INDEPENDENT MEDICAL ALLIANCE

CANCER CARE

Approach to the Use of Repurposed Drugs and Nutraceuticals in Patients With Cancer

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This guide outlines our complementary approach to the use of repurposed drugs and nutraceuticals in cancer treatment. It is not intended as a comprehensive reference. The full guide, "Cancer Care: The Role of Repurposed Drugs and Metabolic Interventions in Treating Cancer," including all scientific references, is available at imahealth.org/research/cancer-care.

Introduction

Cancer treatment must always be individualized. Factors such as tumor type and stage, tumor biology, patient comorbidities, functional status, and personal preferences all play a role in determining the most appropriate plan of care. Repurposed drugs and metabolic therapy can be used in several ways: as adjuncts to conventional oncology treatments or, in select cases, as primary therapy.

There is no ideal regimen; however, this guide centers on the primary use of four agents with consistent evidence and broad activity: ivermectin, mebendazole, doxycycline, and curcumin. These form the foundation of treatment, with other drugs and nutraceuticals layered in as needed. Blocking multiple cancer stem cell (CSC) pathways is critical, as CSCs drive resistance, relapse, and disease progression. Limiting glucose intake and/or a ketogenic diet is a fundamental component of the metabolic approach to cancer care — essentially starving the cancer.

Patients may respond differently to therapy. For example, while many respond to standard ivermectin dosing, a subset requires higher doses to achieve clinical benefit. For this reason, treatment intensity must be adjusted on a case-by-case basis. Some patients may show a dramatic response to a single agent. As a rule, however, multiple agents are required to achieve synergistic anticancer effects.

Two broad therapeutic strategies can be considered, each with a spectrum of options in between:

Limited therapy. Start with a smaller number of core agents at lower doses. Escalate gradually in patients who fail to respond. This strategy is particularly suited to those with early-stage or less aggressive cancers, or those already receiving multiple conventional therapies (e.g., many breast cancer patients).

Aggressive therapy. Begin with higher doses and a wider combination of agents, scaling back as tolerated in patients who respond, or escalating further in those with inadequate response. This approach is preferred in patients with metastatic disease, highly aggressive tumors, or those receiving metronomic chemotherapy.

Regardless of approach, treatment should be supervised by a qualified integrative clinician. Self-treatment is strongly discouraged. The spectrum of agents used should be modified dynamically based on treatment response.

Cancer is a complicated disease, and patient care should be supervised by an integrative clinician; patients should not treat themselves.

Limited Therapy

This regimen is a conservative starting point that can be individualized according to cancer type, disease stage, treatment goals, and patient tolerance.

Diet: Low-carbohydrate, low-glycemic diet; intermittent fasting or OMAD (one meal a day); add matcha tea, brewed green tea, and 4 cups of coffee daily
Ivermectin: 0.2-0.4 mg/kg/day (commonly 0.3 mg/kg/day)
Vitamin D3 and K2: Vitamin D3 10,000 IU daily and vitamin K2 100 mcg, with monitoring of 25-OH vitamin D3 and parathyroid hormone (PTH) levels
Curcumin: 1,000-2,000 mg per day (500-1,000 mg twice daily); use a highly bioavailable preparation, such as phytosome curcumin, nano-curcumin, or the proprietary brand CurcuWIN
Melatonin: 20 mg at night, titrated upward from 5 mg
Propranolol: 10-40 mg twice daily as tolerated
Green tea extract (EGCG): Less than 800 mg per day, divided into two doses
Berberine: 500 mg twice daily; hold during multi-day fast
Resveratrol: 500 mg twice daily; use a preparation with high bioavailability

Aggressive Therapy

Diet: Low-glycemic ketogenic diet; OMAD; periodic 48- and 72-hour fasts
Ivermectin: 0.4-0.8 mg/kg/day (commonly 0.6 mg/kg/day), with titration up to 1 mg/kg/day if response is poor and the drug is well tolerated; take with food; reduce dose if headaches, dizziness, or other neurological symptoms occur
Mebendazole: 200 mg daily (100 mg twice daily)
Curcumin: 1,000-2,000 mg per day (500-1,000 mg twice daily); use a highly bioavailable preparation, such as phytosome curcumin, nano-curcumin, or the proprietary brand CurcuWIN
Vitamin D3 + K2: Vitamin D3 10,000 IU daily and vitamin K2 100 mcg, with monitoring of 25-OH vitamin D3, calcium, and PTH levels; titrate to achieve a low-normal PTH level (Coimbra Protocol)
Green tea extract (EGCG): Twice daily, less than 800 mg per day
Berberine: 500 mg twice daily (monitor glucose if taking metformin)
Resveratrol: 500 mg twice daily (high bioavailability)
Sulforaphane: Free stabilized sulforaphane from broccoli seed extract (dosage varies)
Metformin: 500-1,000 mg twice daily; hold during multi-day fast
Propranolol: 10-40 mg twice daily as tolerated
Melatonin: 20 mg at night, titrated upward from 5 mg
Doxycycline: 100 mg twice daily for 12 weeks or 100 mg daily during alternate months (indefinitely)
Modified citrus pectin (PectaSol): 14.4 g daily; six capsules three times a day
Aged garlic extract: 1,000 mg daily
Omega-3 fatty acids: 2-4 g daily
Statins: Atorvastatin 40-80 mg daily or simvastatin 40 mg daily; avoid long-term use or precipitous LDL reduction, which may increase dementia risk
Quercetin: 500-1,000 mg twice daily (stagger the dose with ivermectin)
Alpha lipoic acid: 300-600 mg daily
Luteolin: 100-200 mg daily
Genistein: 50-100 mg per day
Dandelion extract: 250-1,000 mg twice daily
Artesunate: 200 mg daily
Low-dose naltrexone: 2-4.5 mg daily
Apigenin (epigenin): Plant-derived flavonoid, 50-400 mg per day
Pomegranate extract: 250 mg daily
Monk fruit sweetener: As needed
Consider high-dose IV vitamin C: 75-100 g, two to three times weekly, together with standard chemotherapy in patients with cancers that express low catalase activity (melanoma, breast, pancreatic, esophageal, and lung cancer); screen for G6PD deficiency and kidney insufficiency

Tables 1 and 2 were generated using artificial intelligence (AI) engines to rank repurposed agents according to anticancer activity, cancer stem cell (CSC) pathways affected, and safety profile.

Table 1. Ranking of repurposed agents by anticancer activity, CSC pathway activity, and safety.

Rank	Compound	Pathways Targeted	Safety Category
1	Ivermectin	WNT, Notch, Hedgehog	Safe
2	Mebendazole	WNT, Hedgehog	Safe
3	Fenbendazole	WNT, Hedgehog	Safe
4	Curcumin	All except JAK/STAT	Safe
5	Resveratrol	WNT, Notch	Safe

Table 2. Top 10 repurposed agents ranked by CSC pathway blockade, with pathway inhibition summarized and safety evaluated according to therapeutic index and commonly used doses.

Rank	Compound	Pathways Blocked	Safety
1	Ivermectin	WNT, Hedgehog, Notch, NFκB, STAT3, PI3K/Akt	Safe
2	Curcumin	WNT, Hedgehog, Notch, NFκB STAT3, TGF-β	Safe
3	Sulforaphane	WNT, Hedgehog, NFκB, STAT3	Safe
4	Doxycycline	WNT, Hedgehog, Notch	Safe
5	EGCG	WNT, STAT3, NFκB Notch, PI3K/Akt	Safe
6	Resveratrol	NFκB, STAT3, TGF-β, PI3K/Akt	Safe
7	Omega-3 (DHA)	STAT3, JAK-STAT, NFκB WNT	Extremely Safe
8	Mebendazole	Hedgehog	Safe
9	Metformin	PI3K/Akt	Extremely Safe
10	Vitamin D	Notch, Hedgehog	Extremely Safe

The limited and aggressive therapeutic approaches described above broadly apply to patients with common cancers. Based on limited clinical data and AI-supported analyses, we outline below the agents we believe should be incorporated into the treatment of the most common types of cancer in the typical cancer patient. These protocols are informed by exploratory AI analyses and limited data; head-to-head studies have not been conducted, and the AI algorithms are not fully transparent. Accordingly, this information should be viewed as guidance for formulating patient-specific treatment plans. Furthermore, we believe that these repurposed agent combinations may help prevent stage 1 or stage 2 cancers from progressing to deadly stage 4 disease and support remission.

Prostate Cancer

The repurposed drugs and nutraceuticals I consider most important for prostate cancer are ranked below.

Tier 1

- Metformin
- Ivermectin
- Berberine
- Melatonin
- EGCG
- Sulforaphane
- Curcumin
- Vitamin D3

Tier 2

- Mebendazole
- Doxycycline
- Omega-3 fatty acids
- Propranolol
- Luteolin
- Genistein
- Quercetin
- Resveratrol

Tier 3

- Atorvastatin
- Thymosin-α1
- Mistletoe
- Modified citrus pectin
- Honokiol
- Lycopene
- Aged garlic extract

One notable change in the rankings compared with those I would have made a year ago is that luteolin has moved up substantially due to its impressive preclinical activity against androgen receptor signaling, PI3K-AKT-mTOR, STAT3, EMT, metastasis, and CSCs — pathways central to prostate cancer progression.

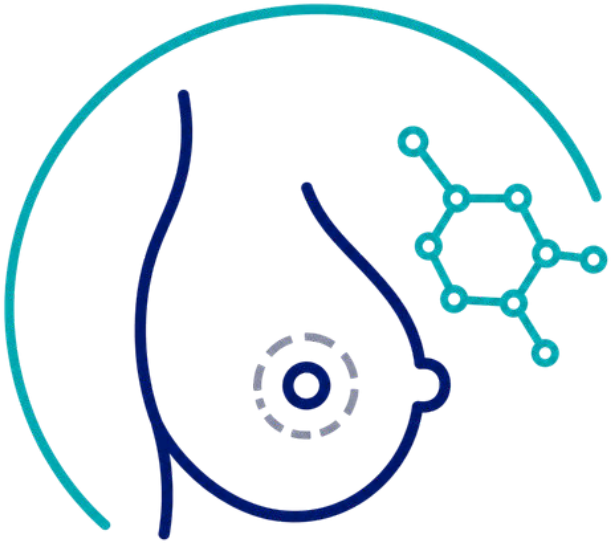
Avoid ashwagandha, fenugreek, and galactomannan as they may increase free testosterone.

Breast Cancer

The repurposed drugs and nutraceuticals I consider most important for breast cancer are ranked below:

Tier 1

- Metformin
- Melatonin
- Ivermectin
- Curcumin
- Sulforaphane
- EGCG
- Vitamin D3
- Berberine



Tier 2

- Doxycycline
- Mebendazole
- Luteolin
- Quercetin
- Omega-3 fatty acids
- Propranolol
- Resveratrol/pterostilbene

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Mistletoe
- Modified citrus pectin
- Apigenin
- Genistein
- Boswellia
- Aged garlic extract

Overall, I would place metformin, melatonin, ivermectin, curcumin, sulforaphane, and epigallocatechin gallate (EGCG) at the core of a metabolic strategy for breast cancer because together they target many of the key biological drivers across breast cancer subtypes, including insulin signaling, PI3K-AKT-mTOR, inflammation, EMT, CSCs, and immune modulation.

Triple-Negative Breast Cancer (TNBC)
Because TNBC is highly enriched for CSCs and EMT, I would slightly modify the ranking.

Breast Cancer Continued...

Highest-Priority Agents

- Metformin
- Ivermectin
- Sulforaphane
- Doxycycline
- Curcumin
- Mebendazole
- EGCG
- Melatonin
- Luteolin
- Berberine

Hormone Receptor-Positive (ER+/HER2−) Breast Cancer

For hormone-sensitive disease, melatonin ranks higher because of its antiestrogenic properties.

Highest-Priority Agents

- Metformin
- Melatonin
- Curcumin
- EGCG
- Ivermectin
- Sulforaphane
- Vitamin D3
- Berberine
- Doxycycline
- Luteolin

HER2-Positive Breast Cancer

Highest-Priority Agents

- Metformin
- EGCG
- Curcumin
- Melatonin
- Sulforaphane
- Ivermectin
- Berberine
- Doxycycline
- Vitamin D3
- Luteolin

Colorectal Cancer

For colorectal cancer, the metabolic biology differs from that of both prostate and breast cancer. The dominant drivers include:

- Wnt/β-catenin signaling (APC mutations in ~80%)
- KRAS/MAPK signaling
- PI3K-AKT-mTOR
- Cancer stem cells (CSCs)
- Inflammation (NF-κB, COX-2, IL-6/STAT3)
- Warburg metabolism
- Gut microbiome and tumor microenvironment

The repurposed drugs and nutraceuticals I consider most important for colorectal cancer are ranked below.

Tier 1
- Metformin
- Ivermectin
- Berberine
- Curcumin
- Sulforaphane
- EGCG
- Vitamin D3
- Melatonin

Tier 2
- Mebendazole
- Doxycycline
- Omega-3 fatty acids
- Propranolol
- Luteolin
- Quercetin
- Resveratrol/pterostilbene

Tier 3
- Atorvastatin
- Thymosin-α1
- Modified citrus pectin
- Honokiol
- Mistletoe
- Boswellia
- Aged garlic extract
- Apigenin
- Genistein

Colorectal Cancer Continued...

KRAS-Mutant Colorectal Cancer
For tumors with KRAS mutations, I would modify the ranking because KRAS drives glycolysis, glutamine metabolism, and CSC biology.

Highest-Priority Agents
- Metformin
- Berberine
- Ivermectin
- Curcumin
- Sulforaphane
- EGCG
- Mebendazole
- Doxycycline
- Melatonin
- Vitamin D3

Metastatic Colorectal Cancer
For patients with metastatic disease, greater emphasis should be placed on CSCs and metastasis.

Highest-Priority Agents
- Metformin
- Ivermectin
- Curcumin
- Berberine
- Sulforaphane
- Mebendazole
- Doxycycline
- Omega-3 fatty acids
- Propranolol
- EGCG

Overall Perspective

Among all solid tumors, colorectal cancer has one of the strongest mechanistic rationales for a multi-target metabolic strategy because of its dependence on Wnt/β-catenin signaling, altered glucose metabolism, chronic inflammation, and CSCs.

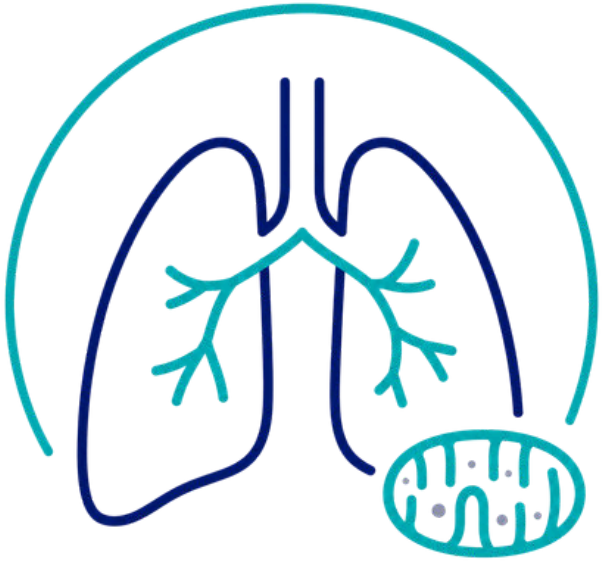
A core combination of metformin, ivermectin, berberine, curcumin, sulforaphane, EGCG, vitamin D3, melatonin, mebendazole, and doxycycline provides broad coverage of these pathways. While many of these agents have extensive preclinical support and favorable safety profiles, high-quality clinical trials evaluating these combinations are still lacking, so this ranking should be viewed as a hypothesis-driven framework rather than an evidence-based treatment standard.

Lung Cancer

The repurposed drugs and nutraceuticals I consider most important for lung cancer are ranked below.

Tier 1

- Metformin
- Ivermectin
- Melatonin
- Curcumin
- EGCG
- Sulforaphane
- Vitamin D3
- Berberine



Tier 2

- Doxycycline
- Mebendazole
- Propranolol
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Mistletoe
- Boswellia
- Modified citrus pectin
- Apigenin
- Genistein
- Aged garlic extract

Lung Cancer Continued...

KRAS-Mutant NSCLC
KRAS-mutant tumors are particularly dependent on glycolysis, PI3K signaling, and metabolic plasticity.

Highest-Priority Agents
- Metformin
- Berberine
- Ivermectin
- Curcumin
- Sulforaphane
- EGCG
- Doxycycline
- Mebendazole
- Melatonin
- Vitamin D3

EGFR-Mutant NSCLC
For EGFR-driven tumors, agents that modulate EGFR signaling and potentially enhance sensitivity to EGFR inhibitors become especially attractive.

Highest-Priority Agents
- Metformin
- EGCG
- Curcumin
- Ivermectin
- Melatonin
- Sulforaphane
- Berberine
- Doxycycline
- Vitamin D3
- Luteolin

Lung Cancer Continued...

Small Cell Lung Cancer (SCLC)
Because SCLC is highly proliferative and rich in CSCs, greater emphasis should be placed on mitochondrial and CSC-targeting strategies.

Highest-Priority Agents

- Metformin
- Ivermectin
- Doxycycline
- Mebendazole
- Curcumin
- Melatonin
- Sulforaphane
- EGCG
- Vitamin D3
- Berberine

Overall Perspective

Among solid tumors, lung cancer — particularly NSCLC — has a strong mechanistic rationale for a multi-target metabolic strategy because of its reliance on EGFR/KRAS signaling, PI3K-AKT-mTOR, altered glucose metabolism, EMT, and CSCs. A core combination of metformin, ivermectin, melatonin, curcumin, EGCG, sulforaphane, vitamin D3, berberine, doxycycline, and mebendazole provides broad coverage of these pathways. While there is encouraging preclinical evidence and some supportive clinical data for individual agents such as metformin and melatonin, well-designed clinical trials evaluating multi-agent metabolic regimens are still needed, so these rankings should be viewed as a biologically informed, hypothesis-driven framework rather than an evidence-based treatment standard.

Melanoma

For melanoma, the biology differs substantially from that of epithelial cancers. The major drivers include:

- MAPK signaling (BRAF/NRAS mutations)
- PI3K-AKT-mTOR
- YAP/TAZ signaling
- CSCs
- Immune evasion
- Oxidative stress adaptation
- Metabolic plasticity (glycolysis ↔ oxidative phosphorylation [OXPHOS] switching)
- Mitochondrial metabolism, particularly in treatment-resistant disease

These rankings are based on mechanistic rationale, preclinical evidence, safety, and limited clinical data and should be viewed as hypothesis-driven rather than evidence-based treatment recommendations.

The repurposed drugs and nutraceuticals I consider most important for melanoma are ranked below.

Tier 1

- Metformin
- Ivermectin
- Melatonin
- Curcumin
- Sulforaphane
- Vitamin D3
- EGCG
- Berberine

Tier 2

- Doxycycline
- Mebendazole
- Omega-3 fatty acids
- Propranolol
- Luteolin
- Quercetin
- Resveratrol/pterostilbene

Melanoma Continued...

Tier 3

- Atorvastatin
- Thymosin-α1
- Honokiol
- Mistletoe
- Boswellia
- Modified citrus pectin
- Apigenin
- Genistein
- Lycopene
- Aged garlic extract

BRAF-Mutant Melanoma

Treatment resistance to BRAF inhibitors is often associated with a metabolic shift toward mitochondrial respiration and increased CSC activity.

Highest-Priority Agents

- Metformin
- Doxycycline
- Ivermectin
- Melatonin
- Sulforaphane
- Curcumin
- EGCG
- Berberine
- Mebendazole
- Vitamin D3

Immunotherapy-Treated Melanoma

For patients receiving immune checkpoint inhibitors, agents that support immune function while reducing chronic inflammation may be particularly attractive.

Highest-Priority Agents

- Vitamin D3
- Melatonin
- Metformin
- Ivermectin
- Curcumin
- Sulforaphane
- EGCG
- Omega-3 fatty acids
- Berberine
- Thymosin-α1

Melanoma Continued...

Overall Perspective

Melanoma is particularly well suited to a multi-target metabolic strategy because treatment resistance is often accompanied by metabolic plasticity, increased dependence on mitochondrial oxidative phosphorylation, and enrichment of cancer stem cell populations. A core regimen of metformin, ivermectin, melatonin, curcumin, sulforaphane, vitamin D3, EGCG, berberine, doxycycline, and mebendazole provides broad mechanistic coverage of these pathways. Although many of these agents have compelling preclinical evidence and favorable safety profiles, there is currently insufficient clinical evidence to conclude that these combinations improve melanoma-specific outcomes, so they should be considered investigational adjuncts rather than established therapies.

Ovarian Cancer

For ovarian cancer, particularly high-grade serous ovarian carcinoma, the biology differs from that of prostate, breast, and colorectal cancer. Key drivers include:

- PI3K-AKT-mTOR
- Homologous recombination deficiency (BRCA1/2)
- CSCs
- Epithelial-mesenchymal transition (EMT)
- Angiogenesis (VEGF)
- Inflammation (NF-κB, IL-6/STAT3)
- Metabolic plasticity with increasing OXPHOS dependence
- Peritoneal dissemination
- Chemoresistance, often driven by CSCs and mitochondrial metabolism

Because recurrent ovarian cancer frequently develops OXPHOS dependence, I would rank mitochondrial-targeting agents slightly higher than for several other solid tumors.
As before, these rankings are hypothesis-driven, based largely on preclinical evidence and biological rationale rather than randomized clinical trials.

The repurposed drugs and nutraceuticals I consider most important for ovarian cancer are ranked below.

Tier 1

- Metformin
- Ivermectin
- Doxycycline
- Melatonin
- Curcumin
- Sulforaphane
- EGCG
- Vitamin D3

Tier 2

- Berberine
- Mebendazole
- Luteolin
- Propranolol
- Omega-3 fatty acids
- Quercetin
- Resveratrol/pterostilbene

Ovarian Cancer Continued...

Tier 3

- Atorvastatin
- Thymosin-α1
- Honokiol
- Mistletoe
- Modified citrus pectin
- Boswellia
- Apigenin
- Genistein
- Aged garlic extract

BRCA-Mutated Ovarian Cancer

These tumors often respond well to PARP inhibitors initially, but resistant disease frequently becomes metabolically flexible.

Highest-Priority Agents

- Metformin
- Doxycycline
- Ivermectin
- Melatonin
- Sulforaphane
- Curcumin
- EGCG
- Berberine
- Vitamin D3
- Mebendazole

Platinum-Resistant Ovarian Cancer

This setting is characterized by CSC enrichment and increased mitochondrial metabolism.

Highest-Priority Agents

- Doxycycline
- Metformin
- Ivermectin
- Sulforaphane
- Curcumin
- Melatonin
- Mebendazole
- EGCG
- Berberine
- Propranolol

Ovarian Cancer Continued...

Overall Perspective

Among solid tumors, ovarian cancer has one of the strongest biological rationales for targeting mitochondrial metabolism and CSCs, particularly in recurrent and platinum-resistant disease. A core combination of metformin, ivermectin, doxycycline, melatonin, curcumin, sulforaphane, EGCG, vitamin D3, berberine, and mebendazole provides broad mechanistic coverage of the pathways most closely associated with ovarian cancer progression and treatment resistance.

One notable difference from other tumor types is the higher ranking of doxycycline, reflecting increasing evidence that recurrent ovarian cancer becomes highly dependent on mitochondrial oxidative phosphorylation and that ovarian CSCs rely heavily on mitochondrial function. While these mechanistic data are compelling, robust clinical trials evaluating these multi-agent metabolic combinations are still lacking, so this prioritization should be viewed as a biologically informed framework for future investigation rather than a clinically validated treatment algorithm.

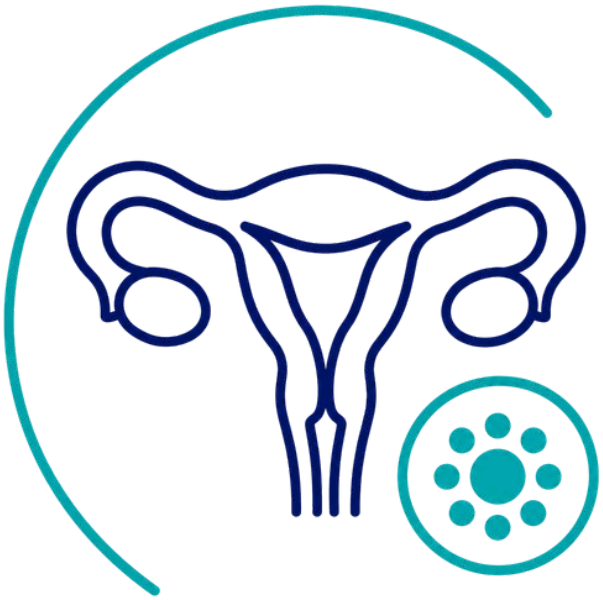
Endometrial Cancer (Uterine Cancer)

For endometrial cancer, especially endometrioid uterine cancer, the dominant biology includes insulin resistance, obesity, estrogen signaling, PI3K-AKT-mTOR activation, inflammation, and CSCs. Therefore, the ranking differs slightly from that for ovarian cancer.

The repurposed drugs and nutraceuticals I consider most important for endometrial cancer are ranked below.

Tier 1

- Metformin
- Berberine
- Melatonin
- Vitamin D3
- Curcumin
- Ivermectin
- Sulforaphane
- EGCG



Tier 2

- Doxycycline
- Mebendazole
- Propranolol
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Mistletoe
- Modified citrus pectin
- Boswellia
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

Overall Perspective

Endometrial cancer is one of the strongest candidates for a metabolic approach because many cases are linked to hyperinsulinemia, obesity, estrogen excess, and PI3K-AKT-mTOR activation. Metformin and berberine move to the top of the list because they target the metabolic terrain driving this disease.

Liver Cancer

For hepatocellular carcinoma (HCC), the biology is unique among solid tumors because it develops in a chronically inflamed, metabolically abnormal liver. The dominant drivers include:

- PI3K-AKT-mTOR
- Wnt/β-catenin (CTNNB1)
- MYC activation
- Chronic inflammation (IL-6, STAT3, NF-κB)
- Oxidative stress
- Angiogenesis (VEGF)
- Cancer stem cells (EpCAM+, CD133+)
- Warburg metabolism and glutamine dependence
- Liver fibrosis and cirrhosis

Unlike many other cancers, metabolic syndrome, MASLD/NASH, obesity, insulin resistance, hepatitis B/C, and cirrhosis are major contributors to tumor development.

Accordingly, therapies that improve systemic metabolism, reduce hepatic inflammation, and suppress CSC biology move higher in priority.

The repurposed drugs and nutraceuticals I consider most important for liver cancer are ranked below.

Tier 1

- Metformin
- Berberine
- Curcumin
- Vitamin D3
- Melatonin
- Ivermectin
- Sulforaphane
- EGCG

Liver Cancer Continued...

Tier 2

- Omega-3 fatty acids
- Doxycycline
- Mebendazole
- Luteolin
- Propranolol
- Quercetin
- Resveratrol/pterostilbene

Tier 3

- Atorvastatin
- Thymosin-α1
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract

Overall Perspective

Among solid tumors, HCC is perhaps the most metabolically driven, making it particularly well suited to a multi-target metabolic strategy. A core combination of metformin, berberine, curcumin, vitamin D3, melatonin, ivermectin, sulforaphane, EGCG, omega-3 fatty acids, and doxycycline provides broad mechanistic coverage of insulin signaling, PI3K-AKT-mTOR, Wnt/β-catenin, inflammation, fibrosis, angiogenesis, and cancer stem cell biology.

One notable difference from several other cancers is the higher ranking of berberine and omega-3 fatty acids, reflecting their favorable effects on metabolic dysfunction-associated steatotic liver disease (MASLD/NASH), insulin resistance, hepatic inflammation, and fibrosis, all of which contribute to liver carcinogenesis. As with the other rankings, these recommendations are hypothesis-driven and based largely on preclinical evidence, with limited clinical trial data evaluating multi-agent metabolic approaches in HCC.

Bladder Cancer

The treatment of bladder cancer depends on the histologic subtype, stage, and whether it is classified as non-muscle-invasive bladder cancer (NMIBC) or muscle-invasive bladder cancer (MIBC). Approximately 90% to 95% of bladder cancers are urothelial (transitional cell) carcinomas.

Bladder cancer is particularly well suited to a metabolic approach because it exhibits many of the hallmark metabolic abnormalities targeted by the Metabolic Trap framework. Urothelial carcinomas commonly demonstrate increased glucose uptake, activation of the PI3K-AKT-mTOR pathway, enhanced glutamine metabolism, mitochondrial plasticity, angiogenesis, chronic inflammation, immune evasion, and a population of therapy-resistant CSCs. These biological characteristics suggest that simultaneous targeting of multiple metabolic and survival pathways may complement standard treatment and potentially reduce recurrence. However, this strategy remains investigational and should be viewed as an adjunct to — not a replacement for — established therapies.

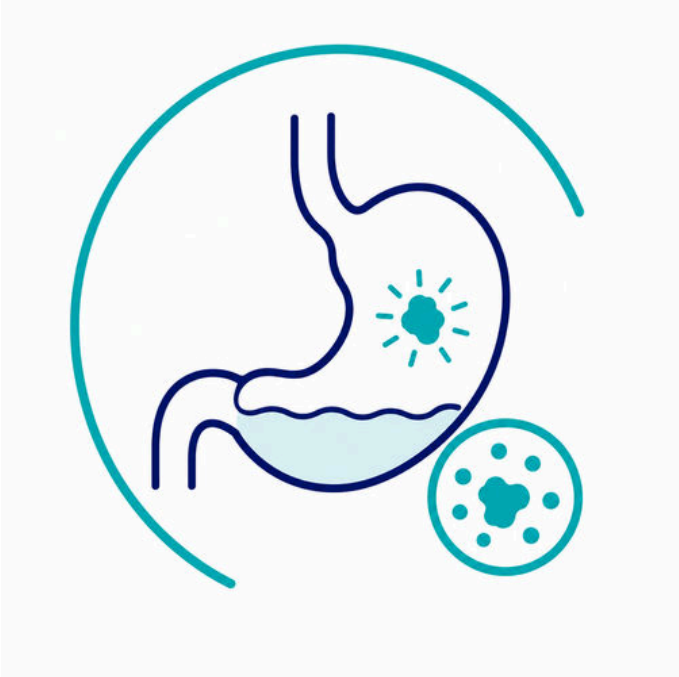
The repurposed drugs and nutraceuticals I consider most important for bladder cancer are ranked below.

Tier 1

- Metformin
- Ivermectin
- Curcumin
- Sulforaphane
- Melatonin
- Vitamin D3
- EGCG
- Berberine

Tier 2

- Doxycycline
- Mebendazole
- Propranolol
- Omega-3 fatty acids
- Resveratrol/pterostilbene
- Genistein
- Modified citrus pectin



Bladder Cancer Continued...

Tier 3

- PSK
- Thymosin-α1
- Honokiol
- Mistletoe
- Atorvastatin
- Quercetin
- Apigenin
- Aged garlic extract

Integration with Standard Therapy

Non-muscle invasive bladder cancer

- Transurethral resection of bladder tumor (TURBT)
- Intravesical Bacillus Calmette–Guérin (BCG) or intravesical chemotherapy

Muscle-invasive bladder cancer

Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy with pelvic lymph node dissection.

Head and Neck Squamous Cell Cancer

For head and neck squamous cell carcinoma (HNSCC), the dominant biology includes EGFR signaling, PI3K-AKT-mTOR, STAT3/NF-κB inflammation, EMT, angiogenesis, CSCs, immune evasion, and mitochondrial plasticity. HPV-positive disease has distinct biology and generally carries a better prognosis, although many metabolic and CSC pathways overlap.

The repurposed drugs and nutraceuticals I consider most important for HNSCC are ranked below.

Tier 1

- Metformin
- Ivermectin
- Curcumin
- EGCG
- Sulforaphane
- Melatonin
- Vitamin D3
- Berberine

Tier 2

- Doxycycline
- Mebendazole
- Propranolol
- Luteolin
- Omega-3 fatty acids
- Quercetin
- Resveratrol/pterostilbene

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Mistletoe
- Modified citrus pectin
- Boswellia
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

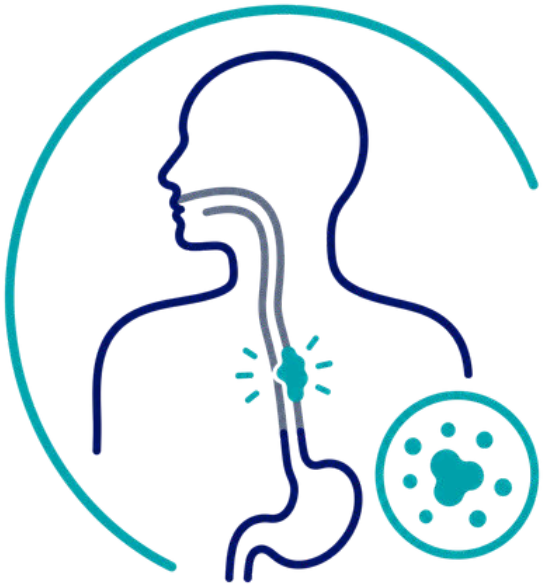
Esophageal Squamous Cell Carcinoma

For esophageal squamous cell carcinoma (ESCC), the dominant biology includes EGFR signaling, PI3K-AKT-mTOR, STAT3/NF-κB inflammation, EMT, angiogenesis, CSCs, mitochondrial plasticity, and field cancerization from chronic epithelial injury.

The repurposed drugs and nutraceuticals I consider most important for ESCC are ranked below.

Tier 1

- Metformin
- Curcumin
- Ivermectin
- EGCG
- Sulforaphane
- Berberine
- Melatonin
- Vitamin D3



Tier 2

- Doxycycline
- Mebendazole
- Luteolin
- Propranolol
- Omega-3 fatty acids
- Quercetin
- Resveratrol/pterostilbene

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Mistletoe
- Modified citrus pectin
- Boswellia
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

Pancreatic Cancer

For pancreatic ductal adenocarcinoma (PDAC), the biological rationale for a metabolic approach is arguably stronger than for any other solid tumor. PDAC is characterized by:

- KRAS mutations (~90%-95%)
- Extreme Warburg metabolism
- Glutamine dependence
- Cancer stem cells
- Marked mitochondrial plasticity
- Autophagy and macropinocytosis
- Dense desmoplastic stroma
- Profound immune suppression
- Hypoxia and angiogenic signaling

Consequently, I would place greater emphasis on agents targeting mitochondrial metabolism, CSCs, KRAS-associated pathways, inflammation, and the tumor microenvironment.

These rankings are hypothesis-driven, based on mechanistic rationale, preclinical evidence, safety, and limited clinical data rather than randomized clinical trials.

The repurposed drugs and nutraceuticals I consider most important for pancreatic cancer are ranked below.

Tier 1

- Metformin
- Ivermectin
- Doxycycline
- Berberine
- Curcumin
- Sulforaphane
- Melatonin
- Vitamin D3

Tier 2

- Mebendazole
- EGCG
- Propranolol
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene

Pancreatic Cancer Continued...

Tier 3

- Atorvastatin
- Thymosin-α1
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract

KRAS-Mutant Pancreatic Cancer

Since nearly all PDACs harbor KRAS mutations, therapies targeting the metabolic consequences of KRAS become particularly attractive.

Highest-Priority Agents

- Metformin
- Berberine
- Ivermectin
- Doxycycline
- Curcumin
- Sulforaphane
- EGCG
- Melatonin
- Mebendazole
- Vitamin D3

Metastatic or Chemotherapy-Resistant PDAC

Treatment-resistant disease becomes increasingly dependent on mitochondrial metabolism and CSCs.

Highest-Priority Agents

- Doxycycline
- Metformin
- Ivermectin
- Sulforaphane
- Curcumin
- Berberine
- Melatonin
- Mebendazole
- EGCG
- Propranolol

Pancreatic Cancer Continued...

Overall Perspective

Among all common solid tumors, pancreatic ductal adenocarcinoma may have the strongest biological rationale for a comprehensive metabolic strategy because it is driven by KRAS-mediated metabolic reprogramming, profound dependence on glycolysis and glutamine metabolism, dense stromal remodeling, and marked enrichment of CSCs. A core regimen of metformin, ivermectin, doxycycline, berberine, curcumin, sulforaphane, melatonin, vitamin D3, mebendazole, and EGCG provides broad mechanistic coverage of these vulnerabilities.

One notable distinction from most other cancers is the higher priority assigned to doxycycline, reflecting substantial preclinical evidence that treatment-resistant pancreatic cancer relies heavily on mitochondrial oxidative phosphorylation and CSC biology. Likewise, berberine is ranked highly for its effects on AMP-activated protein kinase (AMPK) activation, glucose metabolism, and metabolic signaling, which closely align with the metabolic phenotype of PDAC. Although these mechanistic data are compelling, prospective clinical trials evaluating multi-agent metabolic protocols in pancreatic cancer are still lacking, so these rankings should be viewed as a biologically informed framework for future investigation rather than a clinically validated treatment algorithm.

Gastric Cancer

For gastric adenocarcinoma, the biological rationale for a metabolic approach is strong because tumor progression is driven by:

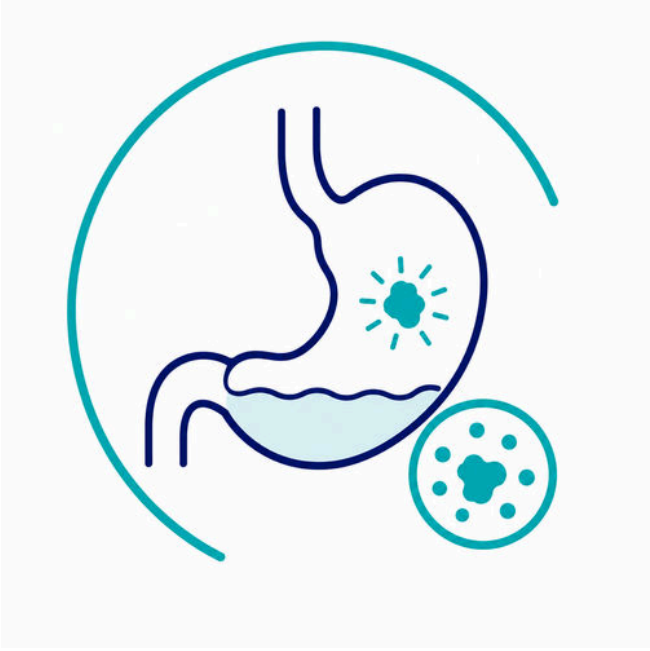
- Chronic inflammation (particularly *Helicobacter pylori*)
- PI3K-AKT-mTOR activation
- Wnt/β-catenin signaling
- STAT3 and NF-κB
- HER2 signaling (in a subset of tumors)
- CSCs
- Epithelial-mesenchymal transition (EMT)
- Angiogenesis
- Metabolic reprogramming (Warburg effect and OXPHOS plasticity)

The ranking below is based on mechanistic rationale, preclinical evidence, safety, and the limited clinical data available. It should be viewed as hypothesis-generating rather than a validated treatment protocol.

The repurposed drugs and nutraceuticals I consider most important for gastric cancer are ranked below.

Tier 1

- Metformin
- Curcumin
- Berberine
- Ivermectin
- Sulforaphane
- EGCG
- Melatonin
- Vitamin D3



Tier 2

- Doxycycline
- Mebendazole
- Luteolin
- Omega-3 fatty acids
- Propranolol
- Quercetin
- Resveratrol/pterostilbene

Gastric Cancer Continued...

Tier 3

- Atorvastatin
- Thymosin-α1
- Honokiol
- Mistletoe
- Modified citrus pectin
- Boswellia
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

HER2-Positive Gastric Cancer

For HER2-positive disease, agents that suppress HER2 and PI3K signaling become more attractive.

Highest-Priority Agents

- Metformin
- EGCG
- Curcumin
- Berberine
- Ivermectin
- Sulforaphane
- Melatonin
- Vitamin D3
- Doxycycline
- Luteolin

Diffuse-Type Gastric Cancer

Diffuse gastric cancers often show greater EMT, invasion, and CSC activity.

Gastric Cancer Continued...

Overall Perspective

Among gastrointestinal malignancies, gastric cancer has a strong biological rationale for a multi-target metabolic strategy because of its dependence on chronic inflammation, PI3K-AKT-mTOR signaling, Wnt/β-catenin activation, EMT, angiogenesis, and CSCs. A core combination of metformin, curcumin, berberine, ivermectin, sulforaphane, EGCG, melatonin, vitamin D3, doxycycline, and mebendazole provides broad mechanistic coverage of these pathways.

A distinguishing feature of gastric cancer is the prominent role of chronic inflammation and, in many patients, antecedent *Helicobacter pylori* infection, making curcumin and berberine particularly attractive because of their combined anti-inflammatory, metabolic, and Wnt-modulating effects. In HER2-positive gastric cancer, EGCG and luteolin may have additional mechanistic relevance because of their preclinical effects on HER-family signaling. As with the other cancer-specific rankings, this prioritization is based primarily on mechanistic and preclinical evidence, and prospective clinical trials are needed to determine whether multi-agent metabolic strategies improve patient outcomes.

Glioblastoma

For glioblastoma (GBM), the dominant biology includes extreme metabolic plasticity, mitochondrial dependence in therapy-resistant cells, CSCs, hypoxia, angiogenesis, invasion, PI3K-AKT-mTOR activation, STAT3/NF-κB inflammation, and blood-brain barrier penetration.

The repurposed drugs and nutraceuticals I consider most important for GBM are ranked below.

Tier 1

- Metformin
- Doxycycline
- Melatonin
- Ivermectin*
- Curcumin
- Sulforaphane
- Berberine
- Vitamin D3

Tier 2

- Mebendazole
- EGCG
- Propranolol
- Luteolin
- Quercetin
- Omega-3 fatty acids
- Resveratrol/pterostilbene

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Boswellia
- Mistletoe
- Modified citrus pectin
- Apigenin
- Aged garlic extract
- Lycopene

Glioblastoma Continued...

* Despite its limited penetration of the blood-brain barrier (BBB), several factors suggest ivermectin may still exert immune activity against GBM. These include the inherent disruption of the BBB in GBM tumors, ivermectin's systemic immunomodulatory effects, and its potential for enhanced delivery through combination approaches. Most importantly, ivermectin has demonstrated the ability to transform "cold" tumors (with little immune infiltration) into "hot" tumors (with significant immune infiltration). This ability is particularly relevant because GBM is profoundly immunosuppressive and is often considered a "cold" tumor resistant to immunotherapy.

Triple Combination Synergy Assessment

In vitro evidence indicates that the triple combination of modified citrus pectin, PD-1 inhibitors, and ivermectin may provide substantial synergistic anticancer activity in GBM. While each agent has shown individual activity or paired synergy, the combined approach targets multiple complementary pathways that could help overcome the complex immunosuppressive mechanisms in GBM. It should be noted, however, that no clinical data currently support this combination.

Bottom Line

Glioblastoma has a strong rationale for targeting mitochondria and CSCs. Doxycycline and mebendazole move higher because therapy-resistant glioma stem cells often rely on mitochondrial metabolism and cytoskeletal/invasive programs.

Kidney Cancer – Renal Cell Carcinoma

For most adults with kidney cancer (usually renal cell carcinoma), surgery to remove part of the kidney (partial nephrectomy) or the entire kidney (radical nephrectomy) is the standard treatment when the tumor is confined to the kidney. Active surveillance (close monitoring without immediate treatment) may be appropriate for very small tumors in older or frail patients. For patients with stage 4 metastatic disease, targeted therapies (such as VEGF or mTOR inhibitors) and immunotherapies (such as PD-1/PD-L1 or CTLA-4 inhibitors) may be given before or after surgery.

For renal cell carcinoma (RCC), especially clear-cell RCC, the dominant biology includes VHL loss, HIF-1α/HIF-2α activation, VEGF-driven angiogenesis, PI3K-AKT-mTOR, immune evasion, metabolic reprogramming, mitochondrial dysfunction, lipid accumulation, and hypoxia adaptation.

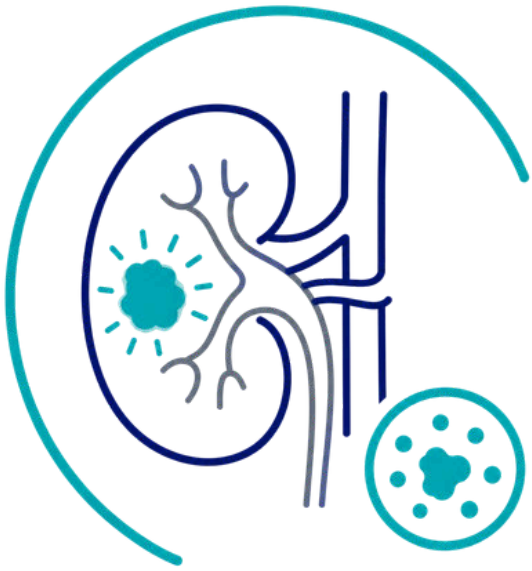
The repurposed drugs and nutraceuticals I consider most important for RCC are ranked below.

Tier 1

- Metformin
- Ivermectin
- Berberine
- Curcumin
- Sulforaphane
- Melatonin
- EGCG
- Vitamin D3

Tier 2

- Doxycycline
- Mebendazole
- Propranolol
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene



Kidney Cancer – Renal Cell Carcinoma Continued...

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Mistletoe
- Modified citrus pectin
- Boswellia
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

Basal Cell Carcinoma

In basal cell carcinoma (BCC), the biology differs somewhat from that of squamous cell carcinoma. BCC is characterized by a near-universal dependence on aberrant Hedgehog signaling (most commonly through mutations in PTCH1 or SMO), with additional contributions from PI3K-AKT-mTOR, Wnt/β-catenin, EGFR, inflammation, and metabolic reprogramming. Compared with SCC, BCC is generally less glycolytic, grows more slowly, and rarely metastasizes, but it remains metabolically adaptable.

Because most BCCs are cured with surgery or local therapies, the following tiered approach should be viewed as a hypothesis-driven adjunctive strategy based primarily on mechanistic rationale and preclinical evidence. It is not a substitute for guideline-based management. Standard surgical excision with appropriate margins is the mainstay of treatment and offers high cure rates for most primary basal cell carcinomas. External-beam radiation therapy may be used as definitive treatment when surgery is not possible or would be disfiguring. Repurposed drugs and nutraceuticals play a secondary role, particularly in prevention. Evidence supporting these second-line therapies as primary treatment is limited.

Practical Multi-Axis Strategy for BCC

Tier 1 (Foundation)

- Metformin
- Ivermectin
- Curcumin
- EGCG
- Sulforaphane
- Melatonin
- Vitamin D3

Tier 2 (Add if Appropriate)

- Berberine
- Doxycycline
- Mebendazole
- Genistein
- Omega-3 fatty acids
- Propranolol
- Resveratrol/pterostilbene

Basal Cell Carcinoma Continued...

Tier 3 (Selected Patients)

- Atorvastatin
- Honokiol
- Apigenin
- Quercetin
- Modified citrus pectin
- Thymosin-α1
- High-dose IV vitamin C
- Mistletoe

Important Clinical Note

For localized basal cell carcinoma, standard treatments — including surgical excision, Mohs micrographic surgery, curettage and electrodesiccation, cryotherapy, topical therapies for selected superficial lesions, and radiotherapy when appropriate — provide excellent cure rates. The tiered metabolic approach outlined above is best considered an investigational adjunct in BCC, supported primarily by laboratory and mechanistic evidence rather than by randomized clinical trials. It should complement, not replace, established evidence-based treatment.

Topical Ivermectin

The rationale for topical ivermectin is somewhat stronger for BCC than for squamous cell carcinoma because BCC is typically slow growing, locally invasive, and often confined to the epidermis and superficial dermis, making it more amenable to topical drug delivery. Nevertheless, there are currently no clinical trials demonstrating the efficacy of topical ivermectin for BCC, with or without dimethyl sulfoxide (DMSO), and its use remains investigational.

Squamous Cell Carcinoma of the Skin

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, accounting for approximately 20% of non-melanoma skin cancers. Most tumors are cured with surgery, but a small proportion become locally advanced or metastatic, where prognosis is substantially worse. Standard treatment remains surgical excision (including Mohs micrographic surgery in appropriate cases), with radiotherapy and systemic therapies reserved for selected high-risk or advanced disease.

From the perspective of the Metabolic Trap, cSCC is an attractive candidate for metabolic intervention because it demonstrates activation of many of the same interconnected signaling pathways targeted by the multi-axis approach, including glycolysis, mitochondrial plasticity, CSC biology, inflammatory signaling, angiogenesis, and immune evasion. However, the metabolic approach remains investigational and should be viewed as a complementary strategy rather than a replacement for standard treatment. Most evidence indicates that cSCC exhibits a moderate-to-strong Warburg phenotype.

Practical Multi-Axis Strategy for cSCC

Tier 1 (Foundation)

- Metformin
- Ivermectin
- Curcumin
- EGCG
- Sulforaphane
- Melatonin
- Vitamin D3

Tier 2 (Add if Appropriate)

- Berberine
- Doxycycline
- Mebendazole
- Genistein
- Omega-3 fatty acids
- Propranolol
- Resveratrol/pterostilbene

Squamous Cell Carcinoma of the Skin Continued...

Tier 3 (Selected Patients)

- Atorvastatin
- Honokiol
- Apigenin
- Quercetin
- Modified citrus pectin
- Thymosin-α1
- High-dose IV vitamin C
- Mistletoe

Important Clinical Note

For localized cSCC, complete surgical excision (often with Mohs micrographic surgery for appropriate lesions) remains the standard treatment with the highest cure rates. The tiered approach above should be viewed as a research-based adjunctive framework intended to complement, not replace, evidence-based surgical and oncologic management. For advanced or metastatic cSCC, systemic therapies such as PD-1 inhibitors remain the standard of care, and the role of these repurposed drugs and nutraceuticals has not been established in clinical trials.

Topical Ivermectin

At present, there is no clinical evidence supporting the use of topical ivermectin for cSCC, and no published evidence that mixing ivermectin with DMSO improves response. Most of the available data on ivermectin in cancer come from cell culture and animal studies using systemic exposure, not topical application.

Bottom Line

- Topical ivermectin is not an established treatment for cSCC.
- There is a strong laboratory rationale but no clinical evidence demonstrating efficacy.
- DMSO would likely increase skin penetration, but no published studies have shown that ivermectin-DMSO combinations improve outcomes in cSCC.
- For superficial premalignant lesions or carcinoma in situ, topical metabolic therapies are an interesting research direction, but for invasive cSCC, surgery remains the standard of care, with metabolic approaches considered investigational adjuncts rather than replacements.

Stage 4 Metastatic Disease

For stage 4 metastatic cancer, regardless of the primary tumor, the biology becomes increasingly convergent. Metastatic cancers typically acquire common hallmarks that include:

- CSC enrichment
- Metabolic plasticity (glycolysis ↔ OXPHOS switching)
- Mitochondrial oxidative phosphorylation (especially in therapy-resistant disease)
- EMT and invasion
- Immune suppression
- Angiogenesis
- PI3K-AKT-mTOR activation
- NF-κB and STAT3 activation
- Systemic inflammation
- Therapeutic resistance

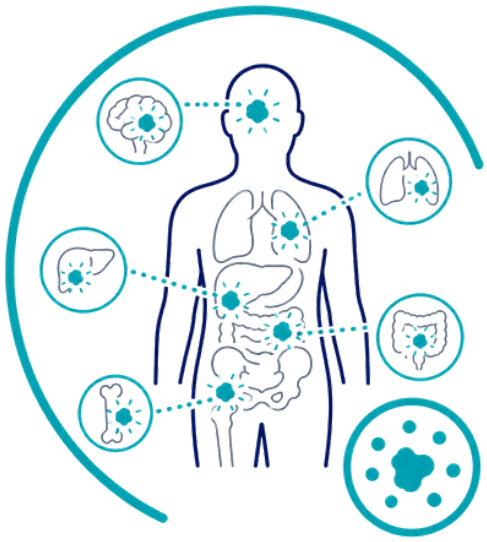
Consequently, a broad, multi-target metabolic strategy is more biologically attractive than focusing on a single pathway.

The ranking below is hypothesis-driven, based on mechanistic rationale, preclinical evidence, safety, and limited clinical data. It is not a substitute for established systemic therapies such as chemotherapy, immunotherapy, targeted therapy, endocrine therapy, or radiotherapy when these are indicated.

The repurposed drugs and nutraceuticals I consider most important for stage 4 metastatic cancer are ranked below.

Tier 1

- Metformin
- Ivermectin
- Doxycycline
- Curcumin
- Melatonin
- Sulforaphane
- Berberine
- Vitamin D3



Stage 4 Metastatic Disease Continued...

Tier 2

- Mebendazole
- EGCG
- Propranolol
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Modified citrus pectin
- Boswellia
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract
- Pomegranate extract

Patients Receiving Immunotherapy

For patients receiving immune checkpoint inhibitors, greater emphasis should be placed on agents that support antitumor immunity.

Highest-Priority Agents

- Vitamin D3
- Melatonin
- Metformin
- Ivermectin
- Curcumin
- Sulforaphane
- EGCG
- Omega-3 fatty acids
- Berberine
- Thymosin-α1

Stage 4 Metastatic Disease Continued...

OXPHOS-Dependent Metastatic Disease
Examples include pancreatic cancer, recurrent ovarian cancer, glioblastoma, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), melanoma, and some sarcomas.

Highest-Priority Agents
- Doxycycline
- Metformin
- Berberine
- Ivermectin
- Melatonin
- Sulforaphane
- Curcumin
- Mebendazole
- EGCG
- Vitamin D3

Overall Perspective

From a biological perspective, stage 4 metastatic disease is the strongest rationale for a multi-axis metabolic strategy, because metastatic tumors frequently converge on a common set of vulnerabilities, including CSCs, mitochondrial oxidative phosphorylation, metabolic plasticity, immune evasion, angiogenesis, and chronic inflammation. Rather than targeting a single mutation, a rational strategy aims to apply simultaneous pressure to multiple pathways that support metastatic survival and therapeutic resistance.

Among the repurposed agents, metformin, ivermectin, doxycycline, curcumin, melatonin, sulforaphane, berberine, vitamin D3, mebendazole, and EGCG provide the broadest mechanistic coverage across these shared vulnerabilities. Nevertheless, there is currently no high-quality clinical evidence demonstrating that this combination improves survival in stage 4 cancer, and it should therefore be regarded as an investigational adjunct to, rather than a replacement for, evidence-based oncologic therapy. Prospective clinical trials are needed to determine the safety, optimal dosing, and clinical efficacy of such multi-agent metabolic strategies.

Stage 0: Carcinoma in Situ

For stage 0 cancer, also known as carcinoma in situ (CIS), the biological goals are fundamentally different from those in invasive cancer. There is no invasion, metastasis, or established cancer stem cell niche. The emphasis is on:

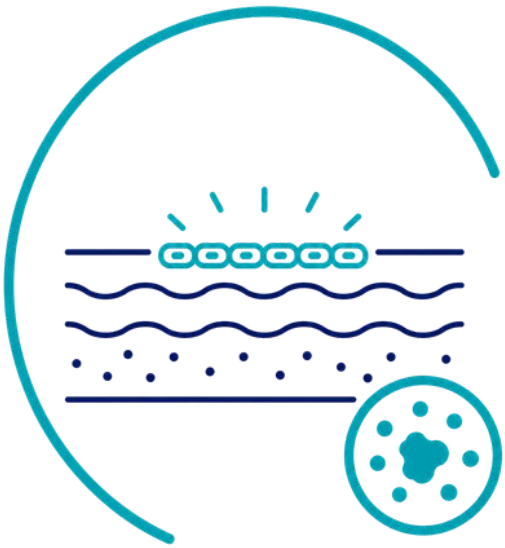
- Preventing progression to invasive cancer
- Reversing metabolic dysfunction
- Reducing chronic inflammation
- Restoring immune surveillance
- Suppressing early clonal expansion
- Maintaining epithelial differentiation
- Preventing angiogenic switching
- Targeting early cancer stem-like cells (where present)

Because of these goals, the emphasis shifts toward metabolic optimization and chemoprevention, rather than aggressive mitochondrial inhibition.

The ranking below is hypothesis-driven and reflects mechanistic rationale, safety, and available observational or preclinical evidence. It should not replace definitive local therapy (e.g., surgery or ablation), which remains the standard of care for most carcinomas in situ. The repurposed drugs and nutraceuticals I consider most important for stage 0 cancer are ranked below.

Tier 1

- Vitamin D3
- Metformin
- Curcumin
- Sulforaphane
- Melatonin
- Berberine
- EGCG
- Omega-3 fatty acids



Stage 0: Carcinoma in Situ Continued...

Tier 2

- Luteolin
- Quercetin
- Resveratrol/pterostilbene
- Apigenin
- Aged garlic extract
- Modified citrus pectin
- Propranolol (selected patients)

Tier 3

- Doxycycline
- Mebendazole
- Ivermectin
- Atorvastatin (when otherwise indicated)
- Thymosin-α1
- Honokiol
- Boswellia
- Mistletoe

Low-Risk Carcinoma in Situ

Examples include:

- Low-grade ductal carcinoma in situ (DCIS)
- Low-grade cervical intraepithelial neoplasia after treatment
- Successfully treated carcinoma in situ with no residual disease

Highest-Priority Agents

- Vitamin D3
- Metformin (particularly in insulin resistance or diabetes)
- Curcumin
- Sulforaphane
- Melatonin
- Berberine
- Omega-3 fatty acids
- EGCG
- Luteolin
- Quercetin

Stage 0: Carcinoma in Situ Continued...

High-Risk Carcinoma in Situ

Examples include:
- Extensive high-grade DCIS
- Multifocal CIS
- Positive margins awaiting definitive treatment
- Patients with strong inherited cancer predisposition (e.g., BRCA mutation)

Highest-Priority Agents
- Metformin
- Vitamin D3
- Curcumin
- Sulforaphane
- Melatonin
- Berberine
- EGCG
- Luteolin
- Quercetin
- Ivermectin (investigational, if used at all)

Overall Perspective

For stage 0 disease, the therapeutic objective is prevention of progression, not treatment of established invasive cancer. Consequently, agents that improve metabolic health, reduce chronic inflammation, support immune surveillance, and favor normal cellular differentiation deserve the highest priority. In contrast, drugs primarily aimed at disrupting mitochondrial metabolism or rapidly proliferating cancer stem cells (such as doxycycline or mebendazole) have a weaker biological rationale in this setting.

The strongest evidence supporting prevention of progression still lies with definitive local treatment and appropriate surveillance. Repurposed drugs and nutraceuticals should therefore be viewed as investigational adjuncts to optimize the metabolic and inflammatory environment, rather than as substitutes for established management of carcinoma in situ.

Non-Hodgkin Lymphoma (Adjunctive Treatment)

For non-Hodgkin lymphoma (NHL), the biology varies considerably by subtype (e.g., diffuse large B-cell lymphoma [DLBCL], follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, and T-cell lymphomas). Nevertheless, most B-cell NHLs share several important biological features:

- B-cell receptor signaling
- PI3K-AKT-mTOR
- NF-κB activation
- JAK/STAT signaling
- BCL-2-mediated apoptosis resistance
- Cancer stem-like populations (particularly in aggressive and relapsed disease)
- Mitochondrial OXPHOS, especially in subsets of DLBCL and indolent lymphomas
- Immune dysregulation
- Tumor microenvironment dependence

Unlike many solid tumors, many lymphomas — particularly indolent NHLs — are more OXPHOS-dependent than glycolytic, making mitochondrial-targeting agents somewhat more attractive.
The ranking below is hypothesis-driven, based on mechanistic rationale, preclinical evidence, safety, and limited clinical data. It is not a validated treatment protocol.

The repurposed drugs and nutraceuticals I consider most important for NHL are ranked below.

Tier 1
- Metformin
- Curcumin
- Doxycycline
- Melatonin
- Vitamin D3
- Ivermectin
- Berberine
- EGCG

Tier 2
- Sulforaphane
- Thymosin-α1
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene
- Propranolol

Non-Hodgkin Lymphoma (Adjunctive Treatment) Continued...

Tier 3

- Mebendazole
- Atorvastatin/simvastatin
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

Indolent Non-Hodgkin Lymphoma (Follicular, Marginal Zone)
Because these lymphomas tend to rely more on mitochondrial metabolism and immune interactions, I would prioritize:

- Metformin
- Doxycycline
- Melatonin
- Curcumin
- Vitamin D3
- Ivermectin
- Berberine
- Thymosin-α1
- EGCG
- Sulforaphane

Aggressive Non-Hodgkin Lymphoma (DLBCL)

For aggressive disease, stronger emphasis is placed on apoptosis, PI3K signaling, and CSC-like populations.

Highest-Priority Agents

- Metformin
- Curcumin
- Doxycycline
- Ivermectin
- Melatonin
- EGCG
- Berberine
- Sulforaphane
- Vitamin D3
- Mebendazole

Overall Perspective

Many B-cell non-Hodgkin lymphomas exhibit a greater dependence on mitochondrial oxidative phosphorylation, B-cell receptor signaling, PI3K-AKT-mTOR activation, and NF-κB than do many solid tumors. Consequently, mitochondrial-targeting agents (such as doxycycline), AMPK activators (metformin and berberine), and immune-modulating compounds (melatonin, vitamin D3, and thymosin-α1) are ranked relatively highly. Curcumin also stands out because of its broad effects on NF-κB, STAT3, and BCL-2-mediated survival pathways. Although these mechanistic considerations provide a strong rationale for further study, clinical evidence supporting multi-agent metabolic protocols in NHL remains limited, and these rankings should be viewed as a biologically informed framework for future investigation rather than an established standard of care.

Hodgkin Lymphoma

In classical Hodgkin lymphoma, the biology differs substantially from that of most solid tumors. The malignant Reed-Sternberg cells comprise only a small fraction of the tumor mass, with the remainder consisting of an immunologically active tumor microenvironment. Major biological drivers include:

- NF-κB activation (nearly universal)
- JAK/STAT signaling (especially STAT3 and STAT6)
- PD-1/PD-L1 immune evasion
- PI3K-AKT-mTOR
- CD30 signaling
- Cancer stem-like populations (less prominent than in epithelial cancers)
- Inflammatory cytokines (IL-6, IL-13, TNF-α)
- Epstein-Barr virus (EBV)-associated pathways (in a subset of patients)
- Metabolic reprogramming and mitochondrial adaptation

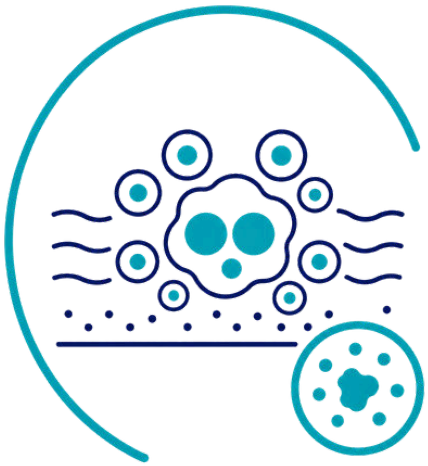
Because immune dysregulation is central to Hodgkin lymphoma, agents with immune-modulating and anti-inflammatory properties rank somewhat higher than in many solid tumors.

The ranking below is hypothesis-driven, based primarily on mechanistic rationale, preclinical evidence, safety, and limited clinical data. It should not be interpreted as a validated treatment protocol.

The repurposed drugs and nutraceuticals I consider most important for Hodgkin lymphoma are ranked below.

Tier 1

- Metformin
- Curcumin
- Melatonin
- Vitamin D3
- Ivermectin
- EGCG
- Berberine
- Sulforaphane



Hodgkin Lymphoma Continued...

Tier 2

- Thymosin-α1
- Doxycycline
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene
- Propranolol

Tier 3

- Mebendazole
- Atorvastatin/simvastatin
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

EBV-Positive Hodgkin Lymphoma

In EBV-associated disease, immune modulation becomes even more important.

Highest-Priority Agents

- Metformin
- Melatoni
- Vitamin D3
- Curcumin
- Thymosin-α1
- Ivermectin
- EGCG
- Sulforaphane
- Berberine
- Doxycycline

Hodgkin Lymphoma Continued...

Relapsed or Refractory Hodgkin Lymphoma
Following relapse, metabolic adaptation and immune escape become increasingly important.

Highest-Priority Agents
- Metformin
- Curcumin
- Thymosin-α1
- Melatonin
- Ivermectin
- Vitamin D3
- Doxycycline
- Berberine
- EGCG
- Sulforaphane

Overall Perspective

Unlike most solid tumors, Hodgkin lymphoma is characterized by profound immune dysregulation, with relatively few malignant cells embedded in a highly inflammatory tumor microenvironment. Consequently, the highest-priority adjunctive agents are those that combine immune modulation, inhibition of NF-κB and JAK/STAT signaling, metabolic reprogramming, and mitochondrial support. A core combination of metformin, curcumin, melatonin, vitamin D3, ivermectin, EGCG, berberine, sulforaphane, thymosin-α1, and doxycycline provides broad mechanistic coverage of these pathways. While the biological rationale is compelling, there is very limited clinical evidence supporting multi-agent metabolic protocols in Hodgkin lymphoma, and these rankings should be regarded as a framework for future investigation rather than established clinical recommendations.

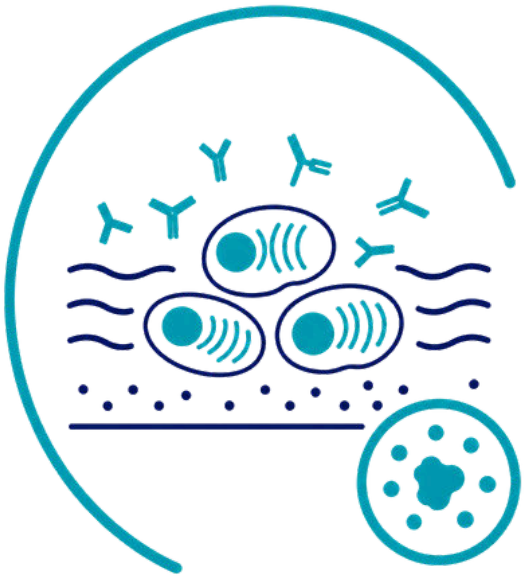
Multiple Myeloma (Adjunctive Treatment)

In multiple myeloma, the dominant biology includes plasma-cell survival signaling, NF-κB activation, IL-6/JAK/STAT3, PI3K-AKT-mTOR, proteasome stress, mitochondrial metabolism, dependence on the bone marrow microenvironment, osteoclast activation, angiogenesis, and immune dysfunction.

The repurposed drugs and nutraceuticals I consider most important for multiple myeloma are ranked below.

Tier 1

- Curcumin
- Metformin
- Melatonin
- Vitamin D3
- Berberine
- Ivermectin
- EGCG
- Sulforaphane



Tier 2

- Doxycycline
- Omega-3 fatty acids
- Thymosin-α1
- Luteolin
- Quercetin
- Resveratrol/pterostilbene
- Propranolol

Tier 3

- Mebendazole
- Atorvastatin/simvastatin
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

Multiple Myeloma (Adjunctive Treatment) Continued ...

Bottom Line

Multiple myeloma is especially driven by NF-κB, IL-6/STAT3, PI3K/mTOR, immune dysfunction, bone marrow stromal support, and mitochondrial adaptation. Curcumin ranks unusually high due to its strong overlap with the NF-κB/STAT3/IL-6 signaling pathway, which is central to myeloma biology.

Myelodysplastic Syndrome (MDS)

MDS is a complex and heterogeneous disease that ranges from a slowly progressive disorder to a highly aggressive form that may progress to AML. Patients should be managed by a hematologist with expertise in MDS; however, repurposed drugs may have an important adjunctive role. Primary treatment is tailored to disease risk, patient age, and overall health. The only curative therapy is hematopoietic stem cell transplantation (bone marrow transplantation), but most patients receive supportive care, medications, or targeted therapies to control symptoms and slow disease progression.

Standard Treatment

- Lenalidomide is recommended for lower-risk patients with the del(5q) cytogenetic abnormality and anemia.
- Chemotherapy regimens similar to those used in AML may be given to high-risk patients.
- Luspatercept and imetelstat are newer agents for lower-risk MDS and refractory anemia, showing promising results in clinical trials.
- Olutasidenib, a targeted drug for MDS patients with IDH1 mutations, has demonstrated strong outcomes in recent studies and is influencing current management.

Repurposed Drugs and Nutraceuticals

For MDS, the biology differs from that of solid tumors because the central problems include abnormal hematopoietic stem/progenitor cells, ineffective blood cell production, chronic marrow inflammation, immune dysregulation, mitochondrial dysfunction, oxidative stress, and the risk of progression to AML.

The Warburg effect is present in MDS, providing a therapeutic target. Some evidence suggests that curcumin, resveratrol, vitamin D3, and EGCG may have potential roles in the treatment or modulation of MDS.

The repurposed drugs and nutraceuticals I consider most important for MDS are ranked below.

Tier 1

- Vitamin D3
- Melatonin
- Curcumin
- Metformin
- Sulforaphane
- Berberine
- EGCG
- Omega-3 fatty acids

Myelodysplastic Syndrome (MDS) Continued ...

Tier 2

- Thymosin-α1
- Luteolin
- Quercetin
- Resveratrol/pterostilbene
- Doxycycline
- Ivermectin
- Aged garlic extract

Tier 3

- Mebendazole
- Atorvastatin/simvastatin
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Lycopene
- High-dose IV vitamin C

Pediatric Acute Myeloid Leukemia (No Radiation; Standard Chemotherapy)

For pediatric AML, the therapeutic priorities differ from adult AML because:

- Cure rates are substantially higher with intensive pediatric chemotherapy.
- Children have a greater susceptibility to long-term toxicities.
- Preserving normal hematopoietic stem cell function, growth, neurodevelopment, fertility, and immune function is critical.
- Any adjunctive therapy must have an excellent safety profile and must not interfere with standard chemotherapy.

From a metabolic perspective, pediatric AML shares many features with adult AML:

- Leukemic stem cells (LSCs) are highly dependent on mitochondrial OXPHOS
- BCL-2 signaling
- PI3K-AKT-mTOR
- NF-κB
- STAT3
- Bone marrow microenvironment
- Reactive oxygen species (ROS) regulation
- Fatty acid oxidation

However, because of the limited clinical evidence in children, I would rank agents much more conservatively than in adults.

The repurposed drugs and nutraceuticals I consider most important for pediatric AML are ranked below.

Tier 1

- Vitamin D3
- Melatonin
- Omega-3 fatty acids
- Curcumin
- Sulforaphane
- Metformin (selected settings)
- Berberine
- EGCG

Pediatric Acute Myeloid Leukemia Continued...

Tier 2

- Doxycycline
- Ivermectin
- Luteolin
- Quercetin
- Resveratrol/pterostilbene
- Thymosin-α1
- Apigenin

Tier 3

- Mebendazole
- Atorvastatin
- Propranolol
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Genistein
- Aged garlic extract
- Lycopene

Overall Perspective

Pediatric AML has one of the strongest biological rationales for targeting leukemic stem cells and mitochondrial oxidative phosphorylation, but it is also a disease in which modern pediatric chemotherapy achieves high cure rates, and preserving long-term health is paramount. For that reason, adjunctive therapies should be selected with particular caution. Among the agents listed, vitamin D3, melatonin, and omega-3 fatty acids have the most favorable safety profiles, while doxycycline, metformin, ivermectin, and other metabolic agents remain investigational in this setting.

Any adjunctive therapy for a child with AML should be considered only in close collaboration with the treating pediatric oncology team, as there is currently no high-quality clinical evidence demonstrating that these repurposed drugs or nutraceuticals improve outcomes in pediatric AML. They should therefore be viewed as promising areas for future research rather than established components of standard care.

Adult Acute Myeloid Leukemia

For adult AML, the biology differs markedly from that of solid tumors. The major drivers include:

- Leukemic stem cells (LSCs) — the principal source of relapse
- Mitochondrial OXPHOS (particularly in LSCs)
- BCL-2-mediated survival
- PI3K-AKT-mTOR
- FLT3, IDH1/2, and TP53 mutations (subset-dependent)
- NF-κB and STAT3
- Bone marrow microenvironment
- ROS homeostasis
- Metabolic flexibility, with increasing fatty acid oxidation and amino acid metabolism

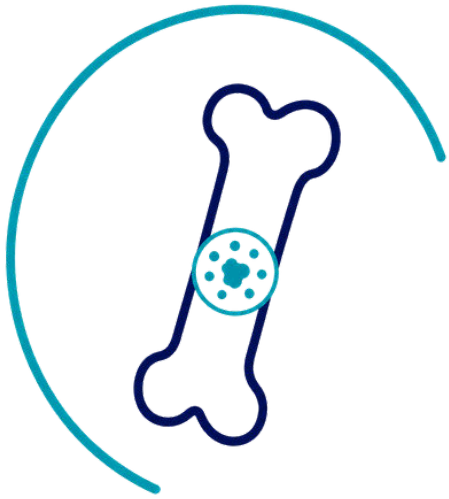
Unlike many solid tumors, AML leukemic stem cells are highly dependent on mitochondrial oxidative phosphorylation, making mitochondrial-targeting strategies particularly attractive from a biological standpoint.

The ranking below is hypothesis-driven, based on mechanistic rationale, preclinical evidence, safety, and limited clinical data. It should not be interpreted as a validated treatment protocol.

The repurposed drugs and nutraceuticals I consider most important for adult AML are ranked below.

Tier 1

- Doxycycline
- Metformin
- Melatonin
- Curcumin
- Vitamin D3
- Berberine
- Sulforaphane
- EGCG



Tier 2

- Ivermectin
- Thymosin-α1
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene
- Propranolol

Adult Acute Myeloid Leukemia Continued...

Tier 3

- Mebendazole
- Atorvastatin
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

FLT3-Mutated Acute Myeloid Leukemia

FLT3-mutated AML has high metabolic activity and aggressive biology.
Highest-Priority Agents

- Doxycycline
- Metformin
- Curcumin
- Melatonin
- Sulforaphane
- Berberine
- EGCG
- Vitamin D3
- Ivermectin
- Thymosin-α1

Relapsed/Refractory Acute Myeloid Leukemia

Relapsed AML is enriched for OXPHOS-dependent leukemic stem cells.

Highest-Priority Agents

- Doxycycline
- Metformin
- Melatonin
- Curcumin
- Sulforaphane
- Berberine
- EGCG
- Ivermectin
- Vitamin D3
- Omega-3 fatty acids

Adult Acute Myeloid Leukemia Continued...

Overall Perspective

Among hematologic malignancies, adult AML has one of the strongest biological rationales for targeting mitochondrial metabolism, particularly because leukemic stem cells are highly dependent on oxidative phosphorylation. This makes doxycycline uniquely attractive from a mechanistic standpoint compared with many solid tumors. Likewise, metformin, melatonin, curcumin, berberine, sulforaphane, and EGCG target complementary pathways involved in leukemic stem cell survival, inflammation, and metabolic adaptation.

One important caveat is that AML is an aggressive, rapidly progressive disease in which established therapies — including intensive chemotherapy, targeted agents (e.g., FLT3 and IDH inhibitors), hypomethylating agents, venetoclax-based regimens, and stem cell transplantation when appropriate — remain the standard of care. The agents ranked above should therefore be viewed, at present, as investigational adjuncts supported primarily by preclinical and mechanistic evidence, rather than proven alternatives or replacements for conventional AML treatment.

Chronic Lymphocytic Leukemia

Recent years have seen a shift from traditional chemotherapy towards targeted drug therapies. Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib, zanubrutinib, acalabrutinib, and pirtobrutinib disrupt cancer cell signaling and are commonly used, alone or with immunotherapy.

In chronic lymphocytic leukemia (CLL), the biology differs from that of both acute leukemias and solid tumors. CLL cells are slowly proliferating but highly metabolically active, relying heavily on mitochondrial OXPHOS, fatty acid oxidation, and B-cell receptor signaling rather than a classic Warburg phenotype. Other major biological drivers include:

- B-cell receptor signaling
- PI3K-AKT-mTOR
- NF-κB
- BCL-2-mediated apoptosis resistance
- Mitochondrial OXPHOS
- Fatty acid oxidation
- Bone marrow and lymph node microenvironment
- Immune dysfunction
- Oxidative stress

Because of this biology, mitochondrial-targeting agents are considerably more effective in CLL than in most solid tumors.

The rankings below are hypothesis-driven, based on mechanistic rationale, preclinical evidence, safety, and limited clinical data. They are not substitutes for established therapies such as BTK inhibitors, BCL-2 inhibitors, anti-CD20 antibodies, or chemoimmunotherapy when indicated.

The repurposed drugs and nutraceuticals I consider most important for CLL are ranked below.

Tier 1

- Doxycycline
- Metformin
- Melatonin
- Curcumin
- Vitamin D3
- Berberine
- EGCG
- Ivermectin

Chronic Lymphocytic Leukemia Continued ...

Tier 2

- Sulforaphane
- Omega-3 fatty acids
- Thymosin-α1
- Luteolin
- Quercetin
- Resveratrol/pterostilbene
- Propranolol

Tier 3

- Mebendazole
- Atorvastatin
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

Early-Stage (Rai 0-II) Chronic Lymphocytic Leukemia

For patients under observation (watch-and-wait), emphasis should be placed on maintaining metabolic health and reducing chronic inflammation.

Highest-Priority Agents

- Vitamin D3
- Metformin
- Melatonin
- Curcumin
- EGCG
- Berberine
- Omega-3 fatty acids
- Sulforaphane
- Doxycycline
- Luteolin

Chronic Lymphocytic Leukemia Continued ...

Progressive or Relapsed Chronic Lymphocytic Leukemia
Progressive disease is characterized by greater dependence on mitochondrial metabolism and resistance pathways.

Highest-Priority Agents

- Doxycycline
- Metformin
- EGCG
- Melatonin
- Curcumin
- Berberine
- Ivermectin
- Sulforaphane
- Vitamin D3
- Thymosin-α1

Overall Perspective

Among indolent hematologic malignancies, CLL has one of the strongest biological rationales for targeting mitochondrial metabolism because leukemic cells exhibit high mitochondrial mass, increased oxidative phosphorylation, and dependence on fatty acid oxidation, while remaining less glycolytic than many aggressive cancers. Consequently, doxycycline ranks unusually high because of its ability to impair mitochondrial protein synthesis, and metformin ranks highly for its effects on AMPK activation and mTOR inhibition. EGCG is also notable because it has been evaluated in early-phase clinical studies in CLL and has demonstrated biological activity, although it has not become standard therapy. Overall, this ranking emphasizes mitochondrial metabolism, B-cell receptor signaling, immune regulation, and chronic inflammation, while recognizing that current evidence for these adjunctive agents remains largely preclinical or early clinical and does not replace established CLL therapies.

Polycythemia Vera

Treatment for polycythemia vera (PV) focuses on reducing the risk of blood clots and controlling symptoms by keeping the hematocrit (red cell level) low and, when needed, lowering other blood counts. Therapy is individualized based mainly on age, history of thrombosis, symptoms, and tolerance of drugs.

Core first-line treatments include:

- Phlebotomy (regular blood removal) is the mainstay for most people and is used to keep hematocrit below about 45%, which clearly lowers the risk of thrombosis.
- Low-dose aspirin (often 75-100 mg daily) is recommended for essentially all PV patients without contraindications because it further reduces the risk of clotting.

Risk-adapted cytoreductive therapy includes:

- High-risk patients (typically age ≥ 60 or with a prior clot) are usually offered cytoreductive medication in addition to phlebotomy and aspirin to lower blood counts and clot risk.
- Common first-line cytoreductive drugs include hydroxyurea, an oral chemotherapy agent widely used in older or high-risk patients.

In polycythemia vera (PV), the biology differs substantially from that of both solid tumors and acute leukemias. PV is a chronic myeloproliferative neoplasm driven primarily by constitutive activation of JAK2 signaling (JAK2 V617F in approximately 95% of patients), leading to excessive erythrocyte production and a chronic inflammatory state.

Unlike AML, PV is not primarily driven by highly proliferative glycolytic metabolism, but rather by:

- JAK-STAT activation (dominant driver)
- Chronic inflammation (NF-κB, IL-6, TNF-α)
- PI3K-AKT-mTOR
- Abnormal hematopoietic stem cells
- Oxidative stress
- Bone marrow microenvironment
- Thrombo-inflammation
- Progression to myelofibrosis or AML

Consequently, anti-inflammatory and immune-modulating agents rank higher than strongly antiproliferative or mitochondrial-targeting agents.

Polycythemia Vera Continued...

The rankings below are hypothesis-driven, based on mechanistic rationale, preclinical evidence, safety, and limited clinical data. They should not replace established therapies such as phlebotomy, low-dose aspirin, interferon-α, hydroxyurea, or JAK inhibitors (e.g., ruxolitinib) when indicated.

The repurposed drugs and nutraceuticals I consider most important for polycythemia vera are ranked below.

Tier 1

- Vitamin D3
- Curcumin
- Metformin
- Melatonin
- Omega-3 fatty acids
- Berberine
- Sulforaphane
- EGCG

Tier 2

- Thymosin-α1
- Luteolin
- Quercetin
- Resveratrol/pterostilbene
- Ivermectin
- Aged garlic extract
- Propranolol

Tier 3

- Doxycycline
- Mebendazole
- Atorvastatin (when otherwise indicated)
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Lycopene

Polycythemia Vera Continued...

High-Risk Polycythemia Vera
In patients with prior thrombosis or advanced disease, reducing inflammation and vascular risk becomes particularly important.

Highest-Priority Agents
- Vitamin D3
- Curcumin
- Omega-3 fatty acids
- Metformin
- Melatonin
- Berberine
- Sulforaphane
- EGCG
- Aged garlic extract
- Luteolin

Polycythemia Vera Patients Receiving Ruxolitinib
Adjunctive strategies should focus on reducing residual inflammation and improving metabolic health.

Highest-Priority Agents
- Vitamin D3
- Curcumin
- Metformin
- Melatonin
- Omega-3 fatty acids
- Berberine
- Sulforaphane
- EGCG
- Thymosin-α1
- Luteolin

Overall Perspective

Unlike most cancers, polycythemia vera is driven primarily by dysregulated JAK-STAT signaling, chronic inflammation, and abnormal hematopoietic stem-cell function rather than by pronounced glycolysis or mitochondrial dependence. Consequently, anti-inflammatory and immune-modulating agents such as curcumin, vitamin D3, melatonin, omega-3 fatty acids, and sulforaphane are prioritized, while metformin and berberine provide complementary effects through AMPK activation and metabolic regulation. The primary clinical goals in PV remain prevention of thrombosis, control of blood counts, reduction of inflammatory symptoms, and prevention of progression to myelofibrosis or AML. These adjunctive agents have promising mechanistic rationale but should be considered investigational supportive therapies rather than established disease-modifying treatments.

Sarcomas

Sarcomas are cancers that arise from connective tissues such as bone, muscle, fat, and blood vessels, and usually have a poor prognosis for several key reasons:

- Late diagnosis
- High grade and aggressiveness
- Large tumor size
- Metastasis at diagnosis
- Tumor location
- Incomplete surgical removal
- Tumor heterogeneity
- Resistance to conventional therapy

Evidence indicates that sarcomas typically demonstrate the metabolic reprogramming characteristic of the Warburg effect. This metabolic shift contributes to their aggressive growth and provides potential therapeutic targets within cancer cell glycolytic pathways. Although the prognosis remains poor and clinical data on repurposed drugs are limited, the following agents are suggested as adjunctive therapy based on a mechanistic rationale.

For sarcoma, the dominant biology includes mesenchymal invasion, EMT-like programs, angiogenesis, PI3K-AKT-mTOR activation, CSCs, mitochondrial plasticity, hypoxia, and metastatic spread, especially to the lungs.

The repurposed drugs and nutraceuticals I consider most important for sarcoma are ranked below.

Tier 1

- Metformin
- Ivermectin
- Doxycycline
- Curcumin
- Sulforaphane
- Melatonin
- Berberine
- Vitamin D 3

Sarcomas Continued ...

Tier 2

- Mebendazole
- EGCG
- Propranolol
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

Bottom Line

Sarcoma is a strong candidate for a CSC- and mitochondrial-targeted metabolic strategy because invasion, metastatic spread, hypoxia adaptation, PI3K/mTOR signaling, and mitochondrial plasticity are central to sarcoma progression and treatment resistance.

Mesothelioma

Surgery, radiation, and chemotherapy appear to have a limited role in the treatment of mesothelioma. Niclosamide, used for parasitic infections, was found to exhibit antiproliferative and pro-apoptotic activity against mesothelioma tumor cells, with studies showing inhibition of mTORC1 signaling and tumor growth in animal models. However, oral niclosamide has very poor bioavailability.

For malignant mesothelioma, especially pleural mesothelioma, the dominant biology includes chronic asbestos-driven inflammation, NF-κB activation, PI3K-AKT-mTOR signaling, YAP/TAZ activation, CSCs, angiogenesis, immune suppression, mitochondrial plasticity, fibrosis, and invasive local growth.

The repurposed drugs and nutraceuticals I consider most important for mesothelioma are ranked below.

Tier 1

- Ivermectin
- Metformin
- Curcumin
- Melatonin
- Vitamin D3
- Sulforaphane
- Berberine
- EGCG

Tier 2

- Doxycycline
- Mebendazole
- Propranolol
- Omega-3 fatty acids
- Luteolin
- Quercetin
- Resveratrol/pterostilbene

Mesothelioma Continued ...

Tier 3

- Atorvastatin/simvastatin
- Thymosin-α1
- Honokiol
- Boswellia
- Modified citrus pectin
- Mistletoe
- Apigenin
- Genistein
- Aged garlic extract
- Lycopene

Bottom Line

Mesothelioma is a strong candidate for a multi-target strategy because it is driven by chronic inflammation, YAP/TAZ signaling, mTOR activation, immune suppression, angiogenesis, fibrosis, and invasive CSC-like biology.

Safety Considerations

Curcumin and blood thinning

Curcumin has been reported to have blood-thinning properties, which may impair the body's ability to form clots. The bleeding risk is heightened when curcumin is combined with certain medications:

- Anticoagulants: Warfarin, heparin, and other blood thinners
- Antiplatelet drugs: Aspirin, clopidogrel (Plavix)
- NSAIDs: Nonsteroidal anti-inflammatory drugs

Potential manifestations of increased bleeding risk include:

- Easy bruising
- Abnormal bleeding (e.g., nosebleeds, bleeding gums)
- Blood in stool or urine
- Prolonged bleeding times
- Excessive bleeding during surgery

To mitigate risk:

- Discontinue curcumin supplementation at least two weeks before any scheduled surgery.
- Avoid combining curcumin with other herbal supplements that may affect clotting (e.g., garlic, ginkgo biloba, fish oil).
- Monitor for signs of increased bleeding, such as easy bruising or prolonged bleeding from cuts.

Metformin and Berberine

Metformin and berberine both lower blood glucose. To prevent hypoglycemia, blood glucose should be monitored when the two are used simultaneously. Alternatively, reduce the dose of berberine to once daily or metformin to 500 mg twice daily.

Doxycycline and the Microbiome

Doxycycline appears to have minimal impact on the overall composition and diversity of the gut microbiome:

- No significant differences in bacterial taxonomic alpha or beta diversity have been observed between doxycycline users and controls.
- The normalized bacterial mass of the gut microbiome remains stable after doxycycline use.
- No consistent differential abundance of bacterial genera was found between baseline and six months after doxycycline use.

Safety Considerations

Green Tea (EGCG) and Hepatotoxicity

EGCG is rarely associated with liver injury. The risk of toxicity is reduced when the daily dose is kept below 800 mg, the dose is gradually increased over several weeks, and it is taken with food and/or vitamin C. Drinking brewed green tea (≤ 4 cups/day) poses minimal risk of hepatotoxicity.

Curcumin taken with EGCG may increase the risk of hepatotoxicity. Concomitant use with piperine may further elevate this risk.

Liver function tests should be monitored regularly, particularly when initiating therapy. These supplements should be avoided in patients with a history of liver disease or those receiving chronic lymphocytic leukemia-directed therapy. USP-verified supplements are recommended.

Zinc and Prostate Cancer

Prostate cancer cells exhibit a 70% to 80% reduction in zinc levels compared to healthy prostate tissue. Low-dose (1-24 mg per day) zinc supplementation after diagnosis has been associated with a lower risk of lethal prostate cancer and all-cause mortality among men with nonmetastatic disease (stage 1-3). However, high-dose supplementation (> 75 mg per day) and prolonged use (10 years or more) have been linked to increased risk and aggressiveness of prostate cancer. While zinc shows therapeutic potential, its dose-dependent biphasic effects require careful clinical management. Current evidence supports cautious low-dose use, particularly in early-stage patients, while avoiding high-dose or long-term supplementation.

Conclusion

Repurposed drugs and metabolic strategies can provide meaningful adjuncts to conventional cancer therapy, particularly by targeting CSCs and treatment resistance. While promising, their use should be individualized, closely monitored, and integrated with standard care. Continued research is essential to define best practices and confirm therapeutic potential.

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