taxol Promotes Mitochondria-Mediated Cell Apoptosis: Involving in Akt/ β -Catenin Signaling Pathway

<https://www.meta.org/papers/a-combination-therapy-with-baicalein-and-taxol/27414207?fbclid=IwAR1IJrj7Gr6hOFnyExh9vVcr-QFQlaRxFQVWK5r5o1aH8FA2wXe6CjVFZZ4>

Ivermectin Reverses Taxane Resistance in Prostate Cancer Cells (both in vitro and in vivo)

https://www.researchgate.net/figure/Ivermectin-reverses-taxane-resistance-in-prostate-cancer-cells-A-Immunoblotting_fig4_337989200

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Cytotoxicity of Tanshinone IIA Combined with Taxol on Drug-resistant Breast Cancer Cells MCF-7 through Inhibition of Tau (AVOID-CYP3A4 INDUCER)

<https://onlinelibrary.wiley.com/doi/10.1002/ptr.6014>

Betulinic acid chemosensitizes breast cancer by triggering ER stress-mediated apoptosis by directly targeting GRP78

<https://www.nature.com/articles/s41419-018-0669-8>

ω-6 polyunsaturated fatty acid γ-linolenic acid (18:3n-6) enhances docetaxel (Taxotere) cytotoxicity in human breast carcinoma cells: Relationship to lipid peroxidation and HER-2/neu expression GLA is the omega-6 fatty acid being studied here. It is known as being the only anti-inflammatory omega-6.

<https://www.spandidos-publications.com/or/11/6/1241/abstract>

Tocotrienols as an Anti-Breast Cancer Agent

<https://www.mdpi.com/2076-3921/10/9/1383>

(-)-Epigallocatechin gallate sensitizes breast cancer cells to paclitaxel in a murine model of breast carcinoma

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880428/>

Phospho-TCTP as a therapeutic target of Dihydroartemisinin for aggressive breast cancer cells

<https://pubmed.ncbi.nlm.nih.gov/25779659/>

P450 Enzyme Interactions: Supplements to Avoid or Use with Caution Under Guidance of Practitioner

Taxanes, Vinorelbine, Kadcyła, and Enhertu are metabolized by the P450 enzyme CYP3A4, and oncologists are concerned about patients taking herbs that induce or inhibit this enzyme. *Unfortunately, in vitro liver microsome or rodent studies form the basis for most suggested interactions on oncology websites while human studies have proven many of these are unfounded.*

Also note that drugs typically have stronger interactions than herbs, except for St. John's Wort. Other herbs that might have strong interactions with Taxanes are citrus bergamot, artemisinin, black seed oil, baicalein, and danshen, so these should be avoided on active chemo days unless under guidance of an experienced integrative practitioner.

Dr. McKinney and Dr. Alschuler suggest avoiding quercetin, but some integrative practitioners use it to increase the effects of chemo drugs. (Quercetin is a PGP inhibitor, which keeps chemo from leaving the cancer cells but should not affect normal cells.) They also suggest avoiding berberine (perhaps due to effects on liver enzymes but it's a mild CYP3A4 inhibitor according to human research), N-acetyl cysteine (precursor to glutathione, although glutathione is not actually a concern with Taxanes because Taxanes don't create ROS like platinum drugs), Black cohosh (not actually a CYP3A4 inhibitor so not

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sure why), and St. John's Wort, which is a strong CYP3A4 inhibitor. Consult your integrative cancer practitioner before using any of these.

There is conflicting information about resveratrol (Japanese knotweed). Donnie Yance and Dr. Alschuler say it synergizes with Taxanes and reduces resistance to chemotherapy, while Neil McKinney suggests avoiding it. Resveratrol has been shown to inhibit CYP3A4 in human studies so it could increase Taxane side effects if used at a high dose. However, low doses of under 500 mg a day in the Trans-resveratrol form are recommended.

Here are some excellent summaries of human studies on CYP3A4 drug-herb interactions in humans: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4463967/>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4464477/>
<https://pubmed.ncbi.nlm.nih.gov/35056827/>