Cancer Metabolism as a Therapeutic Target and Review of Interventions

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Abstract: Cancer is amenable to low-cost treatments, given that it has a significant metabolic component, which can be effected through diet and lifestyle change at minimal cost. The Warburg hypothesis states that cancer cells have altered cell metabolism towards anaerobic glycolysis. Given this metabolic reprogramming in cancer cells, it is possible to target cancers metabolically by depriving them of glucose. In addition to dietary and lifestyle modifications which work on tumors metabolically, there are a panoply of nutritional supplements and repurposed drugs associated with cancer prevention, and better treatment outcomes. These interventions and their evidentiary basis are covered in the latter half of this review to guide future cancer treatment.

Keywords:

1. Introduction

Warburg's hypothesis for cancer progression is that cancer cells undergo a two-step transformation. First, there is irreversible failure of respiration, and secondly, the cell survives by fermentation energy. While fermentation energy is far less efficient than aerobic glycolysis, producing only 2 ATP for a glucose molecule as opposed to 38 via aerobic glycolysis [1].

Cancerous cells shunt a majority of glucose through the anaerobic pathway [2], and cancerous cells do have enhanced glycolysis [3]. This effect serves as the basis of radiolabeled glucose positron emission tomography (PET) imaging of tumors [4]. Cancerous tumors using anaerobic glycolysis produces waste products and acidifies the intracellular space [5,6], which necessitates the evolution of surrounding cells towards acid-resistant phenotypes [7]. Additionally, the hypoxia-resistant phenotype of cancer cells is especially useful for pre-malignant lesions growing further away from blood vessels [7].

To test the validity of the metabolic theory of cancer, nuclear transplantation experiments were performed, demonstrating that while inserting the nucleus of a cancerous cell into a healthy cell was insufficient to induce the cancer phenotype, swapping the cytoplasm, which contains the mitochondria, was[8].

Until recently, the Warburg hypothesis had not received much attention for its treatment implications for cancer until recently. Case reports on the ketogenic diet for treatment in cancer were published in the 1990's [9], and a pilot trial of 16 participants was published in 2011[10]. Adherence to the diet is a common difficulty [10,11]. Given the profusion of interest in ketogenic diets, there are now more keto-friendly foods and cookbooks available, which can help with diet adherence.

Metabolic approaches work systemically[12], as opposed to targeted therapies, which require specific targeting towards an individual's cancer genetics[13]. Given that the Warburg effect is a hallmark of cancer [14], a reduction in the fuel available to cancer cells can systemically shift the body environment to be more hostile to cancer[15].

There are multiple interventions that one can apply, each of which effects a less conducive environment for cancer growth. Therapeutic combinations that stress the cancer through multiple pathways can prevent cancer progression, encouraging reversal and remission. Typically, therapeutic combinations are studied either in isolation or in combination with a few other (often complementary) therapeutic interventions.

Cancer fitness is a multidimensional landscape, and combinations of interventions can be selected to reduce tumor fitness while maintaining the fitness of normal cells. Metabolic reprogramming in cancer cells opens up a significant number of therapeutic modalities. Not only does dietary ketosis proportionately disfavor cancer cells from an energy availability standpoint, it also deprives the cancer cell of the vital building blocks for cell replication, and ketones may act independently as anti-oncogenic factors [16,17].

The metabolic shift to glycolysis is also useful for the tumor microenvironment prior to angiogenesis, which is a hypoxic condition [7]. Additionally, the rapidly-dividing nature of cancer cells prioritizes glycolytic metabolism [18,19], and the Warburg effect enables faster glucose breakdown, which can be useful for providing substrates for nucleic acid biogenesis in rapidly dividing cancer cells[20], and can produce more energy per unit time compared to non-cancerous cells, despite the inefficiencies[21].

The metabolic paradigm of cancer research is still novel, and requires much more fervent investigation. However, it demonstrates great therapeutic promise, both in terms of mechanistic understanding as well as clinical data.

2. Lifestyle Interventions for preventing and treating cancer

2.1. Glucose management and ketogenic diet

A carbohydrate-restricted diet, specifically a ketogenic diet, high in saturated fat and Omega-3 fatty acids, is suggested for various health benefits, including its potential role in cancer management [22]. The diet emphasizes avoiding processed foods, particularly those with high glycemic index values, and promotes the consumption of real foods such as vegetables, nuts, fish, chicken, eggs, and certain fruits [22–24]. Continuous glucose monitoring is recommended to track blood glucose levels, and a blood ketone meter is advised to confirm the patient's state of ketosis [25].

To flatten the blood glucose curve, various interventions are recommended, including eating foods in the right order (starting with vegetables, followed by protein and fat, and ending with starches), skipping breakfast, avoiding snacking, and incorporating vinegar or fiber tablets before consuming starchy or sweet foods [26]. Establishing and restoring a normal microbiome is highlighted as an essential aspect of regulating blood glucose levels and improving insulin sensitivity, with suggestions including consuming a diverse range of foods, fermented foods, and prebiotic fiber, and reducing stress and unnecessary antibiotic use [27–33]. Avoiding seed oils high in linoleic acid is advised, while using healthy oils such as olive oil, avocado oil, coconut oil, flaxseed oil, walnut, and pecan oils, and butter is recommended [34–37].

Overall, these dietary and lifestyle recommendations aim to support health and potentially impact cancer management positively by optimizing blood glucose levels, promoting a favorable microbiome, and ensuring a balanced intake of fats and oils.

2.1.1. Mechanism

Restircting carbohydrates insduces the body to adopt ketosis as its glucose fuel source is restricted and it must necessarilymeet energy demands through another mechanism. This mechanism is ketosis, for which it is difficult to meet the metabolic demands of cancers with, as these cells have damage to the cellular respiration pathways and ferment glucose preferentially. Therefore, being in a state of ketosisis deleterious to the cancer cells while being neutral or even beneficial to the normal cells.

2.1.2. Clinical Evidence

Multiple trials have been performed in the last decade showing the clinical benefit of ketogenic diets in the treatment of cancer, showing an antitumor effect in the high majority of trials[38].

2.1.3. Dosing Recommendations

It typically takes two weeks to adjust to the state of ketosis when stating a ketogenic diet[39]. Ketogenic diets (KD) are very low carbohydrate, as carbohydrate metabolism will disrupt the onset of ketosis. While standards for the cutoff of carbohydrates vary, keeping daily intake below 50g of carbohydrates (not including fiber) is important to maintaining the state of ketosis[40].

Individuals with the following conditions should not embark on the ketogenic diet [41]: primary carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine translocase deficiency, β-oxidation defects, pyruvate carboxylase deficiency or porphyria. Other relative contraindications are included in a recent review [42].

It is recommended to start at a higher level of carbohydrates and taper down gradually[43]. Before starting on the KD, it is recommended to perform a consultation which provides relevant information, sets expectation, and provides resources, including cookbooks [42–44]. 90% of experts also recommend multivitamin and mineral supplementation for those using KD [42]. Specifically, these include calcium and vitamin D3 [42]. Additionally, adequate fluid intake (30-35mL/kg/d), which works out to 2.7L to 3.2L per day for a 90kg person.

These resources are useful, as adherence is often an issue[45], though development on diet formulation helps with adherence, and is similar to a modified Mediterranean diet [46]. A low-carbohydrate diet study managed to maintain 85% adherence over 2 years [47].

For this reason, we recommend the tools of a continuous glucose monitor and ketone test strips. As the latter can demonstrate ketogenic diet adherence by testing β-hydroxybutyrate (BHB) levels[48], which can provide a definite indication that one is in a state of ketosis.

2.2. Exercise

Lifestyle modification is crucial for reducing the risk of death from cancer and improving quality of life. This includes exercise, a healthy diet, and stress reduction [49,50]. Patients with cancer and metabolic syndrome face an increased risk of distant metastasis compared to those without the syndrome [51]. Regular exercise, combining aerobic activity and resistance training, is recommended during cancer treatment to improve cardiovascular fitness, cognition, mood, and reduce fatigue, anxiety, and depression [52–57]. Resistance training also helps preserve muscle mass, reducing insulin resistance, improving glucose control, and potentially increasing overall survival, as sarcopenia is a negative prognostic factor in cancer patients [58].

The Combined Aerobic and Resistance Exercise (CARE) Trial demonstrated that a combined dose of 50-60 minutes of aerobic and resistance exercise performed three times weekly led to better patient-reported outcomes and health-related quality of life compared to performing aerobic exercise alone during breast cancer chemotherapy [59]. Meta-analyses have shown benefits of exercise in various types of cancer, including breast cancer treated with adjuvant chemotherapy and/or radiotherapy, colorectal cancer treated with chemotherapy, lung cancer treated with chemotherapy, prostate cancer treated with radiation therapy, and hematologic malignancies [52]. Engaging in at least 30 minutes of moderate-intensity physical activity at least five days a week, or 75 minutes of more vigorous exercise, along with two to three weekly strength training sessions, is encouraged for patients [49,57]. There is evidence of an inverse dose-response effect between hours per week engaged in physical activity and breast cancer mortality, indicating that more hours of exercise have increased benefits [60,61]. Walking, particularly in the sunshine, is beneficial for physical, emotional, and psychological well-being [62,63].

2.3. Stress Reduction and Sleep

Psychosocial stress is associated with a higher incidence of cancer and poorer survival in cancer patients [64]. To reduce stress, patients are advised to engage in stress-reducing activities like meditation, yoga, and mindfulness exercises, along with getting at least 8 hours of high-quality sleep [64–70]. Ashwagandha, an adaptogenic herb, has been proven to be safe and effective in combating stress and improving sleep quality [71–73]. In randomized controlled trials, Ashwagandha extract significantly reduced stress levels and cortisol levels, and improved cognition and mood [74]. Meta-analyses also demonstrated that Ashwagandha supplementation significantly reduced anxiety and stress levels compared to placebo, with an optimal dosage of up to 12,000 mg daily for anxiety and 300-600 mg daily for stress [75,76]. However, caution should be exercised as Ashwagandha can activate the immune system and should not be used with immunosuppressive drugs or during pregnancy and breastfeeding [74].

Adequate and high-quality sleep is crucial for neural development, learning, memory, cardiovascular and metabolic regulation [77]. For healthy individuals, the National Sleep Foundation recommends seven to nine hours of sleep for younger adults and seven to eight hours for older adults [78]. Healthy sleep is characterized by good quality, indicated by factors such as short sleep latency, minimal awakenings during the night, and high sleep efficiency [79]. Insomnia, defined as difficulty initiating or maintaining sleep, is associated with daytime symptoms like fatigue, cognitive impairment, or depression [80]. Short sleep duration, less than six hours per 24 hours, is associated with increased mortality [81]. Ashwagandha supplementation has been found to improve sleep, particularly in adults with insomnia, with positive effects on sleep quality, sleep onset latency, total sleep time, wake time after sleep onset, and sleep efficiency [80]. The optimal treatment dosage is > 600 mg daily for more than 8 weeks [80].

3. Recommended Supplements and Medications for the Treatment of Cancer

3.1. Vitamin D

Vitamin D is synthesized in the human skin through the influence of UV B radiation and is then converted into the active form, 1,25-dihydroxyvitamin D3 (calcitriol), in the kidney [82–84]. 25-hydroxyvitamin D3 [25(OH)D3] is considered the best indicator of vitamin D status, with a level >30 ng/ml considered normal, 20-30 ng/ml considered insufficient, and <20 ng/ml considered deficient [83–85]. Recent data suggests that a level >50 ng/ml is desirable, and ideally, targeting a level between 55-90 ng/ml is preferable [82,86–88]. Adequate vitamin D supplementation is important to achieve optimal levels in patients with low vitamin D levels, and using 50,000 IU D3 capsules in divided doses over a few days is recommended [82,87,88] (Supplementary Table 1).

Vitamin D plays a critical role in various physiological pathways, including energy metabolism, immunity, and cellular growth [89]. It has pleiotropic functions and regulates over 1200 genes within the human genome, with a significant role in the modulation of the immune system [82,90,91]. Observational and randomized controlled studies indicate that low vitamin D status is associated with higher mortality from conditions like cancer and cardiovascular disease [92,93]. Vitamin D deficiency increases the risk of breast, colon, prostate, and other cancers, while supplemental vitamin D intake has an inverse relationship with cancer risk [83,94]. Higher latitudes are associated with increased risk of vitamin D deficiency and various cancers, with vitamin D supplementation likely playing a crucial role in cancer prevention [83,95]. Achieving a vitamin D level of 80 ng/mL may reduce cancer incidence rates by 70% [96].
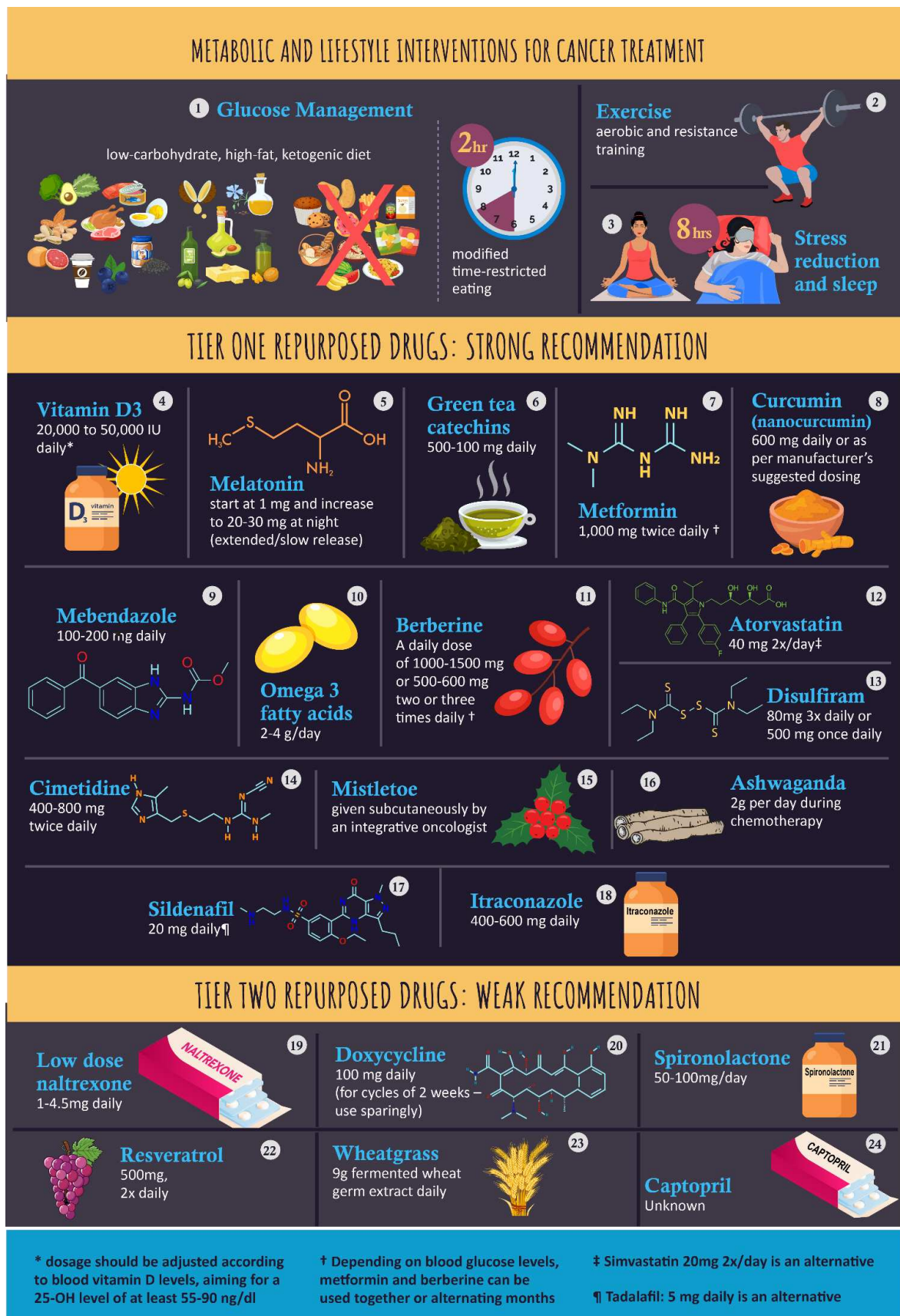
Figure 1.

3.1.1. Mechanism

Vitamin D exhibits diverse antineoplastic activity through various pathways. It binds to the vitamin D receptor and induces differentiation, apoptosis, and inhibits cancer stem cells, proliferation, angiogenesis, and metastatic potential [97]. It promotes apoptosis of cancer cells, inhibits WNT-β catenin signaling, and has anti-inflammatory effects by downregulating nuclear factor-Kβ and inhibiting cyclooxygenase expression [98–100]. Vitamin D also regulates cell cycle, growth factor pathways, and immune responses against tumor cells [96,101]. It triggers autophagic death, promotes cell differentiation, and exhibits antiangiogenic effects [96,102,103]. These mechanisms collectively contribute to vitamin D's anticancer effects and may help reduce cancer incidence and mortality [95].

3.1.2. Clinical Evidence

Multiple studies indicate that a significant proportion of cancer patients are vitamin D deficient (level < 20 ng/ml) and that higher plasma 25-hydroxyvitamin D levels are associated with improved survival in colorectal, breast, gastric, and lymphoma cancer patients [93,97,104–110]. Meta-analyses and clinical trials demonstrate that vitamin D supplementation may reduce cancer mortality and improve survival in cancer patients, especially when used in combination with chemotherapy [111–117]. SUNSHINE, a clinical trial on metastatic colorectal cancer patients, showed that "high dose" vitamin D3 (aiming for a level of > 50 ng/ml) combined with standard chemotherapy resulted in improved progression-free survival compared to standard-dose vitamin D3 [97]. Adequate vitamin D dosing aiming for a level between 55-90 ng/ml may have additional benefits in cancer patients [97]. Vitamin D supplementation is suggested to have additive or synergistic effects when combined with conventional chemotherapy [118,119].

3.1.3. Dosing Recommendation

Vitamin D supplementation is likely beneficial for most types of cancers, especially breast, colorectal, gastric, esophageal, lung, prostate cancer, lymphomas, and melanoma. Due to the severe vitamin D deficiency observed in most cancer patients, a high loading dose of vitamin D is recommended, followed by dose titration aiming for a level of > 50 ng/ml (target 55-90 ng/ml). Some types of cancer may require higher levels, up to 150 ng/ml, to halt growth and metastasis. Daily doses of 20,000 to 50,000 IU/day are suggested until the desired vitamin D level is reached. It is important to monitor vitamin D levels to ensure appropriate maintenance dosing, and daily dosing of vitamin D3 is preferred over large intermittent bolus dosing. Vitamin K2 (Menaquinone [MK4/MK7]) and magnesium are recommended in conjunction with high vitamin D doses (> 8,000 IU/day). Measuring parathyroid levels and calcium levels can help titrate the vitamin D dose according to the Coimbra Protocol [120,121].

3.2. Melatonin

Melatonin, a lipophilic molecule synthesized by the pineal gland with a circadian pattern, exhibits elevated levels at night and contributes to homeostatic metabolic rhythms and disease protection [122]. It acts through MT1 and MT2 receptors found throughout the body, functioning as a potent antioxidant and playing a crucial role in normal mitochondrial function and oxidative phosphorylation [123]. Exposure to light at night can disrupt melatonin production and the circadian rhythm, and its levels decrease with age after 40 [124]. Melatonin's widespread biological effects are facilitated by its receptors, and it is also produced in mitochondria under near-infrared irradiation, further adding to its diverse properties [125,126].

3.2.1. Mechanism

Low melatonin levels have been associated with cancer development, and various studies have shown reduced melatonin levels in cancer patients compared to healthy individuals of the same age [124]. Disruption of nocturnal melatonin secretion, as seen in night shift workers, is linked to a

modestly increased risk of breast and other cancers [127,128], and a long-term study found elevated breast cancer incidence among female airline cabin crew. Experimental models have demonstrated melatonin's broad spectrum of anticancer activity, involving cytotoxic, anti-mitotic, and pro-apoptotic actions in breast cancer cells, primarily mediated by the MT1 membrane receptor [129,130]. Melatonin inhibits cancer stem cell proliferation, reduces Ki67 and matrix metalloproteinase 9 expression [131], and switches cancer cells from anaerobic glycolysis to oxidative phosphorylation, slowing their proliferation, reducing metastatic potential, and inducing apoptosis [132,133]. Additionally, melatonin exhibits anti-angiogenic effects, modulates PI3K and MAPK signaling pathways [131], stimulates T cell and natural killer cell production while reducing regulatory T cells [134,135].

3.2.2. Clinical Evidence

In addition to case studies, [136,137] the clinical benefit of melatonin in patients with cancer is supported by the highest level of evidence, namely meta-analyses of RCTs [138,139]. Seely et al systematically reviewed the effects of melatonin in conjunction with chemotherapy, radiotherapy, supportive care, and palliative care on 1-year survival, complete response, partial response, stable disease, and chemotherapy-associated toxicities [139]. This analysis included 21 randomized studies all of which studied solid tumors. The pooled relative risk (RR) for 1-year mortality was 0.63 (95% CI = 0.53-0.74; P < 0.001). Improved effects were found for complete response, partial response, and stable disease. In trials combining melatonin with chemotherapy, adjuvant melatonin decreased 1-year mortality (RR = 0.60; 95% CI = 0.54-0.67).

3.2.3. Dosing

Melatonin may be active in several cancers including cancers of the breast, ovary, pancreas, liver, kidney, mouth, stomach, colon/rectum, brain, lung, prostate, head and neck, and various leukemias and sarcomas [129,130]. Providers should advise patients to begin with 1 mg at night; a slow-release/extended-release preparation is suggested to minimize REM sleep-induced nightmares (best taken an hour before retiring). The dose should be increased up to 20-30 mg, as tolerated [122].

3.3. Green tea

3.3.1. Mechanism

The biochemical impact of green tea on cancer is multifarious, as green tea is a combination of many bioactive compounds. Of particular interest are the catechins, of which epigallocatechin gallate (EGCG) is the most abundant [140]. Green tea catechins (GTCs), especially EGCG, have demonstrated anticancer effects in various experimental models by inhibiting cancer growth and modulating multiple signal pathways involved in cancer cells [141–143]. EGCG inhibits mitochondrial glutamate dehydrogenase (GDH) [144] and interferes with VEGF, STAT3, MAPK, and Wnt pathways, leading to the suppression of angiogenesis and tumor cell proliferation [145]. It also suppresses invasion and metastasis by inhibiting MMP activities and promotes tissue inhibitor of MMPs expression [145]. Moreover, GTCs alter the tumor microenvironment, enhancing anticancer immunity by increasing active cytotoxic T lymphocytes and switching "cold" tumors to "hot," with improved anti-tumor immune therapeutics [146]. EGCG also downregulates the TLR-4 signaling pathway implicated in cancer cachexia [147]. Green tea extract has been shown to suppress cancer stem cells [148,149]. GTCs may have synergistic anticancer activity when combined with other phytochemicals, such as resveratrol [150].

3.3.2. Clinical Evidence

Numerous experimental models and epidemiological data support the anticancer effects of green tea catechins (GTCs). A meta-analysis showed an inverse association between tea catechin intake and various cancers [140], and another meta-analysis demonstrated that GTCs reduced the

risk of gastrointestinal, breast, gynecological, leukemia, lung, and thyroid cancers [151]. Case reports and clinical studies also observed positive outcomes in patients with B cell malignancies and chronic lymphocytic leukemia (CLL) treated with GTCs [152,153]. In a [154] randomized trial, GTCs significantly reduced the risk of prostate cancer. [155] Green tea catechins may be effective against various tumors, including prostate, breast, uterus, ovary, colorectal, glioma, liver, gallbladder, melanoma, and lung cancers [140].

3.3.3. Dosing

Green tea catechins are recommended to be taken at a dose of 500-1000 mg/day during or after a meal to minimize the risk of liver toxicity [156]. The US Pharmacopeia Dietary Supplement Information Expert Committee has concluded that green tea extract is safe when used and formulated appropriately, but regular liver function tests are advised for those taking it, and caution should be exercised in patients with underlying liver disease [157].

3.4. Metformin

3.4.1. Mechanism

Metformin exhibits anticancer activity through direct effects on cancer cells [158], including inhibition of the AMPK/mTOR pathway [159], as well as indirect effects on the host through blood glucose-lowering properties and anti-inflammatory effects. It inhibits complex I of the electron transport chain, forcing cancer cells to rely on glycolysis for ATP synthesis [160]. Metformin activates AMPK, leading to the suppression of protein synthesis and cell development, ultimately reducing mTOR action [161]. Additionally, metformin upregulates PGC-1, which is involved in mitochondrial biogenesis, and interacts with the SIRT1 pathway, connecting metabolism with cell proliferation [162]. Moreover, metformin regulates the EGFR and IGFR pathways, which play vital roles in cell growth, proliferation, and metabolic processes, suggesting its potential to exert an antitumor effect [162]. Furthermore, metformin suppresses cancer stem cells, offering a unique approach in targeting the root of cancer [163].

3.4.2. Clinical Evidence

Meta-analyses and observational studies have shown that metformin plays a significant role in the primary prevention of cancer, reducing overall cancer incidence [164,165]. It has been associated with improved survival and reduced mortality in patients with various cancers, including colorectal, lung, breast, and prostate cancer [166–168]. Moreover, metformin demonstrated significant benefits as an adjunctive treatment for colorectal and prostate cancer, especially in those undergoing radical radiotherapy [169].

3.4.3. Dosing

Metformin shows a broad spectrum of anticancer activity and may be beneficial in preventing various malignancies, including breast, pancreatic, gastric, colorectal, endometrial, prostate, non-small cell lung cancer (NSCLC), and bladder cancers [162,167,169–174]. The recommended dose is 1,000 mg twice daily, and it is considered a safe drug with few side effects. However, prolonged use may lead to vitamin B12 deficiency, so supplementation is suggested. Caution should be exercised when combining metformin with berberine, as it may cause very low blood glucose levels. Close monitoring is advised, and alternating metformin and berberine monthly may be considered if low glucose occurs.

3.5. Curcumin

Curcumin, popularly called "curry powder" or turmeric, is a polyphenol extracted from Curcuma longa. Curcumin has antioxidant, anti-inflammatory, antimicrobial, antiviral, and anticancer properties [175].

3.5.1. Mechanism

Curcumin, a bioactive compound found in turmeric, exhibits a wide range of anticancer effects by targeting multiple cell signaling pathways in cancer cells [175]. It interferes with the cell cycle, apoptosis, proliferation, survival, invasion, angiogenesis, metastasis, and inflammation [176]. Curcumin suppresses the activity of NF-κB, a key regulator of cancer-related processes, and inhibits STAT3 activation, which promotes cancer growth and survival [177,178]. It downregulates HER2-tyrosine kinase and interferes with EGFR signaling, inhibiting breast cancer cell growth and proliferation [179–181]. Curcumin induces apoptosis and inhibits angiogenesis, even in the hypoxic tumor microenvironment, and also shows activity against cancer stem cells [182]. It triggers apoptosis through ROS-mediated ER stress and mitochondrion-dependent pathways and acts on the Wnt/-catenin pathway [183]. Overall, curcumin demonstrates a promising potential as a natural anticancer agent with multiple mechanisms of action [184].

3.5.2. Clinical Evidence

The clinical use of curcumin for its broad anticancer activities has been limited by its poor bioavailability, attributed to low absorption, extensive biotransformation, and rapid elimination [176]. Various curcumin analogs and drug delivery systems are being investigated to enhance bioavailability [176]. Despite limited clinical studies, some have shown promising results. In patients with multiple myeloma, the addition of curcumin to standard treatment increased remission rates and reduced inflammatory markers [185]. In metastatic colorectal cancer, curcumin as an adjunctive therapy to chemotherapy improved overall survival. In advanced pancreatic cancer, a phytosome complex of curcumin showed a response rate and disease control rate [186,187]. In advanced metastatic breast cancer, intravenous curcumin in combination with paclitaxel resulted in a significantly higher objective response rate [188]. Dose escalation studies demonstrated that daily doses of up to 10 g of curcumin were well tolerated in patients with breast and prostate cancer.

3.5.3. Dosing

Curcumin (turmeric) may be beneficial for various types of cancers, including colorectal, lung, pancreatic, breast, prostate, chronic myeloid leukemia, liver, gastric, brain tumors, ovarian, skin, head and neck, lymphoma, esophageal cancer, and myeloma [175,187,188]. Its clinical use has been limited by poor solubility, absorption, and bioavailability [184,189]. Formulating curcumin into nanocarrier formulations can overcome these limitations and enhance therapeutic efficacy [190]. It is recommended to use USP-grade supplements to ensure product quality. Curcumin is generally safe with doses of up to 8-10 g/day, but diarrhea may occur if the daily dose exceeds 4 g [191]. Long-term use should be monitored for potential hepatotoxicity, and curcumin may interact with certain drugs, including anticoagulants and antibiotics [189,192].

3.6. Mebendazole

3.6.1. Mechanism

Mebendazole (MBZ), originally developed to treat parasitic worms, disrupts cellular microtubule formation in abnormal cancer cells, inhibiting tumor progression factors such as tubulin polymerization, angiogenesis, pro-survival pathways, matrix metalloproteinases, and drug resistance proteins [193,194]. It targets cancer stem cells, inhibits the Hedgehog pathway, activates apoptosis through Bcl-2 inactivation and caspase activation, and modulates the MAPK pathway [195,196]. MBZ interferes with cancer cells' glycolysis-dependent metabolism and inhibits mitochondrial oxidative phosphorylation. It crosses the blood-brain barrier, slowing the growth of gliomas, enhancing sensitivity to chemotherapy and radiotherapy [197]. MBZ can also sensitize cancer cells to conventional therapy, making it a potential adjuvant therapeutic in combination with traditional chemotherapy. When combined with low-dose chemotherapy, MBZ may also help

destroy tumor-associated macrophage cells, creating an unfavorable environment for cancer growth [198].

3.6.2. Clinical Evidence

Clinical studies on the use of benzimidazoles in cancer are limited to a few case reports [199,200] and a small case series [201]. Mebendazole is part of the multidrug cocktail used in the METRICS study [202]. The use of benzimidazoles, especially fenbendazole, has gained attention as a repurposed drug for cancer, following the reported experience of Joe Tippens, who achieved apparent remission from non-small-cell lung cancer with extensive metastatic disease after taking Fenbendazole and nanocurcumin [203]. However, further research is needed to confirm the efficacy and safety of these treatments.

3.6.3. Dosing

Mebendazole has demonstrated potential benefits in a wide range of cancers, including NSCLC, adrenocortical, colorectal, chemo-resistant melanoma, glioblastoma multiforme, colon, leukemia, osteosarcoma/soft tissue sarcoma, acute myeloid sarcoma, breast (ER+ invasive ductal), kidney, and ovarian carcinoma [193,194,198,204]. A suggested dose of Mebendazole is 100-200 mg/day, and it can be obtained at a more affordable cost from international compounding pharmacies in India (27c for a 100 mg tablet) [204].

3.7. Omega-3

Polyunsaturated fatty acids (PUFA), including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), have been extensively studied for their therapeutic effects against various human diseases, including cardiovascular and neurodegenerative diseases, and cancer [204]. These studies have shown the clinical usefulness and safety of these natural substances. Recent research has also demonstrated the potential of omega-3 FAs in improving outcomes in certain types of cancer, enhancing the efficacy and tolerability of chemotherapy, and improving quality of life indicators. Additionally, omega-3 FAs have been found to have a positive impact on cancer cachexia [204].

3.7.1. Mechanism

Omega-3 fatty acids (omega-3 FAs) have been proposed to exhibit four main antineoplastic activities: modulation of cyclooxygenase (COX) activity, alteration of membrane dynamics and cell surface receptor function, increased cellular oxidative stress, and the production of novel anti-inflammatory lipid mediators such as resolvins, protectins, and maresins [205,206]. Omega-3 FAs compete with omega-6 fatty acids (omega-6 FAs), particularly linoleic acid (LA), which is associated with a pro-inflammatory response. The balance between omega-3 and omega-6 FAs in the diet influences cancer progression, with omega-3 FAs promoting tumor cell self-destruction and limiting cancer expansion, while LA supports tumor cell survival. Omega-3 FAs affect cancer cell replication, cell cycle, and cell death, and have been shown to sensitize tumor cells to anticancer drugs [207]. They also modulate various signaling pathways, including NF-κB, Notch, Hedgehog, Wnt, and mitogen-activated protein kinases (MAPKs), and suppress the formation of pro-inflammatory prostaglandins, thereby influencing inflammatory response, cell growth, apoptosis, angiogenesis, and metastasis [208,209]. Omega-3 FAs have been found to induce apoptosis in breast cancer cells, block the activity of colon cancer stem cells, and exhibit potential anticancer effects [210].

3.7.2. Clinical Evidence

Clinical studies have shown promising results regarding the beneficial effects of omega-3 fatty acids (omega-3 FAs) in reducing the risk of developing cancer and improving outcomes in cancer patients. Prospective randomized controlled trials (RCTs) and cohort studies have demonstrated that intake of omega-3 FAs is associated with a reduced risk of breast cancer, colorectal neoplasia, and

prostate cancer-related death [211–214]. Additionally, supplementation with omega-3 FAs, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been shown to enhance the efficacy of chemotherapy in breast cancer and non-small cell lung cancer patients [215], improve survival in leukemia and lymphoma patients, and ameliorate cancer cachexia symptoms, leading to an improvement in quality of life and duration of survival [216–218]. These findings suggest that omega-3 FAs may serve as a potential complementary or adjuvant therapy in cancer management.

3.7.3. Dosing

Omega-3 fatty acids may be beneficial in breast cancer, colorectal cancer, leukemia, gastric cancer, pancreatic cancer, esophageal cancer, prostate cancer, lung cancer, and head and neck cancer when taken at a dose of 2-4 g daily, but caution should be exercised in patients on anticoagulants due to the potential risk of bleeding [214].

3.8. Berberine

3.8.1. Mechanisms

Berberine exhibits multiple anticancer mechanisms, including reducing cancer cell growth, preventing metastasis, inducing apoptosis, and enhancing the effects of other cancer treatments [219]. It achieves these effects through various pathways, such as upregulating miR-214-3p and downregulating SCT protein levels, inhibiting telomerase activity, deactivating MAPK signaling, and modulating AMPK-p53, PI3K/AKT/mTOR, and miR19a/TF/MAPK pathways [220–222]. Additionally, berberine influences the gut microbiota by increasing the Firmicutes/Bacteroidetes ratio and the relative abundance of specific bacteria. These actions contribute to its antibacterial properties, which further impact the tumor microenvironment [223]. Berberine's ability to enhance radiation sensitivity and the effects of anticancer drugs like cisplatin, 5-fluorouracil, doxorubicin, niraparib, and icotinib highlights its potential as an effective adjunct therapy for cancer treatment [224].

3.8.2. Clinical Evidence

While there is limited clinical data on the benefits of berberine, a randomized, double-blind study demonstrated that berberine in a dose of 300 mg twice daily significantly reduced the risk of recurrent colorectal adenomas following polypectomy [225].

3.8.3. Dosing

Berberine demonstrates anticancer effects in various cancer types, including breast, lung, gastric, liver, colorectal, ovarian, cervical, and prostate cancers [219]. A suggested daily dose of 1000-1500 mg is recommended, taken in divided doses throughout the day. Caution should be exercised when using berberine with certain medications, and its use should be avoided in combination with cyclosporine. Regular monitoring of blood glucose levels is important, especially when combined with other diabetes medications like metformin. Patients scheduled for surgery should inform their anesthesia team about berberine use, as it may need to be discontinued one week before the procedure [220].

3.9. Atorvastatin

3.9.1. Mechanism

Statins exert direct anticancer effects by inhibiting the cholesterol-producing enzyme HMG CoA, leading to reduced availability of cholesterol needed for cell membrane formation in rapidly proliferating tumors [226,227]. This limitation of cellular proliferation may hinder cancer growth and metastasis. Statins also modulate gene expression, promote cancer cell death through caspase

reactivation and upregulation of PPARγ, decrease cell surface glucose receptors, and deplete isoprenoids critical for controlling cancer cell growth and spread [228].

3.9.2. Clinical Evidence

Clinical studies have consistently shown that lipophilic statins, such as simvastatin, reduce the incidence and mortality of various cancers, including prostate, breast, colorectal, hepatocellular, and lung cancer [229,230]. Statin use has been associated with improved recurrence-free survival and reduced cancer-specific mortality in different cancer types [231,232].

3.9.3. Dosing

Studies have used 40mg as a dose [233].

3.10. Disulfiram

Disulfiram (DSF) inhibits aldehyde dehydrogenase, leading to acetaldehyde accumulation and unpleasant effects when alcohol is consumed, making it an anti-alcoholism drug; however, it has been repurposed as a potent cancer treatment, showing anti-tumor effects in preclinical studies and recent success in treating seven types of cancer in humans [234].

3.10.1. Mechanism

Disulfiram (DSF) exhibits multiple anticancer pathways, including inhibition of NF-kB signaling, proteasome activity, and ALDH, induction of ER stress and autophagy, and targeting of cancer stem cells [234]. DSF's cytotoxicity relies on copper (Cu), as DSF/Cu induces ROS production and inhibits NF-κB, activating pro-apoptotic pathways while downregulating anti-apoptotic pathways [235,236]. DSF also forms a complex with Cu, leading to DNA repair pathway downregulation [237]. Clinical trials have shown that DSF/Cu exerts antitumor effects in various cancers, such as head and neck squamous cell carcinoma, glioblastoma, and others, effectively inducing apoptosis in cancer cells and synergistically enhancing the efficacy of conventional chemotherapeutic drugs when administered in combination [238,239].

3.10.2. Clinical Evidence

In a double-blind trial with breast cancer patients, treatment with sodium ditiocarb (diethyldithiocarbamate) significantly improved overall survival (81% vs. 55%) and disease-free survival (76% vs. 55%) compared to the placebo group [240]. A phase IIb clinical trial showed that adding DSF to cisplatin and vinorelbine combination regimen prolonged survival in newly diagnosed non-small cell lung cancer patients, and DSF plus copper added to temozolomide appeared to prolong disease-free survival in glioblastoma patients [241,242].

3.10.3. Dosing

DSF may be beneficial in treating breast, lung, pancreatic, prostate, liver, and ovarian cancer, as well as acute myeloid leukemia, glioblastoma, and melanoma, with a particular role in glioblastoma patients [234,235]. The recommended dosing for DSF is generally 80 mg three times a day or 500 mg once daily, and copper should be added at a dose of 2 mg three times a day [241,243].

3.11. Cimetidine

3.11.1. Mechanism

Cimetidine, commonly used to treat ulcers and gastroesophageal reflux disease, exhibits multiple anti-tumor effects [193], including anti-proliferative actions by blocking H2 receptors and inducing apoptosis, immunomodulation by decreasing immunosuppressive cells and increasing

natural killer cell activity, anti-cell adhesion effects, and anti-angiogenic effects through the downregulation of angiogenesis-promoting factors [244,245].

3.11.2. Clinical Studies

The clinical benefits of cimetidine in cancer patients are not extensively studied, with most research focusing on post-operative colorectal surgery patients [193]. However, a Cochrane meta-analysis of five studies involving 421 patients prescribed cimetidine as an adjunct to curative surgical resection of colorectal cancers showed a significant improvement in overall survival (HR 0.53; 95% CI 0.32 to 0.87) [246]. In addition, two small series of patients with melanoma treated with a combination of cimetidine and interferon demonstrated positive clinical responses, including complete regression, partial regression, and prolonged disease stabilization [247]. Furthermore, a report from Denmark found that oral cimetidine, given at a dose of 400 mg twice daily for 2 years, was associated with increased median survival in gastric cancer patients compared to the placebo group (450 days vs. 316 days, p = 0.02), and higher relative survival rates were observed in the cimetidine-treated patients at 1 year (45% vs. 28%) [248].

3.11.3. Dosing

Cimetidine may be beneficial in patients with colorectal cancer, melanoma, gastric cancer, pancreatic cancer, ovarian carcinoma, prostate cancer, Kaposi's Sarcoma, salivary gland tumors, renal cell carcinoma, breast cancer, glioblastoma, and bladder cancer [193]. The standard dosing of cimetidine is 400 mg twice daily, and it is generally well-tolerated, with the most common side effect being gynecomastia [249].

3.12. Mistletoe

The European white-berry mistletoe (Viscum album L.) is commonly used in continental Europe as an adjunctive treatment for cancer patients, with mistletoe extracts administered subcutaneously or intravenously to reduce disease- and treatment-related symptoms and improve quality of life [250].

3.12.1. Mechanism

Mistletoe extracts exhibit various anticancer effects, including antitumor, apoptotic, anti-proliferative, and immunomodulatory activities. These effects are attributed to the presence of biologically active molecules such as lectins, flavonoids, viscotoxins, and polysaccharides, which mediate immunological activities, increase natural killer cytotoxicity, induce apoptosis, and interfere with protein synthesis in cancer cells [251–254]. Additionally, mistletoe has been found to enhance chemosensitivity in both cisplatin-sensitive and resistant ovarian cancer cells and may possess anti-angiogenic properties [255,256].

3.12.2. Clinical Evidence

Over 50 prospective studies, including more than 30 randomized controlled trials (RCTs), have investigated the role of mistletoe in cancer patients, showing benefits in terms of improved quality of life, performance index, symptom scales, and reduced adverse effects of chemotherapy [253]. A Cochrane review published in 2008, which included 21 studies, demonstrated the positive impact of mistletoe on various aspects of patient well-being [257]. Subsequent meta-analyses have further supported these findings, revealing that mistletoe extracts significantly improve global quality of life (SMD = 0.61, 95% CI 0.41-0.81, p < 0.00001) and may have a favorable effect on survival in cancer patients (HR = 0.81, 95% CI 0.69-0.95, P = 0.01) when used as an adjunct to conventional treatments [258]. A phase I trial of intravenous mistletoe extract in patients with advanced cancer showed a disease control rate of 23.8% and improved quality of life indicators. Mistletoe is commonly used by integrative oncologists to enhance quality of life, increase chemotherapy tolerability, and potentially contribute to better tumor control and survival [259].

3.12.3. Dosing

Mistletoe has shown benefits in improving the quality of life in patients with various types of cancers, including breast, bladder, gynecological (cervical, corpus uteri, and ovarian), colorectal, gastric, pancreatic, glioma, head and neck, lung, melanoma, and osteosarcoma. However, as mistletoe is administered parenterally (subcutaneously or intravenously), it requires supervision by an integrative oncologist as part of a personalized treatment protocol [260].*3.13. Ashwaganda*

3.13.1. Mechanism

Ashwagandha (Withania somnifera, WS), historically employed in the Mediterranean and Ayurvedic medicine, functions as both a functional food and medicinal plant with potential anticancer attributes [261]. Its active compounds, including withanolides and alkaloids, underpin its pharmacological effects [262]. Preclinical investigations highlight Ashwagandha's capacity to modulate mitochondrial function, facilitate apoptosis, and mitigate inflammation by targeting cytokines, nitric oxide, and reactive oxygen species [262–264]. It significantly contributes to apoptosis induction, suppression of cell proliferation and migration [262–264], and prompts cell cycle arrest and apoptosis in glioblastoma cells [265]. Notably, Ashwagandha's impact extends to molecular pathways like p53, insulin/IGF, STAT3, and Notch [266–268]. Its anti-inflammatory potential can significantly alter the tumor microenvironment, curtailing angiogenesis and metastasis [269]. An intriguing study proposes that combining Ashwagandha extract with intermittent fasting could emerge as a promising approach for breast cancer treatment, effectively curbing cell proliferation, inducing apoptosis, and ameliorating cisplatin-related toxicity [264].3.13.2. Clinical Evidence

In the context of cancer, Ashwagandha has been primarily investigated through experimental models, with limited clinical data on its efficacy. Biswell et al. conducted an open-label prospective nonrandomized trial involving breast cancer patients, administering a combination of chemotherapy and Ashwagandha or chemotherapy alone. The study group receiving Withania somnifera root extract exhibited significantly lower fatigue levels and improved quality of life scores. Although the 24-month overall survival rates were higher in the study group (72%) compared to the control group (56%), the difference was not statistically significant [270]. Apart from its potential in cancer therapy, Ashwagandha is recognized as a safe and effective adaptogen, supported by randomized controlled trials showcasing its stress reduction, cognitive enhancement, mood improvement, and sleep quality benefits [71–73]. A meta-analysis of 12 trials demonstrated its significant reduction of anxiety (p = .005) and stress levels (p = .005) compared to placebo [76]. Although Ashwagandha's impact on cancer outcomes remains unproven, its positive effects on stress, sleep, and quality of life suggest its potential as a recommended therapy for cancer patients.3.13.3. Dosing

Ashwagandha may be effective against cancers such as breast, colon, lung, prostate, glioblastoma multiforme, melanoma and blood cancers. [261,262] Ashwagandha can be used to treat cancer alone or in combination with other chemotherapeutic agents.

3.14. Phosphodiesterase 5 inhibitors

Selective phosphodiesterase 5 inhibitors, including sildenafil, tadalafil, and vardenafil, are widely used in the treatment of erectile dysfunction and pulmonary arterial hypertension. These drugs may also be effective cancer treatments.

3.14.1. Mechanism

PDE5 inhibitors, such as sildenafil and tadalafil, have shown promising anticancer effects in various types of cancers [244]. These inhibitors induce apoptosis and attenuate Wnt/β-catenin mediated transcription in breast tumor cells, affect HSP90 expression to inhibit cancer cell proliferation, and reduce the development and progression of hepatocellular carcinoma induced by aflatoxin B1 [271]. Additionally, PDE5 inhibitors alter epithelial homeostasis, reduce polyp formation, and promote autophagy, leading to enhanced cell death when combined with cytotoxic agents [272,273]. They have also been shown to interact in a greater than additive fashion with NSAIDs, platinum-based chemotherapeutic agents, and curcumin, increasing their efficacy in controlling colorectal and lung tumors [274,275]. Moreover, PDE5 inhibitors can inhibit colonic tumorigenesis by blocking the recruitment of MDSCs, reducing Tregs and cancer stem cells, and inducing PKA signaling to eliminate cancer stem cells [273,276,277].

3.14.2. Clinical Evidence

Several studies have demonstrated the potential anticancer benefits of PDE5 inhibitors. A large study involving 192,661 patients showed that PDE5 inhibitor use was associated with a reduced risk of developing colon cancer, and in men with benign colorectal neoplasms, it was associated with a lower risk of colorectal cancer [278]. Clinical trials in patients with head and neck squamous cell carcinoma revealed that tadalafil could enhance immune responsiveness and tumor-specific immunity by reducing MDSCs, regulatory T cells, and improving T-cell function [279,280]. In patients with colorectal cancer and prostate cancer, post-diagnostic use of PDE5 inhibitors was associated with a decreased risk of cancer-specific mortality, metastasis, and biochemical recurrence [281,282].

3.14.3. Dosing

Phosphodiesterase 5 inhibitors, such as sildenafil and tadalafil, may be beneficial for the treatment of prostate, breast, hepatocellular, colorectal, lung, head and neck, glioblastoma, and leukemias [273]. The recommended dosing includes sildenafil 20 mg daily or tadalafil 5 mg daily, but caution is advised in patients receiving nitrates or with a history of non-arteritic anterior ischemic optic neuropathy due to potential serious cardiovascular side effects.

3.15. Itraconazole

Itraconazole, a well-established antifungal agent inhibiting lanosterol 14α-demethylase, has demonstrated potential as an anticancer agent through mechanisms unrelated to its antifungal effects.

3.15.1. Mechanism

Its anticancer activity involves the reversal of P-glycoprotein-mediated chemoresistance, modulation of Hedgehog, mTOR, and Wnt/β-catenin pathways, angiogenesis and lymphangiogenesis inhibition, and potential interference with cancer-stromal interactions [283]. Mechanistically, it impedes P-glycoprotein, disrupts abnormal Hedgehog and Wnt/β-catenin signaling, hinders angiogenesis, and triggers autophagocytosis [283–293]. Itraconazole further suppresses the PI3K/AKT/mTOR/S6K pathway, affecting cancer cell growth and proliferation [284,288,294], and inhibits HER2/Akt signaling by reducing HER2 phosphorylation [295]. Its induction of apoptosis is attributed to ROS pathway activation and death receptor pathway stimulation [288]. The drug curbs angiogenesis by obstructing VEGF/VEGFR2 interaction and endothelial cell cycle progression [291,294]. Itraconazole's multifaceted modes of action suggest its potential as an innovative anticancer therapy beyond its antifungal properties [283–294].

3.15.2. Clinical Evidence

Itraconazole demonstrates potential anticancer efficacy either as a single agent or in combination therapy based on preclinical and clinical data [284–287,289,290,292,293,296–302]. Notably, a phase II clinical study with lung cancer patients showed that itraconazole combined with conventional chemotherapy (pemetrexed) significantly improved progression-free and overall survival, attributed to its antiangiogenic effects [284]. Retrospective studies supported the survival advantage of itraconazole treatment in refractory malignancies, including ovarian clear cell, triple-negative breast, pancreatic, and biliary tract cancer, compared to previous reports [296,300,301,303]. Clinical trials involving progressive pancreatic cancer and metastatic castration-resistant prostate cancer indicated positive outcomes with itraconazole-based combination treatments [289,300]. Moreover, itraconazole displayed concentration-dependent anticancer effects in non-small cell lung cancer patients [302]. The drug's potential adjuvant role was identified in various cancers, encompassing prostate, pancreatic, lung, breast, acute myeloid leukemia, basal cell carcinoma, medulloblastoma, hepatocellular carcinoma, esophageal, and gastric cancer [283,284,286,288,290,293,295,297,298,300].

3.15.3. Dosing

Itraconazole in a dose of 400-600 mg /day is recommended. Itraconazole is a conventional antifungal drug that has received FDA approval and has an excellent safety record. [284] However, several studies have suggested that itraconazole has some contraindications, particularly when it comes to interactions with other cancer medications including rituximab or statins [304,305].

4.1. Potential Adjunctive Therapies

4.1.1. Tumour Treating Fields

Tumor treating fields (TTF) are non-invasive alternating electric fields administered via the Optune® system, utilizing transdermally transmitted 100-400 kHz AC electric fields through orthogonal transducer arrays to disrupt mitosis [306,307]. This disrupts the mitotic spindle assembly checkpoint and leads to cell-cycle arrest, cell death, or senescence, while also promoting autophagy and immunological effects such as STING pathway activation and enhanced dendritic cell and macrophage activity [307]. Although extensively studied in glioblastoma multiforme (GBM), TTF is being evaluated in NSCLC, pancreatic, and ovarian cancer [307]. In GBM, TTF in combination with maintenance temozolomide demonstrated significantly improved progression-free survival and overall survival [308] 856). The National Comprehensive Cancer Network (NCCN) recommends TTF combined with temozolomide for both newly diagnosed and recurrent glioblastoma patients, suggesting it as an adjunctive treatment option [309,310]. Compliance is crucial as TTF's therapeutic effects are limited to actively dividing cancer cells during its application [306].

4.1.2. Photodynamic Therapy

Photodynamic therapy (PDT) involves tissue destruction through visible light when combined with a photosensitizer and oxygen [311]. When exposed to light, sensitizer molecules transition to high-energy states, interacting with oxygen to produce reactive oxygen species that induce cell death through apoptosis, necrosis, and autophagy [312]. Historical use of light for therapeutic purposes dates back thousands of years, particularly combined with reactive chemicals to treat conditions like vitiligo, psoriasis, and skin cancer. Sunlight, encompassing ultraviolet-B (UVB) and near infrared (NIR) radiation, offers significant health benefits including vitamin D synthesis and mitochondrial melatonin production [313,314]. However, modern lifestyles lead to deficient NIR exposure [314]. NIR-A radiation, with deep tissue penetration, demonstrated efficacy during the 1918 influenza pandemic, and recent studies link sun avoidance to higher all-cause mortality rates [315,316]. PDT, widely used by dermatologists for actinic keratoses and nonmelanoma skin cancers, holds potential for broader applications, including solid tumors, achieved through preferentially accumulated sensitizers activated by light [311,312]. Topical photosensitizers such as 5-aminolevulinic acid or

methyl aminolevulinate are commonly employed for cutaneous indications, while visceral tumors require agents like porfimer sodium [311,317]. PDT's efficacy in experimental cancer cell destruction is proven, yet clinical evidence supporting its benefits in non-cutaneous malignancies is limited [317] [318–320]. PDT's role in non-cutaneous cancer and photobiomodulation necessitates further assessment. To enhance mitochondrial function, regular midday sun exposure is recommended (at least 3 times a week), ideally through brisk walks [317].

4.1.3. Hyperbaric Oxygen

Hypoxia is a critical hallmark of solid tumors, associated with enhanced cell survival, angiogenesis, glycolytic metabolism, and metastasis [321]. Hyperbaric oxygen treatment (HBOT) has been employed for centuries to address hypoxia-related disorders, enhancing plasma oxygen levels and tissue delivery of oxygen [321]. HBOT induces hyperoxia and elevated reactive oxygen species (ROS), overwhelming cancer cell defenses and triggering cell death [322,323]. This process involves intricate signaling through protein kinases and receptors such as RAGE, CXCR2, TLR3, and TLR4 [324]. Despite limited direct impact on cancer growth, HBOT may synergize with other treatments; for instance, a ketogenic diet combined with HBOT exhibited significant anticancer effects [12]. Hypoxia contributes to chemoresistance, and HBOT as an adjuvant has demonstrated enhanced effects both in vitro and in vivo, although certain chemotherapeutic agents might interact negatively [321]. Radiotherapy combined with HBOT serves therapeutic and radiosensitizing purposes, particularly for head and neck tumors [321]. A recent Cochrane review cautioned that while HBOT might improve local tumor control and mortality for head and neck tumors, its benefits should be interpreted cautiously due to unusual fractionation schemes [325]. While HBOT holds promise as an anticancer intervention, particularly in combination with other modalities, clinical data supporting its efficacy remain limited [321].

Table 1.

Intervention	Mechanism	Evidence	Toxicity	Dosage per day
METABOLIC AND LIFESTYLE INTERVENTIONS FOR CANCER TREATMENT				
Glucose management and ketogenic diet	Restricting carbohydrates prevents their conversion to glucose, impacting the body's metabolic and energy functions. [326,327]	Prevent the high glucose spikes that fuel cancer [328]	Some possible complications for select populations	Ketogenic diet (<50g carbohydrates per day) in 8 hour eating window
Exercise	Multiple mechanisms[329]	Improved survival outcomes [330–335]	Possible overuse	30 minutes per day
Stress Reduction	Multiple mechanisms [336]	Stress associated with higher cancer risk and poorer survival outcome[64,337,338]	No known fatalities	Daily mindfulness
Sleep	Multiple mechanisms [339]	Healthy sleep is essential for metabolic regulation [77]		8 hours per night
TIER ONE REPURPOSED DRUGS – STRONG RECOMMENDATION				
Vitamin D	Inhibiting Angiogenesis [340] Stimulating adherence of cells [341] Enhancing intercellular communication [342,343]	Statistically significant reductions in cancer mortality [344]. More significant reductions in cancer risk for those with	Serum 25-hydroxyvitamin D higher than 150ng/mL are hallmark of vitamin D toxicity due to	20,000 to 50,000 IU daily

		normal BMI (<25) [345]	hypercalcemia [346]	
Melatonin	Multiple mechanisms [129,130]	Low levels of melatonin increase breast cancer risk [347] Increases cancer remission and survival rates [348]	Oral LD50 in mice: 1.25g/kg [349]	Start at 1 mg and increase to 20-30 mg at night (extended/slow release)
Green tea	Inhibition of mitochondrial glutamate dehydrogenase by epigallocatechin gallate [350]. Suppression of cancer stem cells [351,352]	Green tea drinkers have lower risk of breast cancer[353]. Lowers risk of multiple cancers [354]. Lower risk of non-Hodgkin's Lymphoma [355] Lower incidence and higher survivability[357] of colorectal cancer [358].	EGCG: Mouse oral LD50 2.2g/kg	500-1,000 mg daily
Metformin	Blood glucose stabilization [160] Inhibition of AMPK/mTOR pathway [356]	Survival benefit for people with prostate cancer and concurrent diabetes [359]. Lower risk of cancer in people with type 2 diabetes [360].	Oral LD50 in rats: 1g/kg [361]	1,000 mg twice daily
Curcumin	Inducing Apoptosis selectively in cancer cells [362]. Multiple mechanisms [175]	Significant heterogeneity in trials depending on curcumin formulation [363]	Oral LD50 in rats: >5g/kg [364]	600 mg daily or as per manufacturer's suggested dosing
Mebendazole	Inhibits cancer-associated signaling pathways [365]	Case reports show improvement [366,367]. Case series with related drug fenbendazole show promise in treating genitourinary malignancies [368]	Oral LD50 in mice: >1280 mg/kg [369]	100-200 mg daily
Omega 3	modulation of cyclooxygenase activity alteration of membrane and cell surface receptor function[206,370]	Protective against breast cancer in Asian patients [371] Lower levels of Omega 3 relative to Omega 6 associated	N/A Possible heavy metal toxicity from extreme overuse [373]	2-4 g/day

Berberine	Multiple mechanisms [374,375]	with higher cancer mortality [372] Can reduce risk of colorectal cancer [376]. Reduces tumor volume in animal studies [377]	Mouse oral LD50: 329 mg/kg [378]	A daily dose of 1000-1500 mg or 500-600 mg two or three times daily
Atorvastatin	Multiple mechanisms [379,380]	Improvement [230,381–387]	oral LD50 in mice: >5g/kg [388]	40 mg 2x/day‡.
Simvastatin	Multiple mechanisms [380,389]	Case series shows simvastatin may increase radiosensitivity of cancer cells [390] Statin use in US population associated with lower cancer mortality[383]	Oral mouse LD50: 3g/kg [391]	
Disulfiram	Multiple mechanisms [235,392]	Reduce tumor activity in breast cancer [393]	Oral rat LD50: 9g/kg [394]	80mg 3x daily or 500 mg once daily
Cimetidine	Interferes with tumor cell adhesion, angiogenesis and proliferation [395]	Improvement in gastric cancer survivability [396] Improvement in survivability of surgical treatment of colorectal cancers [397]	Oral rat LD50: 5g/kg [398]	400-800 mg twice daily
Mistletoe	protein synthesis interference, cell-cycle inhibition, and induced apoptosis [251,256]	evidence of the efficacy of mistletoe extracts in gastric and female genital cancer [399]	Peritoneal rat LD50: 1-3g/kg for stem aqueous extract [400]	given subcutaneously by an integrative oncologist, Typical dose 600mg 3x/week [401]
Sildenafil	Enhances drug sensitivity [402]	N/A	Increase in adverse events above 200mg [403]	20 mg daily
TIER TWO REPURPOSED DRUGS – WEAK RECOMMENDATION				
Low dose naltrexone (LDN)	Interfering with cell signalling [404] Immunomodulation [405] Anti-inflammatory [406]	Improvement in tumors including non-small cell lung cancer (NSCLC) [407] suppress human ovarian cancer [408]	Oral mouse LD50: 1g/kg [409]	1-4.5mg daily
Doxycycline	Inhibiting anti-apoptotic and angiogenic proteins [410]	N/A	Oral rat LD50: 2g/kg [411]	100 mg daily (for cycles of 2 weeks – use sparingly)

Wheatgrass	Inhibition of metastasis and angiogenesis, Induction of apoptosis [412]	N/A	No observed toxicity at >2g/kg oral dose in mice for 14 days [413]	9g fermented wheat germ extract daily

Table 2.

Intervention	Mechanism	Evidence	Toxicity	Dosage per day
TIER THREE REPURPOSED DRUGS -EQUIVOCAL EVIDENCE				
Resveratrol	Induction of apoptosis [414] Inhibition of cancer stem cells [415]	In vivo evidence for anti-cancer effect, high heterogeneity in humans [416]	Predicted Oral Rat LD50, 48h: 870 mg/kg/day [417]	500mg, 2x daily
Aspirin	Multiple mechanisms [418]	Protective effect on esophageal cancer [419], and other cancers [420]	Oral mouse LD50: 250mg/kg [421]	325 mg daily
Diclofenac	Multiple, mechanisms [422]	Improved disease free survival in breast cancer surgery[423]. Normalizes skin lesions when applied topically [424]. Case studies shows improvement [425–429]	Mouse oral LD50: 170mg/kg [430]	Diclofenac 75-100 mg daily
Nigella Sativa (thymoquinone)	p53, NF-κB, PPARγ, STAT3, MAPK, and PI3K/AKT signaling pathways [431]	improved treatment outcome in acute lymphoblastic leukemia in children[432]	Oral mouse LD50: 29mL/kg [433]	400-500mg encapsulated oil twice daily, avoid during pregnancy
Reishi	Immunomodulation [434,435]	50% increased effectiveness of cancer chemotherapy [436]	Oral mouse LD50: >10g/kg[437]	6-12g of Reishi extract per day
Ivermectin	Regulates multiple signaling pathways[438,439]	Case series showed improvement in patient symptoms when combined with dichloroacetate [440]	Mouse oral LD50: >27mg/kg [441]	12-60mg 2x/week
Dipyridamole	Increases tumor chemosensitivity [442]	Increases efficacy of other anti-cancer agents [443–445]	Rat oral LD50: 8g/kg [446]	100 mg twice daily
Intravenous Vitamin C	Targeted killing (through intracellular generation of H_2O_2) of cancer cells [447]	Improved life quality in cancer patients [448], lowered inflammation [449]	Rat intravenous LD50 >4g/kg [450]	50-75 g IV as per protocol
Dichloroacetate	Inhibits dehydrogenase kinase to inhibit metabolic reprogramming by cancer cells [451]	Greater treatment response, but no impact on survival [452]	Rat oral LD50 5 g/kg [453]	500 mg two/three times daily
Cannabinoids	induction of cancer cell death by apoptosis and	Useful in treating refractory chemotherapy	THC	Daily doses range from 10 to 800mg CBD and

	the inhibition of cancer cell proliferation [454]	induced nausea and vomiting Case studies show possible benefit [455]	Mouse oral LD50: 500mg/kg[456] CBD Mouse oral LD50: >100mg/kg [457]	5-8mg THC [458]
Fenofibrate	Stimulation of peroxisome proliferator activated receptor α (PPARα) [459]	No clinical data	Mouse oral LD50: 1.6g/kg [460]	N/A
Pao Pereira	Inhibition of NF kappa B Signaling [461]	Effectiveness in prostate cancer [462]	Limited information	N/A
Potential Adjunctive Therapies				
Tumor Treating Fields	Multiple mechanisms, induction of apoptosis and autophagy [463]	N/A	N/A	
Photodynamic therapy	Direct cellular damage, vascular shutdown and activation of immune response against tumor cells [464]	N/A	N/A	
Hyperbaric Oxygen	Elevates levels of reactive oxygen species to signal cell death in cancer cells[465]	N/A	Possible adverse reactions[466]	
TIER FOUR REPURPOSED DRUGS – RECOMMEND AGAINST				
Shark cartilage	inhibition of angiogenesis. sphyrnastatin 1 and 2 have antiangiogenic activity and to inhibit neovascularization [467]	N/A	Gastric adverse events[468], potential neurotoxicity [469]	
Laetrile (amygdalin)	Multiple mechanisms [470]	produced few clinical side effects [471]	Rat oral LD50: 0.9g [472]	
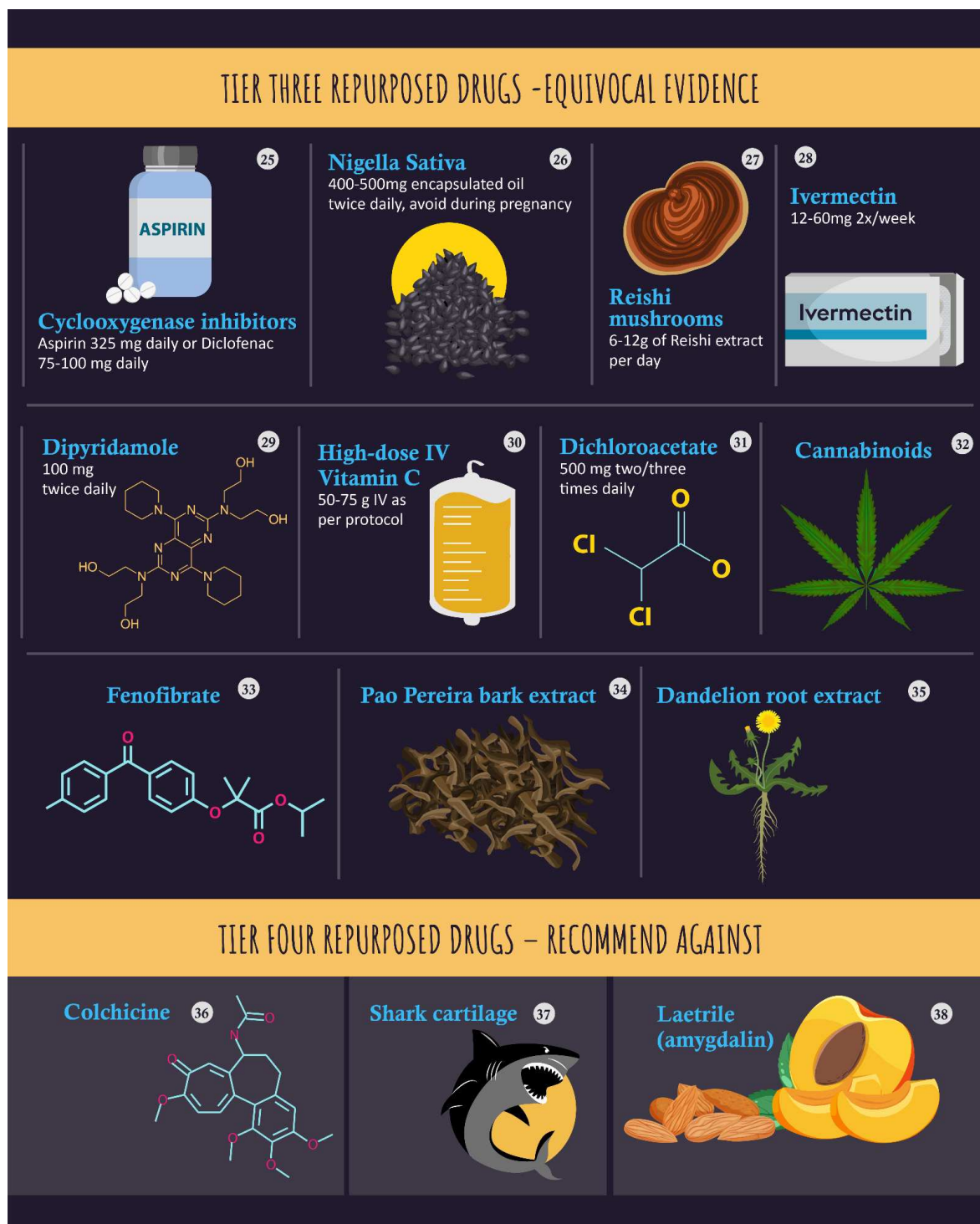
Figure 2.

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References

1. Devic, S. Warburg effect-a consequence or the cause of carcinogenesis? *J Cancer* **2016**, *7*, 817.
2. Koppenol, W.H.; Bounds, P.L.; Dang, C.V. Otto Warburg's contributions to current concepts of cancer metabolism. *Nat Rev Cancer* **2011**, *11*, 325-337, doi:10.1038/nrc3038.
3. Pauwels, E.K.J.; Ribeiro, M.J.; Stoot, J.H.M.B.; McCready, V.R.; Bourguignon, M.; Mazière, B. FDG Accumulation and Tumor Biology. *Nuclear Medicine and Biology* **1998**, *25*, 317-322, doi:10.1016/S0969-8051(97)00226-6.
4. Bar-Shalom, R.; Valdivia, A.Y.; Blaufox, M.D. PET imaging in oncology. *Seminars in Nuclear Medicine* **2000**, *30*, 150-185, doi:https://doi.org/10.1053/snuc.2000.7439.
5. Smallbone, K.; Gatenby, R.A.; Gillies, R.J.; Maini, P.K.; Gavaghan, D.J. Metabolic changes during carcinogenesis: potential impact on invasiveness. *J Theor Biol* **2007**, *244*, 703-713, doi:10.1016/j.jtbi.2006.09.010.
6. Pugachev, A.; Ruan, S.; Carlin, S.; Larson, S.M.; Campa, J.; Ling, C.C.; Humm, J.L. Dependence of FDG uptake on tumor microenvironment. *Int J Radiat Oncol Biol Phys* **2005**, *62*, 545-553, doi:10.1016/j.ijrobp.2005.02.009.
7. Gatenby, R.A.; Gillies, R.J. Why do cancers have high aerobic glycolysis? *Nat Rev Cancer* **2004**, *4*, 891-899, doi:10.1038/nrc1478.
8. Seyfried, T. Mitochondria: the ultimate tumor suppressor. *Cancer As a Metabolic Disease: On the Origin, Management, and Prevention of Cancer* **2012**, 195-205.
9. Nebeling, L.C.; Miraldi, F.; Shurin, S.B.; Lerner, E. Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. *Journal of the American College of Nutrition* **1995**, *14*, 202-208, doi:10.1080/07315724.1995.10718495.
10. Schmidt, M.; Pfetzer, N.; Schwab, M.; Strauss, I.; Kämmerer, U. Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial. *Nutrition & Metabolism* **2011**, *8*, 54, doi:10.1186/1743-7075-8-54.
11. Tinguely, D.; Gross, J.; Kosinski, C. Efficacy of Ketogenic Diets on Type 2 Diabetes: a Systematic Review. *Curr Diab Rep* **2021**, *21*, 32, doi:10.1007/s11892-021-01399-z.
12. Poff, A.M.; Ari, C.; Seyfried, T.N.; D'Agostino, D.P. The ketogenic diet and hyperbaric oxygen therapy prolong survival in mice with systemic metastatic cancer. *PloS one* **2013**, *8*, e65522.
13. Afghahi, A.; Sledge, G.W.J. Targeted Therapy for Cancer in the Genomic Era. *The Cancer Journal* **2015**, *21*, 294-298, doi:10.1097/ppo.0000000000000135.
14. Schwartz, L.; T. Supuran, C.; O. Alfarouk, K. The Warburg Effect and the Hallmarks of Cancer. *Anti-Cancer Agents in Medicinal Chemistry- Anti-Cancer Agents)* **2017**, *17*, 164-170.
15. Klement, R.J.; Kämmerer, U. Is there a role for carbohydrate restriction in the treatment and prevention of cancer? *Nutrition & Metabolism* **2011**, *8*, 75, doi:10.1186/1743-7075-8-75.
16. Feng, S.; Wang, H.; Liu, J.; Aa, J.; Zhou, F.; Wang, G. Multi-dimensional roles of ketone bodies in cancer biology: Opportunities for cancer therapy. *Pharmacological Research* **2019**, *150*, 104500, doi:10.1016/j.phrs.2019.104500.
17. Ferrere, G.; Alou, M.T.; Liu, P.; Goubet, A.-G.; Fidelle, M.; Kepp, O.; Durand, S.; Iebba, V.; Fluckiger, A.; Daillère, R. Ketogenic diet and ketone bodies enhance the anticancer effects of PD-1 blockade. *JCI insight* **2021**, *6*.
18. Davies, P.; Demetrius, L.A.; Tuszynski, J.A. Implications of quantum metabolism and natural selection for the origin of cancer cells and tumor progression. *AIP Advances* **2012**, *2*, doi:10.1063/1.3697850.
19. T, E.; L, X.; RJ, G.; RA, G. Separation of metabolic supply and demand: aerobic glycolysis as a normal physiological response to fluctuating energetic demands in the membrane. *Cancer & metabolism* **2014**, *2*, doi:10.1186/2049-3002-2-7.
20. Wittig, R.; Coy, J.F. The Role of Glucose Metabolism and Glucose-Associated Signalling in Cancer. *https://doi.org/10.1177/1177391X0700100006* **2007**, 10.1177_1177391X0700100006, doi:10.1177_1177391X0700100006.
21. Heiden, M.G.V.; Cantley, L.C.; Thompson, C.B. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. **2009**, 10.1126/science.1160809, doi:10.1126/science.1160809.
22. Fiolet, T.; Srour, B.; Sellem, L.; Kesse-Guyot, E.; Allès, B.; Méjean, C.; Deschasaux, M.; Fassier, P.; Latino-Martel, P.; Beslay, M. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *bmj* **2018**, *360*.
23. Barclay, A.W.; Augustin, L.S.A.; Brighenti, F.; Delport, E.; Henry, C.J.; Sievenpiper, J.L.; Usic, K.; Yuexin, Y.; Zurbau, A.; Wolever, T.M.S. Dietary glycaemic index labelling: A global perspective. *Nutrients* **2021**, *13*, 3244.
24. Matthan, N.R.; Ausman, L.M.; Meng, H.; Tighiouart, H.; Lichtenstein, A.H. Estimating the reliability of glycemic index values and potential sources of methodological and biological variability. *The American journal of clinical nutrition* **2016**, *104*, 1004-1013.

25. Meidenbauer, J.J.; Mukherjee, P.; Seyfried, T.N. The glucose ketone index calculator: a simple tool to monitor therapeutic efficacy for metabolic management of brain cancer. *Nutrition & metabolism* **2015**, *12*, 1-7.

26. Inchauspé, J. *Glucose Revolution: The life-changing power of balancing your blood sugar*; Simon and Schuster: 2022.

27. Maruvada, P.; Leone, V.; Kaplan, L.M.; Chang, E.B. The human microbiome and obesity: moving beyond associations. *Cell host & microbe* **2017**, *22*, 589-599.

28. Nieuwdorp, M.; Gilijamse, P.W.; Pai, N.; Kaplan, L.M. Role of the microbiome in energy regulation and metabolism. *Gastroenterology* **2014**, *146*, 1525-1533.

29. Pedersen, H.K.; Gudmundsdottir, V.; Nielsen, H.B.; Hyotylainen, T.; Nielsen, T.; Jensen, B.A.H.; Forslund, K.; Hildebrand, F.; Prifti, E.; Falony, G. Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature* **2016**, *535*, 376-381.

30. Rebello, C.J.; Burton, J.; Heiman, M.; Greenway, F.L. Gastrointestinal microbiome modulator improves glucose tolerance in overweight and obese subjects: A randomized controlled pilot trial. *Journal of Diabetes and its Complications* **2015**, *29*, 1272-1276.

31. Sung, M.M.; Kim, T.T.; Denou, E.; Soltys, C.-L.M.; Hamza, S.M.; Byrne, N.J.; Masson, G.; Park, H.; Wishart, D.S.; Madsen, K.L. Improved glucose homeostasis in obese mice treated with resveratrol is associated with alterations in the gut microbiome. *Diabetes* **2017**, *66*, 418-425.

32. Vallianou, N.G.; Stratigou, T.; Tsagarakis, S. Microbiome and diabetes: where are we now? *Diabetes research and clinical practice* **2018**, *146*, 111-118.

33. Yu, E.W.; Gao, L.; Stastka, P.; Cheney, M.C.; Mahabamunuge, J.; Torres Soto, M.; Ford, C.B.; Bryant, J.A.; Henn, M.R.; Hohmann, E.L. Fecal microbiota transplantation for the improvement of metabolism in obesity: The FMT-TRIM double-blind placebo-controlled pilot trial. *PLoS medicine* **2020**, *17*, e1003051.

34. Astrup, A.; Teicholz, N.; Magkos, F.; Bier, D.M.; Brenna, J.T.; King, J.C.; Mente, A.; Ordovas, J.M.; Volek, J.S.; Yusuf, S. Dietary saturated fats and health: are the US guidelines evidence-based? *Nutrients* **2021**, *13*, 3305.

35. Ramsden, C.E.; Zamora, D.; Leelarthaepin, B.; Majchrzak-Hong, S.F.; Faurot, K.R.; Suchindran, C.M.; Ringel, A.; Davis, J.M.; Hibbeln, J.R. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *Bmj* **2013**, *346*, e8707.

36. Teicholz, N. *The big fat surprise: why butter, meat and cheese belong in a healthy diet*; Simon and Schuster: 2014.

37. Teicholz, N. A short history of saturated fat: the making and unmaking of a scientific consensus. *Current Opinion in Endocrinology, Diabetes, and Obesity* **2023**, *30*, 65.

38. Weber, D.D.; Aminazdeh-Gohari, S.; Kofler, B. Ketogenic diet in cancer therapy. *Aging (Albany NY)* **2018**, *10*, 164-165, doi:10.18632/aging.101382.

39. Augustus, E.; Granderson, I.; Rocke, K.D. The Impact of a Ketogenic Dietary Intervention on the Quality of Life of Stage II and III Cancer Patients: A Randomized Controlled Trial in the Caribbean. *Nutrition and Cancer* **2021**, *73*, 1590-1600, doi:10.1080/01635581.2020.1803930.

40. Kirkpatrick, C.F.; Willard, K.-E.; Maki, K.C. Keto is Trending: Implications for Body Weight and Lipid Management. *Current Cardiology Reports* **2022**, *24*, 1093-1100, doi:doi:10.1007/s11886-022-01731-3.

41. EH, K.; BA, Z.-K.; PE, A.; KR, B.-G.; AG, C.B.; R, B.; JR, B.; RH, C.; J, H.C.; MG, D., et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia* **2009**, *50*, doi:10.1111/j.1528-1167.2008.01765.x.

42. Cervenka, M.C.; Wood, S.; Bagary, M.; Balabanov, A.; Bercovici, E.; Brown, M.-G.; Devinsky, O.; Lorenzo, C.D.; Doherty, C.P.; Felton, E., et al. International Recommendations for the Management of Adults Treated With Ketogenic Diet Therapies. **2021**, 10.1212/CPJ.0000000000001007, doi:10.1212/CPJ.0000000000001007.

43. K, R.; SL, S. Practice Paper of the Academy of Nutrition and Dietetics: Classic and Modified Ketogenic Diets for Treatment of Epilepsy. *Journal of the Academy of Nutrition and Dietetics* **2017**, *117*, doi:10.1016/j.jand.2017.06.006.

44. Martenz, D.M.; Zupec-Kania, B. *The Modified Keto Cookbook: Quick, Convenient Great-tasting Recipes for Following a Low-ratio Ketogenic Diet*; Springer Publishing Company: 2015.

45. Lightstone, L.; Shinnar, S.; Callahan, C.M.; O'Dell, C. Reasons for failure of the ketogenic diet. *Journal of Neuroscience Nursing* **2001**, *33*, 292.

46. Landry, M.J.; Crimarco, A.; Perelman, D.; Durand, L.R.; Petlura, C.; Aronica, L.; Robinson, J.L.; Kim, S.H.; Gardner, C.D. Adherence to ketogenic and mediterranean study diets in a crossover trial: The keto–med randomized trial. *Nutrients* **2021**, *13*, 967.

47. Shai, I.; Schwarzfuchs, D.; Henkin, Y.; Shahar, D.R.; Witkow, S.; Greenberg, I.; Golan, R.; Fraser, D.; Bolotin, A.; Vardi, H. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *New England Journal of Medicine* **2008**, *359*, 229-241.

48. Mohorko, N.; Černelič-Bizjak, M.; Poklar-Vatovec, T.; Grom, G.; Kenig, S.; Petelin, A.; Jenko-Pražnikar, Z. Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults. *Nutrition research* **2019**, *62*, 64-77.

49. Hamer, J.; Warner, E. Lifestyle modifications for patients with breast cancer to improve prognosis and optimize overall health. *Cmaj* **2017**, *189*, E268-E274.

50. Montagnese, C.; Porciello, G.; Vitale, S.; Palumbo, E.; Crispo, A.; Grimaldi, M.; Calabrese, I.; Pica, R.; Prete, M.; Falzone, L. Quality of life in women diagnosed with breast cancer after a 12-month treatment of lifestyle modifications. *Nutrients* **2020**, *13*, 136.

51. Berrino, F.; Villarini, A.; Traina, A.; Bonanni, B.; Panico, S.; Mano, M.P.; Mercandino, A.; Galasso, R.; Barbero, M.; Simeoni, M. Metabolic syndrome and breast cancer prognosis. *Breast cancer research and treatment* **2014**, *147*, 159-165.

52. Ligibel, J.A.; Bohlke, K.; May, A.M.; Clinton, S.K.; Demark-Wahnefried, W.; Gilchrist, S.C.; Irwin, M.L.; Late, M.; Mansfield, S.; Marshall, T.F. Exercise, diet, and weight management during cancer treatment: ASCO guideline. *Journal of Clinical Oncology* **2022**, *40*, 2491-2507.

53. Oberoi, S.; Robinson, P.D.; Cataudella, D.; Culos-Reed, S.N.; Davis, H.; Duong, N.; Gibson, F.; Götte, M.; Hinds, P.; Nijhof, S.L. Physical activity reduces fatigue in patients with cancer and hematopoietic stem cell transplant recipients: a systematic review and meta-analysis of randomized trials. *Critical reviews in oncology/hematology* **2018**, *122*, 52-59.

54. Garcia, D.O.; Thomson, C.A. Physical activity and cancer survivorship. *Nutrition in Clinical Practice* **2014**, *29*, 768-779.

55. Scott, J.M.; Zabor, E.C.; Schwitzer, E.; Koelwyn, G.J.; Adams, S.C.; Nilsen, T.S.; Moskowitz, C.S.; Matsoukas, K.; Iyengar, N.M.; Dang, C.T. Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. *Journal of Clinical Oncology* **2018**, *36*, 2297.

56. Aydin, M.; Kose, E.; Odabas, I.; Bingul, B.M.; Demirci, D.; Aydin, Z. The effect of exercise on life quality and depression levels of breast cancer patients. *Asian Pacific Journal of Cancer Prevention: APJCP* **2021**, *22*, 725.

57. Kenfield, S.A.; Stampfer, M.J.; Giovannucci, E.; Chan, J.M. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *Journal of Clinical Oncology* **2011**, *29*, 726.

58. Lopez, P.; Galvão, D.A.; Taaffe, D.R.; Newton, R.U.; Souza, G.; Trajano, G.S.; Pinto, R.S. Resistance training in breast cancer patients undergoing primary treatment: a systematic review and meta-regression of exercise dosage. *Breast Cancer* **2021**, *28*, 16-24.

59. An, K.Y.; Morielli, A.R.; Kang, D.W.; Friedenreich, C.M.; McKenzie, D.C.; Gelmon, K.; Mackey, J.R.; Reid, R.D.; Courneya, K.S. Effects of exercise dose and type during breast cancer chemotherapy on longer-term patient-reported outcomes and health-related fitness: A randomized controlled trial. *International journal of cancer* **2020**, *146*, 150-160.

60. Beasley, J.M.; Kwan, M.L.; Chen, W.Y.; Weltzien, E.K.; Kroenke, C.H.; Lu, W.; Nechuta, S.J.; Cadmus-Bertram, L.; Patterson, R.E.; Sternfeld, B. Meeting the physical activity guidelines and survival after breast cancer: findings from the after breast cancer pooling project. *Breast cancer research and treatment* **2012**, *131*, 637-643.

61. Chen, X.; Lu, W.; Zheng, W.; Gu, K.; Matthews, C.E.; Chen, Z.; Zheng, Y.; Shu, X.O. Exercise after diagnosis of breast cancer in association with survival. *Cancer Prevention Research* **2011**, *4*, 1409-1418.

62. Kelly, P.; Williamson, C.; Niven, A.G.; Hunter, R.; Mutrie, N.; Richards, J. Walking on sunshine: scoping review of the evidence for walking and mental health. *British journal of sports medicine* **2018**, *52*, 800-806.

63. Lee, I.M.; Buchner, D.M. The importance of walking to public health. *Medicine & Science in Sports & Exercise* **2008**, *40*, S512-S518.

64. Chida, Y.; Hamer, M.; Wardle, J.; Steptoe, A. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Rev Clin Oncol* **2008**, *5*, 466-475, doi:10.1038/ncponc1134.

65. Metin, Z.G.; Karadas, C.; Izgu, N.; Ozdemir, L.; Demirci, U. Effects of progressive muscle relaxation and mindfulness meditation on fatigue, coping styles, and quality of life in early breast cancer patients: An assessor blinded, three-arm, randomized controlled trial. *European Journal of Oncology Nursing* **2019**, *42*, 116-125.

66. Greenlee, H.; DuPont-Reyes, M.J.; Balneaves, L.G.; Carlson, L.E.; Cohen, M.R.; Deng, G.; Johnson, J.A.; Mumber, M.; Seely, D.; Zick, S.M. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA: a cancer journal for clinicians* **2017**, *67*, 194-232.

67. Büttner-Teleagă, A.; Kim, Y.-T.; Osel, T.; Richter, K. Sleep disorders in cancer—a systematic review. *International journal of environmental research and public health* **2021**, *18*, 11696.

68. Chen, Y.; Tan, F.; Wei, L.; Li, X.; Lyu, Z.; Feng, X.; Wen, Y.; Guo, L.; He, J.; Dai, M. Sleep duration and the risk of cancer: a systematic review and meta-analysis including dose–response relationship. *BMC cancer* **2018**, *18*, 1-13.

69. Medysky, M.E.; Temesi, J.; Culos-Reed, S.N.; Millet, G.Y. Exercise, sleep and cancer-related fatigue: are they related? *Neurophysiologie Clinique/Clinical Neurophysiology* **2017**, *47*, 111-122.

70. Lundt, A.; Jentschke, E. Long-term changes of symptoms of anxiety, depression, and fatigue in cancer patients 6 months after the end of yoga therapy. *Integrative cancer therapies* **2019**, *18*, 1534735418822096.

71. Lopresti, A.L.; Smith, S.J.; Malvi, H.; Kodgule, R. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (Withania somnifera) extract: A randomized, double-blind, placebo-controlled study. *Medicine* **2019**, *98*.

72. Salve, J.; Pate, S.; Debnath, K.; Langade, D.; Langade, D.G. Adaptogenic and anxiolytic effects of ashwagandha root extract in healthy adults: a double-blind, randomized, placebo-controlled clinical study. *Cureus* **2019**, *11*.

73. Gopukumar, K.; Thanawala, S.; Somepalli, V.; Rao, T.S.; Thamatam, V.B.; Chauhan, S. Efficacy and safety of ashwagandha root extract on cognitive functions in healthy, stressed adults: a randomized, double-blind, placebo-controlled study. *Evidence-Based Complementary and Alternative Medicine* **2021**, *2021*.

74. Chandrasekhar, K.; Kapoor, J.; Anishetty, S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. *Indian journal of psychological medicine* **2012**, *34*, 255-262.

75. Langade, D.; Thakare, V.; Kanchi, S.; Kelgane, S. Clinical evaluation of the pharmacological impact of ashwagandha root extract on sleep in healthy volunteers and insomnia patients: A double-blind, randomized, parallel-group, placebo-controlled study. *Journal of ethnopharmacology* **2021**, *264*, 113276.

76. Akhgarjand, C.; Asoudeh, F.; Bagheri, A.; Kalantar, Z.; Vahabi, Z.; Shab-bidar, S.; Rezvani, H.; Djafarian, K. Does Ashwagandha supplementation have a beneficial effect on the management of anxiety and stress? A systematic review and meta-analysis of randomized controlled trials. *Phytotherapy Research* **2022**, *36*, 4115-4124.

77. Vyazovskiy, V.V.; Delogu, A. NREM and REM sleep: complementary roles in recovery after wakefulness. *The Neuroscientist* **2014**, *20*, 203-219.

78. Hirshkowitz, M.; Whiton, K.; Albert, S.M.; Alessi, C.; Bruni, O.; DonCarlos, L.; Hazen, N.; Herman, J.; Katz, E.S.; Kheirandish-Gozal, L. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep health* **2015**, *1*, 40-43.

79. Ohayon, M.; Wickwire, E.M.; Hirshkowitz, M.; Albert, S.M.; Avidan, A.; Daly, F.J.; Dauvilliers, Y.; Ferri, R.; Fung, C.; Gozal, D. National Sleep Foundation's sleep quality recommendations: first report. *Sleep health* **2017**, *3*, 6-19.

80. Cheah, K.L.; Norhayati, M.N.; Husniati Yaacob, L.; Abdul Rahman, R. Effect of Ashwagandha (Withania somnifera) extract on sleep: A systematic review and meta-analysis. *PloS one* **2021**, *16*, e0257843.

81. Itani, O.; Jike, M.; Watanabe, N.; Kaneita, Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. *Sleep medicine* **2017**, *32*, 246-256.

82. Wimalawansa, S.J. Physiological Basis for Using Vitamin D to Improve Health. *Biomedicines* **2023**, *11*, 1542.

83. Holick, M.F. Vitamin D Deficiency. *New England Journal of Medicine* **2002**, *357*, 266-281, doi:10.1056/NEJMra070553.

84. Brandi, M.L. Indications on the use of vitamin D and vitamin D metabolites in clinical phenotypes. *Clin Cases Miner Bone Metab* **2010**, *7*, 243-250.

85. Chapuy, M.C.; Preziosi, P.; Maamer, M.; Arnaud, S.; Galan, P.; Hercberg, S.; Meunier, P.J. Prevalence of Vitamin D Insufficiency in an Adult Normal Population. *Osteoporosis International* **1997**, *7*, 439-443, doi:10.1007/s001980050030.

86. Vieth, R. Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults. *The Journal of Steroid Biochemistry and Molecular Biology* **2004**, *89-90*, 575-579, doi:https://doi.org/10.1016/j.jsbmb.2004.03.038.

87. Wimalawansa, S.J. Rapidly Increasing Serum 25(OH)D Boosts the Immune System, against Infections—Sepsis and COVID-19. In *Nutrients*, 2022; Vol. 14.

88. Wimalawansa, S.J. Effective and practical ways to overcome vitamin D deficiency. *J Family Med Community Health* **2021**, *8*, 1185.

89. Carlberg, C.; Velleuer, E. Vitamin D and the risk for cancer: A molecular analysis. *Biochemical Pharmacology* **2022**, *196*, 114735.

90. Baeke, F.; Takiishi, T.; Korf, H.; Gysemans, C.; Mathieu, C. Vitamin D: modulator of the immune system. *Current opinion in pharmacology* **2010**, *10*, 482-496.

91. Bartley, J. Vitamin D: emerging roles in infection and immunity. *Expert review of anti-infective therapy* **2010**, *8*, 1359-1369.

92. Chowdhury, R.; Kunutsor, S.; Vitezova, A.; Oliver-Williams, C.; Chowdhury, S.; Kiefte-de-Jong, J.C.; Khan, H.; Baena, C.P.; Prabhakaran, D.; Hoshen, M.B. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *Bmj* **2014**, *348*.

93. Ng, K.; Venook, A.P.; Sato, K.; Yuan, C.; Hollis, B.W.; Niedzwiecki, D.; Ye, C.; Chang, I.W.; O'Neil, B.H.; Innocenti, F. Vitamin D status and survival of metastatic colorectal cancer patients: Results from CALGB/SWOG 80405 (Alliance). American Society of Clinical Oncology: 2015.

94. Hossain, S.; Beydoun, M.A.; Beydoun, H.A.; Chen, X.; Zonderman, A.B.; Wood, R.J. Vitamin D and breast cancer: A systematic review and meta-analysis of observational studies. *Clinical nutrition ESPEN* **2019**, *30*, 170-184.

95. Zhang, Y.; Fang, F.; Tang, J.; Jia, L.; Feng, Y.; Xu, P.; Faramand, A. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. *Bmj* **2019**, *366*.

96. Muñoz, A.; Grant, W.B. Vitamin D and cancer: an historical overview of the epidemiology and mechanisms. *Nutrients* **2022**, *14*, 1448.

97. Ng, K.; Nimeiri, H.S.; McCleary, N.J.; Abrams, T.A.; Yurgelun, M.B.; Cleary, J.M.; Rubinson, D.A.; Schrag, D.; Miksad, R.; Bullock, A.J. Effect of high-dose vs standard-dose vitamin D3 supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: the SUNSHINE randomized clinical trial. *Jama* **2019**, *321*, 1370-1379.

98. Díaz, G.D.; Paraskeva, C.; Thomas, M.G.; Binderup, L.; Hague, A. Apoptosis is induced by the active metabolite of vitamin D3 and its analogue EB1089 in colorectal adenoma and carcinoma cells: possible implications for prevention and therapy. *Cancer research* **2000**, *60*, 2304-2312.

99. Feldman, D.; Krishnan, A.V.; Swami, S.; Giovannucci, E.; Feldman, B.J. The role of vitamin D in reducing cancer risk and progression. *Nature reviews cancer* **2014**, *14*, 342-357.

100. Mathieu, C.; Adorini, L. The coming of age of 1, 25-dihydroxyvitamin D3 analogs as immunomodulatory agents. *Trends in molecular medicine* **2002**, *8*, 174-179.

101. Yang, E.S.; Burnstein, K.L. Vitamin D inhibits G1 to S progression in LNCaP prostate cancer cells through p27Kip1 stabilization and Cdk2 mislocalization to the cytoplasm. *Journal of Biological Chemistry* **2003**, *278*, 46862-46868.

102. Larriba, M.J.; García de Herreros, A.; Muñoz, A. Vitamin D and the epithelial to mesenchymal transition. *Stem cells international* **2016**, *2016*.

103. Bernardi, R.J.; Johnson, C.S.; Modzelewski, R.A.; Trump, D.L. Antiproliferative effects of 1α, 25-dihydroxyvitamin D3 and vitamin D analogs on tumor-derived endothelial cells. *Endocrinology* **2002**, *143*, 2508-2514.

104. Ng, K.; Meyerhardt, J.A.; Wu, K.; Feskanich, D.; Hollis, B.W.; Giovannucci, E.L.; Fuchs, C.S. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. *Journal of Clinical Oncology* **2008**, *26*, 2984-2991.

105. Johansson, H.; Spadola, G.; Tosti, G.; Mandalà, M.; Minisini, A.M.; Queirolo, P.; Aristarco, V.; Baldini, F.; Cocorocchio, E.; Albertazzi, E. Vitamin D supplementation and disease-free survival in stage II melanoma: a randomized placebo controlled trial. *Nutrients* **2021**, *13*, 1931.

106. Yuan, C.; Sato, K.; Hollis, B.W.; Zhang, S.; Niedzwiecki, D.; Ou, F.-S.; Chang, I.W.; O'Neil, B.H.; Innocenti, F.; Lenz, H.-J. Plasma 25-hydroxyvitamin D levels and survival in patients with advanced or metastatic colorectal cancer: findings from CALGB/SWOG 80405 (Alliance). *Clinical Cancer Research* **2019**, *25*, 7497-7505.

107. Mezawa, H.; Sugiura, T.; Watanabe, M.; Norizoe, C.; Takahashi, D.; Shimojima, A.; Tamez, S.; Tsutsumi, Y.; Yanaga, K.; Urashima, M. Serum vitamin D levels and survival of patients with colorectal cancer: post-hoc analysis of a prospective cohort study. *BMC cancer* **2010**, *10*, 1-8.

108. Zgaga, L.; Theodoratou, E.; Farrington, S.M.; Din, F.V.; Ooi, L.Y.; Glodzik, D.; Johnston, S.; Tenesa, A.; Campbell, H.; Dunlop, M.G. Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. *J Clin Oncol* **2014**, *32*, 2430-2439.

109. Toriola, A.T.; Nguyen, N.; Scheitler-Ring, K.; Colditz, G.A. Circulating 25-hydroxyvitamin D levels and prognosis among cancer patients: a systematic review. *Cancer epidemiology, biomarkers & prevention* **2014**, *23*, 917-933.

110. Tretli, S.; Schwartz, G.G.; Torjesen, P.A.; Robsahm, T.E. Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: a population-based study. *Cancer Causes & Control* **2012**, *23*, 363-370.

111. Chen, Q.-Y.; Kim, S.; Lee, B.; Jeong, G.; Lee, D.H.; Keum, N.; Manson, J.E.; Giovannucci, E.L. Post-diagnosis vitamin D supplement use and survival among cancer patients: a meta-analysis. *Nutrients* **2022**, *14*, 3418.

112. Vaughan-Shaw, P.G.; Buijs, L.F.; Blackmur, J.P.; Theodoratou, E.; Zgaga, L.; Din, F.V.N.; Farrington, S.M.; Dunlop, M.G. The effect of vitamin D supplementation on survival in patients with colorectal cancer: systematic review and meta-analysis of randomised controlled trials. *British journal of cancer* **2020**, *123*, 1705-1712.

113. Kuznia, S.; Zhu, A.; Akutsu, T.; Buring, J.E.; Camargo Jr, C.A.; Cook, N.R.; Chen, L.-J.; Cheng, T.-Y.D.; Hantunen, S.; Lee, I.M. Efficacy of vitamin D3 supplementation on cancer mortality: Systematic review and individual patient data meta-analysis of randomised controlled trials. *Ageing research reviews* **2023**, 101923.

114. Wang, L.; Wang, C.; Wang, J.; Huang, X.; Cheng, Y. Longitudinal, observational study on associations between postoperative nutritional vitamin D supplementation and clinical outcomes in esophageal cancer patients undergoing esophagectomy. *Scientific Reports* **2016**, *6*, 38962.

115. Madden, J.M.; Murphy, L.; Zgaga, L.; Bennett, K. De novo vitamin D supplement use post-diagnosis is associated with breast cancer survival. *Breast cancer research and treatment* **2018**, *172*, 179-190.

116. Marshall, D.T.; Savage, S.J.; Garrett-Mayer, E.; Keane, T.E.; Hollis, B.W.; Horst, R.L.; Ambrose, L.H.; Kindy, M.S.; Gattoni-Celli, S. Vitamin D3 supplementation at 4000 international units per day for one year results in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate cancer under active surveillance. *The Journal of Clinical Endocrinology & Metabolism* **2012**, *97*, 2315-2324.

117. Wagner, D.; Trudel, D.; Van der Kwast, T.; Nonn, L.; Giangreco, A.A.; Li, D.; Dias, A.; Cardoza, M.; Laszlo, S.; Hersey, K. Randomized clinical trial of vitamin D3 doses on prostatic vitamin D metabolite levels and ki67 labeling in prostate cancer patients. *The Journal of Clinical Endocrinology & Metabolism* **2013**, *98*, 1498-1507.

118. Abu el Maaty, M.A.; Wölfl, S. Effects of 1, 25 (OH) 2D3 on cancer cells and potential applications in combination with established and putative anti-cancer agents. *Nutrients* **2017**, *9*, 87.

119. Zeichner, S.B.; Koru-Sengul, T.; Shah, N.; Liu, Q.; Markward, N.J.; Montero, A.J.; Glück, S.; Silva, O.; Ahn, E.R. Improved clinical outcomes associated with vitamin D supplementation during adjuvant chemotherapy in patients with HER2+ nonmetastatic breast cancer. *Clinical breast cancer* **2015**, *15*, e1-e11.

120. Amon, U.; Yaguboglu, R.; Ennis, M.; Holick, M.F.; Amon, J. Safety Data in Patients with Autoimmune Diseases during Treatment with High Doses of Vitamin D3 According to the "Coimbra Protocol". *Nutrients* **2022**, *14*, 1575.

121. Finamor, D.C.; Sinigaglia-Coimbra, R.; Neves, L.C.M.; Gutierrez, M.; Silva, J.J.; Torres, L.D.; Surano, F.; Neto, D.J.; Novo, N.F.; Juliano, Y. A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis. *Dermato-endocrinology* **2013**, *5*, 222-234.

122. Biancatelli, R.M.L.C.; Berrill, M.; Mohammed, Y.H.; Marik, P.E. Melatonin for the treatment of sepsis: the scientific rationale. *Journal of thoracic disease* **2020**, *12*, S54.

123. Jockers, R.; Delagrange, P.; Dubocovich, M.L.; Markus, R.P.; Renault, N.; Tosini, G.; Cecon, E.; Zlotos, D.P. Update on melatonin receptors: IUPHAR Review 20. *British journal of pharmacology* **2016**, *173*, 2702-2725.

124. Jung, B.; Ahmad, N. Melatonin in cancer management: progress and promise. *Cancer research* **2006**, *66*, 9789-9793.

125. Yeager, R.L.; Oleske, D.A.; Sanders, R.A.; Watkins Iii, J.B.; Eells, J.T.; Henshel, D.S. Melatonin as a principal component of red light therapy. *Medical hypotheses* **2007**, *69*, 372-376.

126. Tan, D.-X.; Reiter, R.J.; Zimmerman, S.; Hardeland, R. Melatonin: Both a messenger of darkness and a participant in the cellular actions of non-visible solar radiation of near infrared light. *Biology* **2023**, *12*, 89.

127. Manouchehri, E.; Taghipour, A.; Ghavami, V.; Ebadi, A.; Homaei, F.; Latifnejad Roudsari, R. Night-shift work duration and breast cancer risk: an updated systematic review and meta-analysis. *BMC women's health* **2021**, *21*, 1-16.

128. Wise, J. Danish night shift workers with breast cancer awarded compensation. British Medical Journal Publishing Group: 2009.

129. Reiter, R.J.; Rosales-Corral, S.A.; Tan, D.-X.; Acuna-Castroviejo, D.; Qin, L.; Yang, S.-F.; Xu, K. Melatonin, a Full Service Anti-Cancer Agent: Inhibition of Initiation, Progression and Metastasis. *International Journal of Molecular Sciences* **2017**, *18*, 843, doi:10.3390/ijms18040843.

130. Talib, W.H.; Alsayed, A.R.; Abuawad, A.; Daoud, S.; Mahmod, A.I. Melatonin in Cancer Treatment: Current Knowledge and Future Opportunities. *Molecules* **2021**, *26*, 2506, doi:10.3390/molecules26092506.

131. Akbarzadeh, M.; Movassaghpour, A.A.; Ghanbari, H.; Kheirandish, M.; Fathi Maroufi, N.; Rahbarghazi, R.; Nouri, M.; Samadi, N. The potential therapeutic effect of melatonin on human ovarian cancer by inhibition of invasion and migration of cancer stem cells. *Scientific reports* **2017**, *7*, 1-11.

132. Reiter, R.J.; Sharma, R.; Ma, Q.; Rosales-Corral, S.; Acuna-Castroviejo, D.; Escames, G. Inhibition of mitochondrial pyruvate dehydrogenase kinase: a proposed mechanism by which melatonin causes cancer cells to overcome cytosolic glycolysis, reduce tumor biomass and reverse insensitivity to chemotherapy. *Melatonin Research* **2019**, *2*, 105-119.

133. Sanchez-Sanchez, A.M.; Antolin, I.; Puente-Moncada, N.; Suarez, S.; Gomez-Lobo, M.; Rodriguez, C.; Martin, V. Melatonin cytotoxicity is associated to Warburg effect inhibition in Ewing sarcoma cells. *PLoS One* **2015**, *10*, e0135420.

134. Perfilyeva, Y.V.; Ostapchuk, Y.O.; Abdolla, N.; Tleulieva, R.; Krasnoshtanov, V.C.; Belyaev, N.N. Exogenous melatonin up-regulates expression of CD62L by lymphocytes in aged mice under inflammatory and non-inflammatory conditions. *Immunological Investigations* **2019**, *48*, 632-643.

135. Liu, H.; Xu, L.; Wei, J.E.; Xie, M.R.; Wang, S.E.; Zhou, R.X. Role of CD4+ CD25+ regulatory T cells in melatonin-mediated inhibition of murine gastric cancer cell growth in vivo and in vitro. *The anatomical record: advances in integrative anatomy and evolutionary biology* **2011**, *294*, 781-788.

136. Shiu, S.Y.W.; Law, I.C.; Lau, K.W.; Tam, P.C.; Yip, A.W.C.; Ng, W.T. Melatonin slowed the early biochemical progression of hormone-refractory prostate cancer in a patient whose prostate tumor tissue expressed MT1 receptor subtype. *Journal of pineal research* **2003**, *35*, 177-182.

137. Tomov, B.; Popov, D.; Tomova, R.; Vladov, N.; Den Otter, W.; Krastev, Z. Therapeutic response of untreatable hepatocellular carcinoma after application of the immune modulators IL-2, BCG and melatonin. *Anticancer Research* **2013**, *33*, 4531-4535.

138. Mills, E.; Wu, P.; Seely, D.; Guyatt, G. Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis. *Journal of pineal research* **2005**, *39*, 360-366.

139. Seely, D.; Wu, P.; Fritz, H.; Kennedy, D.A.; Tsui, T.; Seely, A.J.E.; Mills, E. Melatonin as adjuvant cancer care with and without chemotherapy: a systematic review and meta-analysis of randomized trials. *Integrative cancer therapies* **2012**, *11*, 293-303.

140. Li, X.-X.; Liu, C.; Dong, S.-L.; Ou, C.-S.; Lu, J.-L.; Ye, J.-H.; Liang, Y.-R.; Zheng, X.-Q. Anticarcinogenic potentials of tea catechins. *Frontiers in Nutrition* **2022**, *9*, 3024.

141. Caccamo, A.E.; Scaltriti, M.; Caporali, A.; D'Arca, D.; Scorcioni, F.; Astancolle, S.; Mangiola, M.; Bettuzzi, S. Cell detachment and apoptosis induction of immortalized human prostate epithelial cells are associated with early accumulation of a 45 kDa nuclear isoform of clusterin. *Biochemical Journal* **2004**, *382*, 157-168.

142. Scaltriti, M.; Santamaria, A.; Paciucci, R.; Bettuzzi, S. Intracellular clusterin induces G2-M phase arrest and cell death in PC-3 prostate cancer cells1. *Cancer research* **2004**, *64*, 6174-6182.

143. Liao, S.; Umekita, Y.; Guo, J.; Kokontis, J.M.; Hiipakka, R.A. Growth inhibition and regression of human prostate and breast tumors in athymic mice by tea epigallocatechin gallate. *Cancer letters* **1995**, *96*, 239-243.

144. Li, C.; Allen, A.; Kwagh, J.; Doliba, N.M.; Qin, W.; Najafi, H.; Collins, H.W.; Matschinsky, F.M.; Stanley, C.A.; Smith, T.J. Green tea polyphenols modulate insulin secretion by inhibiting glutamate dehydrogenase. *Journal of biological chemistry* **2006**, *281*, 10214-10221.

145. Rashidi, B.; Malekzadeh, M.; Goodarzi, M.; Masoudifar, A.; Mirzaei, H. Green tea and its anti-angiogenesis effects. *Biomedicine & Pharmacotherapy* **2017**, *89*, 949-956.

146. Song, Q.; Zhang, G.; Wang, B.; Cao, G.; Li, D.; Wang, Y.; Zhang, Y.; Geng, J.; Li, H.; Li, Y. Reinforcing the combinational immuno-oncotherapy of switching "cold" tumor to "hot" by responsive penetrating nanogels. *ACS Applied Materials & Interfaces* **2021**, *13*, 36824-36838.

147. McCarty, M.F.; Iloki-Assanga, S.; Lujany, L.M.L. Nutraceutical targeting of TLR4 signaling has potential for prevention of cancer cachexia. *Medical Hypotheses* **2019**, *132*, 109326.

148. Lin, C.-H.; Shen, Y.-A.; Hung, P.-H.; Yu, Y.-B.; Chen, Y.-J. Epigallocathechin gallate, polyphenol present in green tea, inhibits stem-like characteristics and epithelial-mesenchymal transition in nasopharyngeal cancer cell lines. *BMC Complementary and Alternative Medicine* **2012**, *12*, 1-12.

149. Bonuccelli, G.; Sotgia, F.; Lisanti, M.P. Matcha green tea (MGT) inhibits the propagation of cancer stem cells (CSCs), by targeting mitochondrial metabolism, glycolysis and multiple cell signalling pathways. *Aging (Albany NY)* **2018**, *10*, 1867.

150. El-Nashar, H.A.S.; Aly, S.H.; Ahmadi, A.; El-Shazly, M. The Impact of Polyphenolics in the Management of Breast Cancer: Mechanistic Aspects and Recent Patents. *Recent Patents on Anti-Cancer Drug Discovery* **2022**, *17*, 358-379.

151. Kim, T.L.; Jeong, G.H.; Yang, J.W.; Lee, K.H.; Kronbichler, A.; Van Der Vliet, H.J.; Grosso, G.; Galvano, F.; Aune, D.; Kim, J.Y. Tea consumption and risk of cancer: an umbrella review and meta-analysis of observational studies. *Advances in Nutrition* **2020**, *11*, 1437-1452.

152. Shanafelt, T.D.; Call, T.G.; Zent, C.S.; LaPlant, B.; Bowen, D.A.; Roos, M.; Secreto, C.R.; Ghosh, A.K.; Kabat, B.F.; Lee, M.-J. Phase I trial of daily oral Polyphenon E in patients with asymptomatic Rai stage 0 to II chronic lymphocytic leukemia. *Journal of Clinical Oncology* **2009**, *27*, 3808.

153. Lemanne, D.; Block, K.I.; Kressel, B.R.; Sukhatme, V.P.; White, J.D. A case of complete and durable molecular remission of chronic lymphocytic leukemia following treatment with epigallocatechin-3-gallate, an extract of green tea. *Cureus* **2015**, *7*.

154. Kubatka, P.; Mazurakova, A.; Samec, M.; Koklesova, L.; Zhai, K.; Al-Ishaq, R.; Kajo, K.; Biringer, K.; Vybohova, D.; Brockmueller, A. Flavonoids against non-physiologic inflammation attributed to cancer initiation, development, and progression—3PM pathways. *Epma Journal* **2021**, 1-29.

155. Bettuzzi, S.; Brausi, M.; Rizzi, F.; Castagnetti, G.; Peracchia, G.; Corti, A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. *Cancer research* **2006**, *66*, 1234-1240.

156. Sarma, D.N.; Barrett, M.L.; Chavez, M.L.; Gardiner, P.; Ko, R.; Mahady, G.B.; Marles, R.J.; Pellicore, L.S.; Giancaspro, G.I.; Dog, T.L. Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug safety* **2008**, *31*, 469-484.

157. Mazzanti, G.; Di Sotto, A.; Vitalone, A. Hepatotoxicity of green tea: an update. *Archives of toxicology* **2015**, *89*, 1175-1191.

158. Dowling, R.J.; Niraula, S.; Stambolic, V.; Goodwin, P.J. Metformin in cancer: translational challenges. *Journal of molecular endocrinology* **2012**, *48*, R31-43.

159. Dowling, R.J.O.; Zakikhani, M.; Fantus, I.G.; Pollak, M.; Sonenberg, N. Metformin inhibits mammalian target of rapamycin–dependent translation initiation in breast cancer cells. *Cancer research* **2007**, *67*, 10804-10812.

160. Andrzejewski, S.; Siegel, P.M.; St-Pierre, J. Metabolic Profiles Associated With Metformin Efficacy in Cancer. *Frontiers in Endocrinology* **2018**, *9*, 372, doi:10.3389/fendo.2018.00372.

161. Saraei, P.; Asadi, I.; Kakar, M.A.; Moradi-Kor, N. The beneficial effects of metformin on cancer prevention and therapy: a comprehensive review of recent advances. *Cancer management and research* **2019**, 3295-3313.

162. Barrios-Bernal, P.; Zatarain-Barrón, Z.L.; Hernández-Pedro, N.; Orozco-Morales, M.; Olivera-Ramírez, A.; Ávila-Moreno, F.; Colín-González, A.L.; Cardona, A.F.; Rosell, R.; Arrieta, O. Will We Unlock the Benefit of Metformin for Patients with Lung Cancer? Lessons from Current Evidence and New Hypotheses. *Pharmaceuticals* **2022**, *15*, 786.

163. Shi, P.; Liu, W.; Wang, H.; Li, F.; Zhang, H.; Wu, Y.; Kong, Y.; Zhou, Z.; Wang, C.; Chen, W. Metformin suppresses triple-negative breast cancer stem cells by targeting KLF5 for degradation. *Cell discovery* **2017**, *3*, 1-13.

164. Gandini, S.; Puntoni, M.; Heckman-Stoddard, B.M.; Dunn, B.K.; Ford, L.; DeCensi, A.; Szabo, E. Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. *Cancer prevention research* **2014**, *7*, 867-885.

165. Zhang, P.; Li, H.; Tan, X.; Chen, L.; Wang, S. Association of metformin use with cancer incidence and mortality: a meta-analysis. *Cancer epidemiology* **2013**, *37*, 207-218.

166. Lega, I.C.; Shah, P.S.; Margel, D.; Beyene, J.; Rochon, P.A.; Lipscombe, L.L. The effect of metformin on mortality following cancer among patients with diabetes. *Cancer Epidemiology, Biomarkers & Prevention* **2014**, *23*, 1974-1984.

167. Mei, Z.-B.; Zhang, Z.-J.; Liu, C.-Y.; Liu, Y.; Cui, A.; Liang, Z.-L.; Wang, G.-H.; Cui, L. Survival benefits of metformin for colorectal cancer patients with diabetes: a systematic review and meta-analysis. *PLoS One* **2014**, *9*, e91818.

168. Yin, M.; Zhou, J.; Gorak, E.J.; Quddus, F. Metformin is associated with survival benefit in cancer patients with concurrent type 2 diabetes: a systematic review and meta-analysis. *The oncologist* **2013**, *18*, 1248-1255.

169. Coyle, C.; Cafferty, F.H.; Vale, C.; Langley, R.E. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. *Annals of Oncology* **2016**, *27*, 2184-2195.

170. Eibl, G.; Rozengurt, E. Metformin: review of epidemiology and mechanisms of action in pancreatic cancer. *Cancer and Metastasis Reviews* **2021**, *40*, 865-878.

171. Jiménez-Vacas, J.M.; Herrero-Aguayo, V.; Montero-Hidalgo, A.J.; Sáez-Martínez, P.; Gómez-Gómez, E.; León-González, A.J.; Fuentes-Fayos, A.C.; Yubero-Serrano, E.M.; Requena-Tapia, M.J.; López, M. Clinical, cellular, and molecular evidence of the additive antitumor effects of biguanides and statins in prostate cancer. *The Journal of Clinical Endocrinology & Metabolism* **2021**, *106*, e696-e710.

172. Buczyńska, A.; Sidorkiewicz, I.; Krętowski, A.J.; Zbucka-Krętowska, M.; Adamska, A. Metformin intervention—A panacea for cancer treatment? *Cancers* **2022**, *14*, 1336.

173. Stopsack, K.H.; Ziehr, D.R.; Rider, J.R.; Giovannucci, E.L. Metformin and prostate cancer mortality: a meta-analysis. *Cancer causes & control* **2016**, *27*, 105-113.

174. Wang, Y.; Liu, G.; Tong, D.; Parmar, H.; Hasenmayer, D.; Yuan, W.; Zhang, D.; Jiang, J. Metformin represses androgen-dependent and androgen-independent prostate cancers by targeting androgen receptor. *The Prostate* **2015**, *75*, 1187-1196.

175. Giordano, A.; Tommonaro, G. Curcumin and Cancer. *Nutrients* **2019**, *11*, 2376, doi:10.3390/nu11102376.

176. Mansouri, K.; Rasoulpoor, S.; Daneshkhah, A.; Abolfathi, S.; Salari, N.; Mohammadi, M.; Rasoulpoor, S.; Shabani, S. Clinical effects of curcumin in enhancing cancer therapy: A systematic review. *BMC cancer* **2020**, *20*, 1-11.

177. Cho, J.-W.; Lee, K.-S.; Kim, C.-W. Curcumin attenuates the expression of IL-1β, IL-6, and TNF-α as well as cyclin E in TNF-α-treated HaCaT cells; NF-κB and MAPKs as potential upstream targets. *International journal of molecular medicine* **2007**, *19*, 469-474.

178. Panahi, Y.; Darvishi, B.; Ghanei, M.; Jowzi, N.; Beiraghdar, F.; Varnamkhasti, B.S. Molecular mechanisms of curcumins suppressing effects on tumorigenesis, angiogenesis and metastasis, focusing on NF-κB pathway. *Cytokine & growth factor reviews* **2016**, *28*, 21-29.

179. Alexandrow, M.G.; Song, L.J.; Altiok, S.; Gray, J.; Haura, E.B.; Kumar, N.B. Curcumin: a novel stat 3 pathway inhibitor for chemoprevention of lung cancer. *European Journal of Cancer Prevention* **2012**, *21*, 407.

180. Yim-Im, W.; Sawatdichaikul, O.; Semsri, S.; Horata, N.; Mokmak, W.; Tongsima, S.; Suksamrarn, A.; Choowongkomon, K. Computational analyses of curcuminoid analogs against kinase domain of HER2. *BMC bioinformatics* **2014**, *15*, 1-13.

181. Starok, M.; Preira, P.; Vayssade, M.; Haupt, K.; Salomé, L.; Rossi, C. EGFR inhibition by curcumin in cancer cells: a dual mode of action. *Biomacromolecules* **2015**, *16*, 1634-1642.

182. James, M.I.; Iwuji, C.; Irving, G.; Karmokar, A.; Higgins, J.A.; Griffin-Teal, N.; Thomas, A.; Greaves, P.; Cai, H.; Patel, S.R. Curcumin inhibits cancer stem cell phenotypes in ex vivo models of colorectal liver

metastases, and is clinically safe and tolerable in combination with FOLFOX chemotherapy. *Cancer letters* **2015**, *364*, 135-141.

183. Wang, J.Y.; Wang, X.; Wang, X.J.; Zheng, B.Z.; Wang, Y.; Liang, B. Curcumin inhibits the growth via Wnt/β-catenin pathway in non-small-cell lung cancer cells. *European Review for Medical & Pharmacological Sciences* **2018**, *22*.

184. Zoi, V.; Galani, V.; Lianos, G.D.; Voulgaris, S.; Kyritsis, A.P.; Alexiou, G.A. The role of curcumin in cancer treatment. *Biomedicines* **2021**, *9*, 1086.

185. Santosa, D.; Suharti, C.; Riwanto, I.; Dharmana, E.; Pangarsa, E.A.; Setiawan, B.; Suyono, S.; Tobing, M.L.; Suhartono, S.; Hadisapurto, S. Curcumin as adjuvant therapy to improve remission in myeloma patients: A pilot randomized clinical trial. *Caspian Journal of Internal Medicine* **2022**, *13*, 375.

186. Pastorelli, D.; Fabricio, A.S.C.; Giovanis, P.; D'Ippolito, S.; Fiduccia, P.; Soldà, C.; Buda, A.; Sperti, C.; Bardini, R.; Da Dalt, G. Phytosome complex of curcumin as complementary therapy of advanced pancreatic cancer improves safety and efficacy of gemcitabine: Results of a prospective phase II trial. *Pharmacological research* **2018**, *132*, 72-79.

187. Dhillon, N.; Aggarwal, B.B.; Newman, R.A.; Wolff, R.A.; Kunnumakkara, A.B.; Abbruzzese, J.L.; Ng, C.S.; Badmaev, V.; Kurzrock, R. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clinical cancer research* **2008**, *14*, 4491-4499.

188. Saghatelyan, T.; Tananyan, A.; Janoyan, N.; Tadevosyan, A.; Petrosyan, H.; Hovhannisyan, A.; Hayrapetyan, L.; Arustamyan, M.; Arnhold, J.; Rotmann, A.-R. 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. *Phytomedicine* **2020**, *70*, 153218.

189. Panahi, Y.; Saadat, A.; Beiraghdar, F.; Nouzari, S.M.H.; Jalalian, H.R.; Sahebkar, A. Antioxidant effects of bioavailability-enhanced curcuminoids in patients with solid tumors: A randomized double-blind placebo-controlled trial. *Journal of Functional Foods* **2014**, *6*, 615-622.

190. Desai, P.; Ann, D.; Wang, J.; Prabhu, S. Pancreatic cancer: Recent advances in nanoformulation-based therapies. *Critical Reviews™ in therapeutic drug carrier systems* **2019**, *36*.

191. Fda, F. Notice to US Food and Drug Administration of the Conclusion That the Intended Use of Curcumin is Generally Recognized as Safe. *Food and Drug Administration, GRAS Notice* **2018**, *822*.

192. Kim, D.-C.; Ku, S.-K.; Bae, J.-S. Anticoagulant activities of curcumin and its derivative. *BMB reports* **2012**, *45*, 221-226.

193. Pantziarka, P.; Bouche, G.; Meheus, L.; Sukhatme, V.; Sukhatme, V.P. Repurposing Drugs in Oncology (ReDO)—mebendazole as an anti-cancer agent. *ecancermedicalscience* **2014**, *8*.

194. Guerini, A.E.; Triggiani, L.; Maddalo, M.; Bonù, M.L.; Frassine, F.; Baiguini, A.; Alghisi, A.; Tomasini, D.; Borghetti, P.; Pasinetti, N. Mebendazole as a candidate for drug repurposing in oncology: An extensive review of current literature. *Cancers* **2019**, *11*, 1284.

195. Larsen, A.R.; Bai, R.-Y.; Chung, J.H.; Borodovsky, A.; Rudin, C.M.; Riggins, G.J.; Bunz, F. Repurposing the antihelmintic mebendazole as a hedgehog inhibitor. *Molecular cancer therapeutics* **2015**, *14*, 3-13.

196. Fong, D.; Christensen, C.T.; Chan, M.M. Targeting cancer stem cells with repurposed drugs to improve current therapies. *Recent patents on anti-cancer drug discovery* **2021**, *16*, 136-160.

197. Mukherjee, P.; Greenwood, B.; Henao, J.; Kiebish, M.A.; Seyfried, T.N. Ketogenic diet as a metabolic vehicle for enhancing the therapeutic efficacy of mebendazole and devimistat in preclinical pediatric glioma. *bioRxiv* **2023**, 2023-2006.

198. Meco, D.; Attinà, G.; Mastrangelo, S.; Navarra, P.; Ruggiero, A. Emerging Perspectives on the Antiparasitic Mebendazole as a Repurposed Drug for the Treatment of Brain Cancers. *International Journal of Molecular Sciences* **2023**, *24*, 1334.

199. Nygren, P.; Larsson, R. Drug repositioning from bench to bedside: tumour remission by the antihelmintic drug mebendazole in refractory metastatic colon cancer. *Acta oncologica* **2014**, *53*, 427-428.

200. Dobrosotskaya, I.Y.; Hammer, G.D.; Schteingart, D.E.; Maturen, K.E.; Worden, F.P. Mebendazole monotherapy and long-term disease control in metastatic adrenocortical carcinoma. *Endocrine practice* **2011**, *17*, e59-e62.

201. Chiang, R.S.; Syed, A.B.; Wright, J.L.; Montgomery, B.; Srinlavs, S. Fenbendazole enhancing anti-tumor effect: a case series. *Clin. Oncol. Case Rep* **2021**, *4*, 2-5.

202. Agrawal, S.; Vamadevan, P.; Mazibuko, N.; Bannister, R.; Swery, R.; Wilson, S.; Edwards, S. A new method for ethical and efficient evidence generation for off-label medication use in oncology (a case study in glioblastoma). *Frontiers in Pharmacology* **2019**, 681.

203. Dach, J. *Cracking Cancer Toolkit: Using Repurposed Drugs for Cancer Treatment*; Amazon Digital Services LLC - KDP Print US: 2020.

204. Williamson, T.; Bai, R.-Y.; Staedtke, V.; Huso, D.; Riggins, G.J. Mebendazole and a non-steroidal anti-inflammatory combine to reduce tumor initiation in a colon cancer preclinical model. *Oncotarget* **2016**, *7*, 68571.

205. Nabavi, S.F.; Bilotto, S.; Russo, G.L.; Orhan, I.E.; Habtemariam, S.; Daglia, M.; Devi, K.P.; Loizzo, M.R.; Tundis, R.; Nabavi, S.M. Omega-3 polyunsaturated fatty acids and cancer: lessons learned from clinical trials. *Cancer and Metastasis Reviews* **2015**, *34*, 359-380.

206. Cockbain, A.J.; Toogood, G.J.; Hull, M.A. Omega-3 polyunsaturated fatty acids for the treatment and prevention of colorectal cancer. *Gut* **2012**, *61*, 135-149, doi:10.1136/gut.2010.233718.

207. Corsetto, P.A.; Montorfano, G.; Zava, S.; Jovenitti, I.E.; Cremona, A.; Berra, B.; Rizzo, A.M. Effects of n-3 PUFAs on breast cancer cells through their incorporation in plasma membrane. *Lipids in health and disease* **2011**, *10*, 1-16.

208. De Carlo, F.; Witte, T.R.; Hardman, W.E.; Claudio, P.P. Omega-3 eicosapentaenoic acid decreases CD133 colon cancer stem-like cell marker expression while increasing sensitivity to chemotherapy. *PLoS One* **2013**, *8*, e69760.

209. Xue, M.; Wang, Q.; Zhao, J.; Dong, L.; Ge, Y.; Hou, L.; Liu, Y.; Zheng, Z. Docosahexaenoic acid inhibited the Wnt/β-catenin pathway and suppressed breast cancer cells in vitro and in vivo. *The Journal of nutritional biochemistry* **2014**, *25*, 104-110.

210. Vasudevan, A.; Yu, Y.; Banerjee, S.; Woods, J.; Farhana, L.; Rajendra, S.G.; Patel, A.; Dyson, G.; Levi, E.; Maddipati, K.R. Omega-3 fatty acid is a potential preventive agent for recurrent colon cancer. *Cancer Prevention Research* **2014**, *7*, 1138-1148.

211. Aucoin, M.; Cooley, K.; Knee, C.; Fritz, H.; Balneaves, L.G.; Breau, R.; Fergusson, D.; Skidmore, B.; Wong, R.; Seely, D. Fish-derived omega-3 fatty acids and prostate cancer: a systematic review. *Integrative cancer therapies* **2017**, *16*, 32-62.

212. Zheng, J.-S.; Hu, X.-J.; Zhao, Y.-M.; Yang, J.; Li, D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. *Bmj* **2013**, *346*, f3706.

213. Pot, G.K.; Geelen, A.; van Heijningen, E.M.B.; Siezen, C.L.E.; van Kranen, H.J.; Kampman, E. Opposing associations of serum n-3 and n-6 polyunsaturated fatty acids with colorectal adenoma risk: An endoscopy-based case–control study. *International journal of cancer* **2008**, *123*, 1974-1977.

214. Brasky, T.M.; Lampe, J.W.; Potter, J.D.; Patterson, R.E.; White, E. Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. *Cancer epidemiology, biomarkers & prevention* **2010**, *19*, 1696-1708.

215. Murphy, R.A.; Mourtzakis, M.; Chu, Q.S.C.; Baracos, V.E.; Reiman, T.; Mazurak, V.C. Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. *Cancer* **2011**, *117*, 3774-3780.

216. Jin, X.; Xu, X.-T.; Tian, M.-X.; Dai, Z. N-3 polyunsaterated fatty acids improve quality of life and survival, but not body weight in cancer cachexia: A systematic review and meta-analysis of controlled trials. *Nutrition Research* **2022**.

217. West, N.J.; Clark, S.K.; Phillips, R.K.S.; Hutchinson, J.M.; Leicester, R.J.; Belluzzi, A.; Hull, M.A. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut* **2010**, *59*, 918-925.

218. Bougnoux, P.; Hajjaji, N.; Ferrasson, M.N.; Giraudeau, B.; Couet, C.; Le Floch, O. Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial. *British journal of cancer* **2009**, *101*, 1978-1985.

219. Xiong, R.-G.; Huang, S.-Y.; Wu, S.-X.; Zhou, D.-D.; Yang, Z.-J.; Saimaiti, A.; Zhao, C.-N.; Shang, A.O.; Zhang, Y.-J.; Gan, R.-Y. Anticancer effects and mechanisms of berberine from medicinal herbs: An update review. *Molecules* **2022**, *27*, 4523.

220. Pan, Y.; Zhang, F.; Zhao, Y.; Shao, D.; Zheng, X.; Chen, Y.; He, K.; Li, J.; Chen, L. Berberine enhances chemosensitivity and induces apoptosis through dose-orchestrated AMPK signaling in breast cancer. *Journal of Cancer* **2017**, *8*, 1679.

221. Kou, Y.; Tong, B.; Wu, W.; Liao, X.; Zhao, M. Berberine improves chemo-sensitivity to cisplatin by enhancing cell apoptosis and repressing PI3K/AKT/mTOR signaling pathway in gastric cancer. *Frontiers in pharmacology* **2020**, *11*, 616251.

222. Zhu, C.; Li, J.; Hua, Y.; Wang, J.; Wang, K.; Sun, J. Berberine inhibits the expression of SCT through miR-214-3p stimulation in breast cancer cells. *Evidence-Based Complementary and Alternative Medicine* **2020**, *2020*.

223. Li, S.; Wang, N.; Tan, H.Y.; Chueng, F.; Zhang, Z.J.; Yuen, M.F.; Feng, Y. Modulation of gut microbiota mediates berberine-induced expansion of immuno-suppressive cells to against alcoholic liver disease. *Clinical and Translational Medicine* **2020**, *10*, e112.

224. You, H.-Y.; Xie, X.-M.; Zhang, W.-J.; Zhu, H.-L.; Jiang, F.-Z. Berberine modulates cisplatin sensitivity of human gastric cancer cells by upregulation of miR-203. *In Vitro Cellular & Developmental Biology-Animal* **2016**, *52*, 857-863.

225. Chen, Y.-X.; Gao, Q.-Y.; Zou, T.-H.; Wang, B.-M.; Liu, S.-D.; Sheng, J.-Q.; Ren, J.-L.; Zou, X.-P.; Liu, Z.-J.; Song, Y.-Y. Berberine versus placebo for the prevention of recurrence of colorectal adenoma: a multicentre, double-blinded, randomised controlled study. *The Lancet Gastroenterology & Hepatology* **2020**, *5*, 267-275.

226. Cruz, P.M.R.; Mo, H.; McConathy, W.J.; Sabnis, N.; Lacko, A.G. The role of cholesterol metabolism and cholesterol transport in carcinogenesis: a review of scientific findings, relevant to future cancer therapeutics. *Frontiers in pharmacology* **2013**, *4*, 119.

227. Parrales, A.; Thoenen, E.; Iwakuma, T. The interplay between mutant p53 and the mevalonate pathway. *Cell Death & Differentiation* **2018**, *25*, 460-470.

228. Borgquist, S.; Bjarnadottir, O.; Kimbung, S.; Ahern, T.P. Statins: a role in breast cancer therapy? *Journal of internal medicine* **2018**, *284*, 346-357.

229. Shao, J.Y.-H.; Lee, F.-P.; Chang, C.-L.; Wu, S.-Y. Statin-based palliative therapy for hepatocellular carcinoma. *Medicine* **2015**, *94*.

230. Zhong, S.; Zhang, X.; Chen, L.; Ma, T.; Tang, J.; Zhao, J. Statin use and mortality in cancer patients: Systematic review and meta-analysis of observational studies. *Cancer Treat Rev* **2015**, *41*, 554-567, doi:10.1016/j.ctrv.2015.04.005.

231. Lin, J.J.; Ezer, N.; Sigel, K.; Mhango, G.; Wisnivesky, J.P. The effect of statins on survival in patients with stage IV lung cancer. *Lung cancer* **2016**, *99*, 137-142.

232. Manthravadi, S.; Shrestha, A.; Madhusudhana, S. Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis. *International journal of cancer* **2016**, *139*, 1281-1288.

233. Demierre, M.-F.; Higgins, P.D.R.; Gruber, S.B.; Hawk, E.; Lippman, S.M. Statins and cancer prevention. *Nat Rev Cancer* **2005**, *5*, 930-942.

234. Lu, C.; Li, X.; Ren, Y.; Zhang, X. Disulfiram: a novel repurposed drug for cancer therapy. *Cancer Chemotherapy and Pharmacology* **2021**, *87*, 159-172.

235. Kang, X.; Jadhav, S.; Annaji, M.; Huang, C.-H.; Amin, R.; Shen, J.; Ashby Jr, C.R.; Tiwari, A.K.; Babu, R.J.; Chen, P. Advancing Cancer Therapy with Copper/Disulfiram Nanomedicines and Drug Delivery Systems. *Pharmaceutics* **2023**, *15*, 1567.

236. Liu, P.; Wang, Z.; Brown, S.; Kannappan, V.; Tawari, P.E.; Jiang, W.; Irache, J.M.; Tang, J.Z.; Britland, S.; Armesilla, A.L. Liposome encapsulated Disulfiram inhibits NFκB pathway and targets breast cancer stem cells in vitro and in vivo. *Oncotarget* **2014**, *5*, 7471.

237. Yip, N.C.; Fombon, I.S.; Liu, P.; Brown, S.; Kannappan, V.; Armesilla, A.L.; Xu, B.; Cassidy, J.; Darling, J.L.; Wang, W. Disulfiram modulated ROS–MAPK and NFκB pathways and targeted breast cancer cells with cancer stem cell-like properties. *British journal of cancer* **2011**, *104*, 1564-1574.

238. Park, Y.M.; Go, Y.Y.; Shin, S.H.; Cho, J.-G.; Woo, J.-S.; Song, J.-J. Anti-cancer effects of disulfiram in head and neck squamous cell carcinoma via autophagic cell death. *PLoS One* **2018**, *13*, e0203069.

239. Triscott, J.; Lee, C.; Hu, K.; Fotovati, A.; Berns, R.; Pambid, M.; Luk, M.; Kast, R.E.; Kong, E.; Toyota, E. Disulfiram, a drug widely used to control alcoholism, suppresses self-renewal of glioblastoma and overrides resistance to temozolomide. *Oncotarget* **2012**, *3*, 1112.

240. Dufour, P.; Lang, J.M.; Giron, C.; Duclos, B.; Haehnel, P.; Jaeck, D.; Jung, J.M.; Oberling, F. Sodium ditiocarb as adjuvant immunotherapy for high risk breast cancer: a randomized study. *Biotherapy* **1993**, *6*, 9-12.

241. Huang, J.; Campian, J.L.; Gujar, A.D.; Tran, D.D.; Lockhart, A.C.; DeWees, T.A.; Tsien, C.I.; Kim, A.H. A phase I study to repurpose disulfiram in combination with temozolomide to treat newly diagnosed glioblastoma after chemoradiotherapy. *Journal of neuro-oncology* **2016**, *128*, 259-266.

242. Nechushtan, H.; Hamamreh, Y.; Nidal, S.; Gotfried, M.; Baron, A.; Shalev, Y.I.; Nisman, B.; Peretz, T.; Peylan-Ramu, N. A phase IIb trial assessing the addition of disulfiram to chemotherapy for the treatment of metastatic non-small cell lung cancer. *The oncologist* **2015**, *20*, 366-367.

243. Huang, J.; Campian, J.L.; Gujar, A.D.; Tsien, C.; Ansstas, G.; Tran, D.D.; DeWees, T.A.; Lockhart, A.C.; Kim, A.H. Final results of a phase I dose-escalation, dose-expansion study of adding disulfiram with or without copper to adjuvant temozolomide for newly diagnosed glioblastoma. *Journal of neuro-oncology* **2018**, *138*, 105-111.

244. Ghosh, A.K.; Hirasawa, N.; Ohuchi, K. Enhancement by histamine of vascular endothelial growth factor production in granulation tissue via H2 receptors. *British journal of pharmacology* **2001**, *134*, 1419.

245. Ibrahim, S.S.A.; El-Aal, S.A.A.; Reda, A.M.; Achy, S.E.; Shahine, Y. Anti-neoplastic action of Cimetidine/Vitamin C on histamine and the PI3K/AKT/mTOR pathway in Ehrlich breast cancer. *Scientific Reports* **2022**, *12*, 11514.

246. Deva, S.; Jameson, M. Histamine type 2 receptor antagonists as adjuvant treatment for resected colorectal cancer. *Cochrane Database of Systematic Reviews* **2012**.

247. Flodgren, P.; Borgström, S.; Jönsson, P.E.; Lindström, C.; Sjögren, H.O. Metastatic malignant melanoma: Regression induced by combined treatment with interferon [HuIFN-α (Le)] and cimetidine. *International journal of cancer* **1983**, *32*, 657-665.

248. Tønnesen, H.; Bülow, S.; Fischerman, K.; Hjortrup, A.; Pedersen, V.M.; Svendsen, L.B.; Knigge, U.; Damm, P.; Hesselfeldt, P.; Pedersen, I.K. Effect of cimetidine on survival after gastric cancer. *The Lancet* **1988**, *332*, 990-992.

249. Florence, L.; Syril, J.; Isabelle, C.; Jean-Fran, G.; Francis, D.; Jacques, B. Combined cimetidine and temozolomide, compared with temozolomide alone: significant increases in survival in nud mice bearing U373 human glioblastoma multiforme orthotopic xenografts. *J Neurosurg* **2005**, *102*, 706-714.

250. Thronicke, A.; Schad, F.; Debus, M.; Grabowski, J.; Soldner, G. Viscum album L. therapy in oncology: An update on current evidence. *Complementary Medicine Research* **2022**, *29*, 362-368.

251. Harmsma, M.; Grommé, M.; Ummelen, M.; Dignef, W.; Tusenius, K.J.; Ramaekers, F. Differential effects of Viscum album extract Iscador® Qu on cell cycle progression and apoptosis in cancer cells. *International Journal of Oncology* **2004**, *25*, 1521-1529.

252. Huber, R.; Rostock, M.; Goedl, R.; Ludtke, R.; Urech, K.; Buck, S.; Klein, R. Mistletoe treatment induces GM-CSF-and IL-5 production by PBMC and increases blood granulocyte-and eosinophil counts: a placebo controlled randomized study in healthy subjects. *European journal of medical research* **2005**, *10*, 411.

253. Loef, M.; Walach, H. Quality of life in cancer patients treated with mistletoe: a systematic review and meta-analysis. *BMC Complementary Medicine and Therapies* **2020**, *20*, 1-14.

254. Oei, S.L.; Thronicke, A.; Schad, F. Mistletoe and immunomodulation: insights and implications for anticancer therapies. *Evidence-Based Complementary and Alternative Medicine* **2019**, *2019*.

255. Ben-Arye, E.; Lavie, O.; Samuels, N.; Khamaisie, H.; Schiff, E.; Raz, O.G.; Mahajna, J. Safety of herbal medicine use during chemotherapy in patients with ovarian cancer: a "bedside-to-bench" approach. *Medical Oncology* **2017**, *34*, 1-6.

256. Kwon, Y.-S.; Chun, S.-Y.; Kim, M.-K.; Nan, H.-Y.; Lee, C.; Kim, S. Mistletoe extract targets the STAT3-FOXM1 pathway to induce apoptosis and inhibits metastasis in breast cancer cells. *The American Journal of Chinese Medicine* **2021**, *49*, 487-504.

257. Horneber, M.; van Ackeren, G.; Linde, K.; Rostock, M. Mistletoe therapy in oncology. *Cochrane Database of Systematic Reviews* **2008**.

258. Loef, M.; Walach, H. Survival of Cancer Patients Treated with Non-Fermented Mistletoe Extract: A Systematic Review and Meta-Analysis. *Integrative Cancer Therapies* **2022**, *21*, 15347354221133561.

259. Paller, C.J.; Wang, L.; Fu, W.; Kumar, R.; Durham, J.N.; Azad, N.S.; Laheru, D.A.; Browner, I.; Kachhap, S.K.; Boyapati, K. Phase I trial of intravenous mistletoe extract in advanced cancer. *Cancer Research Communications* **2023**, *3*, 338-346.

260. Kienle, G.S.; Mussler, M.; Fuchs, D.; Kiene, H. Intravenous mistletoe treatment in integrative cancer care: a qualitative study exploring the procedures, concepts, and observations of expert doctors. *Evidence-Based Complementary and Alternative Medicine* **2016**, *2016*.

261. Dutta, R.; Khalil, R.; Green, R.; Mohapatra, S.S.; Mohapatra, S. Withania somnifera (Ashwagandha) and withaferin A: Potential in integrative oncology. *International journal of molecular sciences* **2019**, *20*, 5310.

262. Mikulska, P.; Malinowska, M.; Ignacyk, M.; Szustowski, P.; Nowak, J.; Pesta, K.; Szeląg, M.; Szklanny, D.; Judasz, E.; Kaczmarek, G. Ashwagandha (Withania somnifera)—Current research on the health-promoting activities: a narrative review. *Pharmaceutics* **2023**, *15*, 1057.

263. Nagy, Z.; Cheung, B.B.; Tsang, W.; Tan, O.; Herath, M.; Ciampa, O.C.; Shadma, F.; Carter, D.R.; Marshall, G.M. Withaferin A activates TRIM16 for its anti-cancer activity in melanoma. *Scientific reports* **2020**, *10*, 19724.

264. Jawarneh, S.; Talib, W.H. Combination of ashwagandha water extract and intermittent fasting as a therapy to overcome cisplatin resistance in breast cancer: an in vitro and in vivo study. *Frontiers in Nutrition* **2022**, *9*, 863619.

265. Tang, Q.; Ren, L.; Liu, J.; Li, W.; Zheng, X.; Wang, J.; Du, G. Withaferin A triggers G2/M arrest and intrinsic apoptosis in glioblastoma cells via ATF4-ATF3-CHOP axis. *Cell Proliferation* **2020**, *53*, e12706.

266. Widodo, N.; Priyandoko, D.; Shah, N.; Wadhwa, R.; Kaul, S.C. Selective killing of cancer cells by Ashwagandha leaf extract and its component Withanone involves ROS signaling. *PloS one* **2010**, *5*, e13536.

267. Choi, B.Y.; Kim, B.-W. Withaferin-A inhibits colon cancer cell growth by blocking STAT3 transcriptional activity. *Journal of cancer prevention* **2015**, *20*, 185.

268. Koduru, S.; Kumar, R.; Srinivasan, S.; Evers, M.B.; Damodaran, C. Notch-1 inhibition by Withaferin-A: a therapeutic target against colon carcinogenesis. *Molecular cancer therapeutics* **2010**, *9*, 202-210.

269. Sikandan, A.; Shinomiya, T.; Nagahara, Y. Ashwagandha root extract exerts anti-inflammatory effects in HaCaT cells by inhibiting the MAPK/NF-κB pathways and by regulating cytokines. *International journal of molecular medicine* **2018**, *42*, 425-434.

270. Biswal, B.M.; Sulaiman, S.A.; Ismail, H.C.; Zakaria, H.; Musa, K.I. Effect of Withania somnifera (Ashwagandha) on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. *Integrative cancer therapies* **2013**, *12*, 312-322.

271. Chen, L.; Liu, Y.; Becher, A.; Diepold, K.; Schmid, E.; Fehn, A.; Brunner, C.; Rouhi, A.; Chiosis, G.; Cronauer, M. Sildenafil triggers tumor lethality through altered expression of HSP90 and degradation of PKD2. *Carcinogenesis* **2020**, *41*, 1421-1431.

272. Chhonker, S.K.; Rawat, D.; Koiri, R.K. Repurposing PDE5 inhibitor tadalafil and sildenafil as anticancer agent against hepatocellular carcinoma via targeting key events of glucose metabolism and multidrug resistance. *Journal of Biochemical and Molecular Toxicology* **2022**, *36*, e23100.

273. Cruz-Burgos, M.; Losada-Garcia, A.; Cruz-Hernández, C.D.; Cortés-Ramírez, S.A.; Camacho-Arroyo, I.; Gonzalez-Covarrubias, V.; Morales-Pacheco, M.; Trujillo-Bornios, S.I.; Rodríguez-Dorantes, M. New approaches in oncology for repositioning drugs: the case of PDE5 inhibitor sildenafil. *Frontiers in Oncology* **2021**, *11*, 627229.

274. Booth, L.; Roberts, J.L.; Cruickshanks, N.; Conley, A.; Durrant, D.E.; Das, A.; Fisher, P.B.; Kukreja, R.C.; Grant, S.; Poklepovic, A. Phosphodiesterase 5 inhibitors enhance chemotherapy killing in gastrointestinal/genitourinary cancer cells. *Molecular Pharmacology* **2014**, *85*, 408-419.

275. Domvri, K.; Zarogoulidis, K.; Zogas, N.; Zarogoulidis, P.; Petanidis, S.; Porpodis, K.; Kioseoglou, E.; Hohenforst-Schmidt, W. Potential synergistic effect of phosphodiesterase inhibitors with chemotherapy in lung cancer. *Journal of Cancer* **2017**, *8*, 3648.

276. Tai, L.-H.; Alkayyal, A.A.; Leslie, A.L.; Sahi, S.; Bennett, S.; Tanese de Souza, C.; Baxter, K.; Angka, L.; Xu, R.; Kennedy, M.A. Phosphodiesterase-5 inhibition reduces postoperative metastatic disease by targeting surgery-induced myeloid derived suppressor cell-dependent inhibition of Natural Killer cell cytotoxicity. *Oncoimmunology* **2018**, *7*, e1431082.

277. Serafini, P.; Meckel, K.; Kelso, M.; Noonan, K.; Califano, J.; Koch, W.; Dolcetti, L.; Bronte, V.; Borrello, I. Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function. *The Journal of experimental medicine* **2006**, *203*, 2691-2702.

278. Sutton, S.S.; Magagnoli, J.; Cummings, T.H.; Hardin, J.W. The association between phosphodiesterase-5 inhibitors and colorectal cancer in a national cohort of patients. *Clinical and translational gastroenterology* **2020**, *11*.

279. Weed, D.T.; Vella, J.L.; Reis, I.M.; De la Fuente, A.C.; Gomez, C.; Sargi, Z.; Nazarian, R.; Califano, J.; Borrello, I.; Serafini, P. Tadalafil reduces myeloid-derived suppressor cells and regulatory T cells and promotes tumor immunity in patients with head and neck squamous cell carcinoma. *Clinical cancer research* **2015**, *21*, 39-48.

280. Califano, J.A.; Khan, Z.; Noonan, K.A.; Rudraraju, L.; Zhang, Z.; Wang, H.; Goodman, S.; Gourin, C.G.; Ha, P.K.; Fakhry, C. Tadalafil augments tumor specific immunity in patients with head and neck squamous cell carcinoma. *Clinical cancer research* **2015**, *21*, 30-38.

281. Huang, W.; Sundquist, J.; Sundquist, K.; Ji, J. Phosphodiesterase-5 inhibitors use and risk for mortality and metastases among male patients with colorectal cancer. *Nature Communications* **2020**, *11*, 3191.

282. Danley, K.T.; Tan, A.; Catalona, W.J.; Leikin, R.; Helenowski, I.; Jovanovic, B.; Gurley, M.; Kuzel, T.M. The association of phosphodiesterase-5 inhibitors with the biochemical recurrence-free and overall survival of patients with prostate cancer following radical prostatectomy. 2022; pp. 57-e51.

283. Tsubamoto, H.; Ueda, T.; Inoue, K.; Sakata, K.; Shibahara, H.; Sonoda, T. Repurposing itraconazole as an anticancer agent. *Oncology letters* **2017**, *14*, 1240-1246.

284. Ali, T.; Rahman, S.U.; Hao, Q.; Li, W.; Liu, Z.; Ali Shah, F.; Murtaza, I.; Zhang, Z.; Yang, X.; Liu, G. Melatonin prevents neuroinflammation and relieves depression by attenuating autophagy impairment through FOXO3a regulation. *Journal of pineal research* **2020**, *69*, e12667.

285. Pounds, R.; Leonard, S.; Dawson, C.; Kehoe, S. Repurposing itraconazole for the treatment of cancer. *Oncology letters* **2017**, *14*, 2587-2597.

286. Kim, D.J.; Kim, J.; Spaunhurst, K.; Montoya, J.; Khodosh, R.; Chandra, K.; Fu, T.; Gilliam, A.; Molgó Novell, M. Open-label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma. **2014**.

287. Kim, J.; Tang, J.Y.; Gong, R.; Kim, J.; Lee, J.J.; Clemons, K.V.; Chong, C.R.; Chang, K.S.; Fereshteh, M.; Gardner, D. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. *Cancer cell* **2010**, *17*, 388-399.

288. Wang, W.; Dong, X.; Liu, Y.; Ni, B.; Sai, N.; You, L.; Sun, M.; Yao, Y.; Qu, C.; Yin, X. Itraconazole exerts anti-liver cancer potential through the Wnt, PI3K/AKT/mTOR, and ROS pathways. *Biomedicine & Pharmacotherapy* **2020**, *131*, 110661.

289. Antonarakis, E.S.; Heath, E.I.; Smith, D.C.; Rathkopf, D.; Blackford, A.L.; Danila, D.C.; King, S.; Frost, A.; Ajiboye, A.S.; Zhao, M. Repurposing itraconazole as a treatment for advanced prostate cancer: a noncomparative randomized phase II trial in men with metastatic castration-resistant prostate cancer. *The oncologist* **2013**, *18*, 163-173.

290. Chen, C.; Zhang, W. Itraconazole alters the stem cell characteristics of A549 and NCI-H460 human lung cancer cells by suppressing Wnt signaling. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* **2019**, *25*, 9509.

291. Chong, C.R.; Xu, J.; Lu, J.; Bhat, S.; Sullivan Jr, D.J.; Liu, J.O. Inhibition of angiogenesis by the antifungal drug itraconazole. *ACS chemical biology* **2007**, *2*, 263-270.

292. Mamtani, R.; Yang, Y.-X.; Scott, F.I.; Lewis, J.D.; Boursi, B. Association of itraconazole, a hedgehog inhibitor, and bladder cancer. *The Journal of urology* **2016**, *196*, 343-348.

293. Marastoni, S.; Madariaga, A.; Pesic, A.; Nair, S.N.; Li, Z.J.; Shalev, Z.; Ketela, T.; Colombo, I.; Mandilaras, V.; Cabanero, M. Repurposing itraconazole and hydroxychloroquine to target lysosomal homeostasis in epithelial ovarian cancer. *Cancer Research Communications* **2022**, *2*, 293-306.

294. Nacev, B.A.; Grassi, P.; Dell, A.; Haslam, S.M.; Liu, J.O. The antifungal drug itraconazole inhibits vascular endothelial growth factor receptor 2 (VEGFR2) glycosylation, trafficking, and signaling in endothelial cells. *Journal of Biological Chemistry* **2011**, *286*, 44045-44056.

295. Zhang, W.; Bhagwath, A.S.; Ramzan, Z.; Williams, T.A.; Subramaniyan, I.; Edpuganti, V.; Kallem, R.R.; Dunbar, K.B.; Ding, P.; Gong, K. Itraconazole exerts its antitumor effect in esophageal cancer by suppressing the HER2/AKT signaling pathway. *Molecular cancer therapeutics* **2021**, *20*, 1904-1915.

296. Tsubamoto, H.; Sonoda, T.; Yamasaki, M.; Inoue, K. Impact of combination chemotherapy with itraconazole on survival of patients with refractory ovarian cancer. *Anticancer Research* **2014**, *34*, 2481-2487.

297. Lan, K.; Yan, R.; Zhu, K.; Li, W.; Xu, Z.; Dang, C.; Li, K. Itraconazole inhibits the proliferation of gastric cancer cells in vitro and improves patient survival. *Oncology Letters* **2018**, *16*, 3651-3657.

298. Rudin, C.M.; Brahmer, J.R.; Juergens, R.A.; Hann, C.L.; Ettinger, D.S.; Sebree, R.; Smith, R.; Aftab, B.T.; Huang, P.; Liu, J.O. Phase 2 study of pemetrexed and itraconazole as second-line therapy for metastatic nonsquamous non–small-cell lung cancer. *Journal of Thoracic Oncology* **2013**, *8*, 619-623.

299. Shen, P.-W.; Chou, Y.-M.; Li, C.-L.; Liao, E.-C.; Huang, H.-S.; Yin, C.-H.; Chen, C.-L.; Yu, S.-J. Itraconazole improves survival outcomes in patients with colon cancer by inducing autophagic cell death and inhibiting transketolase expression. *Oncology Letters* **2021**, *22*, 1-11.

300. Tsubamoto, H.; Sonoda, T.; Ikuta, S.; Tani, S.; Inoue, K.; Yamanaka, N. Combination chemotherapy with itraconazole for treating metastatic pancreatic cancer in the second-line or additional setting. *Anticancer Research* **2015**, *35*, 4191-4196.

301. Tsubamoto, H.; Sonoda, T.; Inoue, K. Impact of itraconazole on the survival of heavily pre-treated patients with triple-negative breast cancer. *Anticancer Research* **2014**, *34*, 3839-3844.

302. Gerber, D.E.; Putnam, W.C.; Fattah, F.J.; Kernstine, K.H.; Brekken, R.A.; Pedrosa, I.; Skelton, R.; Saltarski, J.M.; Lenkinski, R.E.; Leff, R.D. Concentration-dependent Early Antivascular and Antitumor Effects of Itraconazole in Non–Small Cell Lung Cancer. *Clinical Cancer Research* **2021**, *26*, 6017-6027.

303. Tsubamoto, H.; Sonoda, T.; Ikuta, S.; Tani, S.; Inoue, K.; Yamanaka, N. Impact of itraconazole after first-line chemotherapy on survival of patients with metastatic biliary tract cancer. *Anticancer Research* **2015**, *35*, 4923-4927.

304. Ringshausen, I.; Feuerstacke, Y.; Krainz, P.; den Hollander, J.; Hermann, K.; Buck, A.; Peschel, C.; Meyer zum Bueschenfelde, C. Antifungal therapy with itraconazole impairs the anti-lymphoma effects of rituximab by inhibiting recruitment of CD20 to cell surface lipid rafts. *Cancer Research* **2010**, *70*, 4292-4296.

305. Yang, B.R.; Seong, J.-M.; Choi, N.-K.; Shin, J.-Y.; Lee, J.; Kim, Y.-J.; Kim, M.-S.; Park, S.; Song, H.J.; Park, B.-J. Co-medication of statins with contraindicated drugs. *PLoS One* **2015**, *10*, e0125180.

306. Kinzel, A.; Ambrogi, M.; Varshaver, M.; Kirson, E.D. Tumor treating fields for glioblastoma treatment: Patient satisfaction and compliance with the second-generation Optune® system. *Clinical Medicine Insights: Oncology* **2019**, *13*, 1179554918825449.

307. Moser, J.C.; Salvador, E.; Deniz, K.; Swanson, K.; Tuszynski, J.; Carlson, K.W.; Karanam, N.K.; Patel, C.B.; Story, M.; Lou, E. The mechanisms of action of Tumor Treating Fields. *Cancer research* **2022**, *82*, 3650-3658.

308. Stupp, R.; Taillibert, S.; Kanner, A.; Read, W.; Steinberg, D.M.; Lhermitte, B.; Toms, S.; Idbaih, A.; Ahluwalia, M.S.; Fink, K. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *Jama* **2017**, *318*, 2306-2316.

309. Ghiaseddin, A.P.; Shin, D.; Melnick, K.; Tran, D.D. Tumor treating fields in the management of patients with malignant gliomas. *Current Treatment Options in Oncology* **2020**, *21*, 1-19.

310. National Comprehensive Cancer, N. NCCN clinical practice guidelines in oncology. Availabe online: https://www.nccn.org/login?returnURL=https://www.nccn.org/professionals/physician_gls/pdf/ (accessed on

311. Yanovsky, R.L.; Bartenstein, D.W.; Rogers, G.S.; Isakoff, S.J.; Chen, S.T. Photodynamic therapy for solid tumors: A review of the literature. *Photodermatology, photoimmunology & photomedicine* **2019**, *35*, 295-303.

312. dos Santos, A.F.; de Almeida, D.R.Q.; Terra, L.F.; Baptista, M.S.; Labriola, L. Photodynamic therapy in cancer treatment-an update review. *J. Cancer Metastasis Treat* **2019**, *5*, 10-20517.

313. Reiter, R.J.; Ma, Q.; Sharma, R. Melatonin in mitochondria: mitigating clear and present dangers. *Physiology* **2020**.

314. Zimmerman, S.; Reiter, R.J. Melatonin and the optics of the human body. *Melatonin Research* **2019**, *2*, 138-160.

315. Hobday, R.A.; Cason, J.W. The open-air treatment of pandemic influenza. *American journal of public health* **2009**, *99*, S236-S242.

316.   Lindqvist, P.G.; Epstein, E.; Landin-Olsson, M.; Ingvar, C.; Nielsen, K.; Stenbeck, M.; Olsson, H. Avoidance of sun exposure is a risk factor for all-cause mortality: results from the Melanoma in Southern Sweden cohort. *Journal of internal medicine* **2014**, *276*, 77-86.

317.   Moore, C.M.; Nathan, T.R.; Lees, W.R.; Mosse, C.A.; Freeman, A.; Emberton, M.; Bown, S.G. Photodynamic therapy using meso tetra hydroxy phenyl chlorin (mTHPC) in early prostate cancer. *Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery* **2006**, *38*, 356-363.

318.   Kostron, H. Photodynamic diagnosis and therapy and the brain. *Photodynamic Therapy: Methods and Protocols* **2010**, 261-280.

319.   Windahl, T.; Andersson, S.-O.; Lofgren, L. Photodynamic therapy of localised prostatic cancer. *The Lancet* **1990**, *336*, 1139.

320.   Bredell, M.G.; Besic, E.; Maake, C.; Walt, H. The application and challenges of clinical PD–PDT in the head and neck region: A short review. *Journal of Photochemistry and Photobiology B: Biology* **2010**, *101*, 185-190.

321.   Moen, I.; Stuhr, L.E.B. Hyperbaric oxygen therapy and cancer—a review. *Targeted oncology* **2012**, *7*, 233-242.

322.   Raa, A.; Stansberg, C.; Steen, V.M.; Bjerkvig, R.; Reed, R.K.; Stuhr, L.E.B. Hyperoxia retards growth and induces apoptosis and loss of glands and blood vessels in DMBA-induced rat mammary tumors. *BMC cancer* **2007**, *7*, 1-10.

323.   Stuhr, L.E.B.; Raa, A.; Øyan, A.M.; Kalland, K.H.; Sakariassen, P.O.; Petersen, K.; Bjerkvig, R.; Reed, R.K. Hyperoxia retards growth and induces apoptosis, changes in vascular density and gene expression in transplanted gliomas in nude rats. *Journal of neuro-oncology* **2007**, *85*, 191-202.

324.   Gore, A.; Muralidhar, M.; Espey, M.G.; Degenhardt, K.; Mantell, L.L. Hyperoxia sensing: from molecular mechanisms to significance in disease. *Journal of immunotoxicology* **2010**, *7*, 239-254.

325.   Bennett, M.H.; Feldmeier, J.; Smee, R.; Milross, C. Hyperbaric oxygenation for tumour sensitisation to radiotherapy. *Cochrane Database of Systematic Reviews* **2018**.

326.   Mohammadifard, N.; Haghighatdoost, F.; Rahimlou, M.; Rodrigues, A.P.S.; Gaskarei, M.K.; Okhovat, P.; de Oliveira, C.; Silveira, E.A.; Sarrafzadegan, N. The Effect of Ketogenic Diet on Shared Risk Factors of Cardiovascular Disease and Cancer. *Nutrients* **2022**, *14*, 3499.

327.   Kumar, A.; Kumari, S.; Singh, D. Insights into the Cellular Interactions and Molecular Mechanisms of Ketogenic Diet for Comprehensive Management of Epilepsy. *Current Neuropharmacology* **2022**, *20*, 2034.

328.   Talib, W.H.; Mahmod, A.I.; Kamal, A.; Rashid, H.M.; Alashqar, A.M.; Khater, S.; Jamal, D.; Waly, M. Ketogenic diet in cancer prevention and therapy: molecular targets and therapeutic opportunities. *Current issues in molecular biology* **2021**, *43*, 558-589.

329.   Wang, Q.; Zhou, W. Roles and molecular mechanisms of physical exercise in cancer prevention and treatment. *J Sport Health Sci* **2021**, *10*, 201-210, doi:10.1016/j.jshs.2020.07.008.

330.   Friedenreich, C.M.; Stone, C.R.; Cheung, W.Y.; Hayes, S.C. Physical Activity and Mortality in Cancer Survivors: A Systematic Review and Meta-Analysis. *JNCI Cancer Spectr* **2020**, *4*, pkz080, doi:10.1093/jncics/pkz080.

331.   Kenfield, S.A.; Stampfer, M.J.; Giovannucci, E.; Chan, J.M. Physical Activity and Survival After Prostate Cancer Diagnosis in the Health Professionals Follow-Up Study. *JCO* **2011**, *29*, 726-732, doi:10.1200/JCO.2010.31.5226.

332.   Lopez, P.; Galvão, D.A.; Taaffe, D.R.; Newton, R.U.; Souza, G.; Trajano, G.S.; Pinto, R.S. Resistance training in breast cancer patients undergoing primary treatment: a systematic review and meta-regression of exercise dosage. *Breast Cancer* **2021**, *28*, 16-24, doi:10.1007/s12282-020-01147-3.

333.   Lahart, I.M.; Metsios, G.S.; Nevill, A.M.; Carmichael, A.R. Physical activity, risk of death and recurrence in breast cancer survivors: A systematic review and meta-analysis of epidemiological studies. *Acta Oncol* **2015**, *54*, 635-654, doi:10.3109/0284186X.2014.998275.

334.   Beasley, J.M.; Kwan, M.L.; Chen, W.Y.; Weltzien, E.K.; Kroenke, C.H.; Lu, W.; Nechuta, S.J.; Cadmus-Bertram, L.; Patterson, R.E.; Sternfeld, B., et al. Meeting the physical activity guidelines and survival after breast cancer: findings from the after breast cancer pooling project. *Breast Cancer Res Treat* **2012**, *131*, 637-643, doi:10.1007/s10549-011-1770-1.

335.   Chen, X.; Lu, W.; Zheng, W.; Gu, K.; Matthews, C.E.; Chen, Z.; Zheng, Y.; Shu, X.O. Exercise after diagnosis of breast cancer in association with survival. *Cancer Prev Res (Phila)* **2011**, *4*, 1409-1418, doi:10.1158/1940-6207.CAPR-10-0355.

336.   Eckerling, A.; Ricon-Becker, I.; Sorski, L.; Sandbank, E.; Ben-Eliyahu, S. Stress and cancer: mechanisms, significance and future directions. *Nat Rev Cancer* **2021**, *21*, 767-785, doi:10.1038/s41568-021-00395-5.

337.   Song, H.; Saito, E.; Sawada, N.; Abe, S.K.; Hidaka, A.; Shimazu, T.; Yamaji, T.; Goto, A.; Iwasaki, M.; Sasazuki, S., et al. Perceived stress level and risk of cancer incidence in a Japanese population: the Japan Public Health Center (JPHC)-based Prospective Study. *Sci Rep* **2017**, *7*, 12964, doi:10.1038/s41598-017-13362-8.

338.   Kikuchi, N.; Nishiyama, T.; Sawada, T.; Wang, C.; Lin, Y.; Watanabe, Y.; Tamakoshi, A.; Kikuchi, S. Perceived Stress and Colorectal Cancer Incidence: The Japan Collaborative Cohort Study. *Sci Rep* **2017**, *7*, 40363, doi:10.1038/srep40363.

339. Walker, W.H.; Borniger, J.C. Molecular mechanisms of cancer-induced sleep disruption. *International journal of molecular sciences* **2019**, *20*, 2780.

340. Iseki, K.; Tatsuta, M.; Uehara, H.; Iishi, H.; Yano, H.; Sakai, N.; Ishiguro, S. Inhibition of angiogenesis as a mechanism for inhibition by Lα-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 of colon carcinogenesis induced by azoxymethane in Wistar rats. *International Journal of Cancer* **1999**, *81*, 730-733, doi:10.1002/(SICI)1097-0215(19990531)81:5<730::AID-IJC11>3.0.CO;2-Q.

341. Pálmer, H.G.; González-Sancho, J.M.; Espada, J.; Berciano, M.T.; Puig, I.; Baulida, J.; Quintanilla, M.; Cano, A.; de Herreros, A.G.; Lafarga, M., et al. Vitamin D(3) promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of beta-catenin signaling. *J Cell Biol* **2001**, *154*, 369-387, doi:10.1083/jcb.200102028.

342. Garland, C.F.; Garland, F.C.; Gorham, E.D.; Lipkin, M.; Newmark, H.; Mohr, S.B.; Holick, M.F. The Role of Vitamin D in Cancer Prevention. *Am J Public Health* **2006**, *96*, 252-261, doi:10.2105/AJPH.2004.045260.

343. Fujioka, T.; Suzuki, Y.; Okamoto, T.; Mastushita, N.; Hasegawa, M.; Omori, S. Prevention of renal cell carcinoma by active vitamin D3. *World J Surg* **2000**, *24*, 1205-1210, doi:10.1007/s002680010206.

344. Keum, N.; Lee, D.H.; Greenwood, D.C.; Manson, J.E.; Giovannucci, E. Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. *Annals of Oncology* **2019**, *30*, 733-743, doi:10.1093/annonc/mdz059.

345. Chandler, P.D.; Chen, W.Y.; Ajala, O.N.; Hazra, A.; Cook, N.; Bubes, V.; Lee, I.M.; Giovannucci, E.L.; Willett, W.; Buring, J.E., et al. Effect of Vitamin D3 Supplements on Development of Advanced Cancer: A Secondary Analysis of the VITAL Randomized Clinical Trial. *JAMA Network Open* **2020**, *3*, e2025850, doi:10.1001/jamanetworkopen.2020.25850.

346. Marcinowska-Suchowierska, E.; Kupisz-Urbańska, M.; Łukaszkiewicz, J.; Płudowski, P.; Jones, G. Vitamin D Toxicity–A Clinical Perspective. *Frontiers in Endocrinology* **2018**, *9*.

347. Veiga, E.C.d.A.; Simões, R.; Valenti, V.E.; Cipolla-Neto, J.; Abreu, L.C.; Barros, E.P.M.; Sorpreso, I.C.E.; Baracat, M.C.P.; Baracat, E.C.; Soares, J.M. Repercussions of melatonin on the risk of breast cancer: a systematic review and meta-analysis. *Rev. Assoc. Med. Bras.* **2019**, *65*, 699-705, doi:10.1590/1806-9282.65.5.699.

348. Lim, S.; Park, S.; Koyanagi, A.; Yang, J.W.; Jacob, L.; Yon, D.K.; Lee, S.W.; Kim, M.S.; Il Shin, J.; Smith, L. Effects of exogenous melatonin supplementation on health outcomes: An umbrella review of meta-analyses based on randomized controlled trials. *Pharmacological Research* **2022**, *176*, 106052, doi:10.1016/j.phrs.2021.106052.

349. Sugden, D. Psychopharmacological effects of melatonin in mouse and rat. *J Pharmacol Exp Ther* **1983**, *227*, 587-591.

350. Rehman, H.; Krishnasamy, Y.; Haque, K.; Thurman, R.G.; Lemasters, J.J.; Schnellmann, R.G.; Zhong, Z. Green Tea Polyphenols Stimulate Mitochondrial Biogenesis and Improve Renal Function after Chronic Cyclosporin A Treatment in Rats. *PLOS ONE* **2013**, *8*, e65029, doi:10.1371/journal.pone.0065029.

351. Lin, C.-H.; Shen, Y.-A.; Hung, P.-H.; Yu, Y.-B.; Chen, Y.-J. Epigallocathechin gallate, polyphenol present in green tea, inhibits stem-like characteristics and epithelial-mesenchymal transition in nasopharyngeal cancer cell lines. *BMC Complement Altern Med* **2012**, *12*, 201, doi:10.1186/1472-6882-12-201.

352. Bonuccelli, G.; Sotgia, F.; Lisanti, M.P. Matcha green tea (MGT) inhibits the propagation of cancer stem cells (CSCs), by targeting mitochondrial metabolism, glycolysis and multiple cell signalling pathways. *Aging (Albany NY)* **2018**, *10*, 1867-1883, doi:10.18632/aging.101483.

353. Yu, S.; Zhu, L.; Wang, K.; Yan, Y.; He, J.; Ren, Y. Green tea consumption and risk of breast cancer. *Medicine (Baltimore)* **2019**, *98*, e16147, doi:10.1097/MD.0000000000016147.

354. Abe, S.K.; Inoue, M. Green tea and cancer and cardiometabolic diseases: a review of the current epidemiological evidence. *Eur J Clin Nutr* **2021**, *75*, 865-876, doi:10.1038/s41430-020-00710-7.

355. Mirtavoos-Mahyari, H.; Salehipour, P.; Parohan, M.; Sadeghi, A. Effects of Coffee, Black Tea and Green Tea Consumption on the Risk of Non-Hodgkin's Lymphoma: A Systematic Review and Dose–Response Meta-Analysis of Observational Studies. *Nutrition and Cancer* **2019**, *71*, 887-897, doi:10.1080/01635581.2019.1595055.

356. Dowling, R.J.O.; Zakikhani, M.; Fantus, I.G.; Pollak, M.; Sonenberg, N. Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells. *Cancer Research* **2007**, *67*, 10804-10812, doi:10.1158/0008-5472.CAN-07-2310.

357. He, K.; Hu, H.; Ye, S.; Wang, H.; Cui, R.; Yi, L. The effect of metformin therapy on incidence and prognosis in prostate cancer: A systematic review and meta-analysis. *Sci Rep* **2019**, *9*, 2218, doi:10.1038/s41598-018-38285-w.

358. Ng, C.-A.W.; Jiang, A.A.; Toh, E.M.S.; Ng, C.H.; Ong, Z.H.; Peng, S.; Tham, H.Y.; Sundar, R.; Chong, C.S.; Khoo, C.M. Metformin and colorectal cancer: a systematic review, meta-analysis and meta-regression. *Int J Colorectal Dis* **2020**, *35*, 1501-1512, doi:10.1007/s00384-020-03676-x.

359. Shi, Y.-Q.; Zhou, X.-C.; Du, P.; Yin, M.-Y.; Xu, L.; Chen, W.-J.; Xu, C.-F. Relationships are between metformin use and survival in pancreatic cancer patients concurrent with diabetes. *Medicine (Baltimore)* **2020**, *99*, e21687, doi:10.1097/MD.0000000000021687.

360. Zhang, K.; Bai, P.; Dai, H.; Deng, Z. Metformin and risk of cancer among patients with type 2 diabetes mellitus: A systematic review and meta-analysis. *Primary Care Diabetes* **2021**, *15*, 52-58, doi:10.1016/j.pcd.2020.06.001.

361. PubChem. Metformin.

362. Kunwar, A.; Barik, A.; Mishra, B.; Rathinasamy, K.; Pandey, R.; Priyadarsini, K.I. Quantitative cellular uptake, localization and cytotoxicity of curcumin in normal and tumor cells. *Biochimica et Biophysica Acta (BBA)-General Subjects* **2008**, *1780*, 673-679.

363. de Waure, C.; Bertola, C.; Baccarini, G.; Chiavarini, M.; Mancuso, C. Exploring the Contribution of Curcumin to Cancer Therapy: A Systematic Review of Randomized Controlled Trials. *Pharmaceutics* **2023**, *15*, 1275, doi:10.3390/pharmaceutics15041275.

364. Opdyke, D.J.L.; Letizia, C. Monographs. *Food and Chemical Toxicology* **1983**, *21*, 833-875, doi:10.1016/0278-6915(83)90220-X.

365. Huang, L.; Zhao, L.; Zhang, J.; He, F.; Wang, H.; Liu, Q.; Shi, D.; Ni, N.; Wagstaff, W.; Chen, C., et al. Antiparasitic mebendazole (MBZ) effectively overcomes cisplatin resistance in human ovarian cancer cells by inhibiting multiple cancer-associated signaling pathways. *Aging (Albany NY)* **2021**, *13*, 17407-17427, doi:10.18632/aging.203232.

366. Nygren, P.; Larsson, R. Drug repositioning from bench to bedside: tumour remission by the antihelmintic drug mebendazole in refractory metastatic colon cancer. *Acta Oncol* **2014**, *53*, 427-428, doi:10.3109/0284186X.2013.844359.

367. Dobrosotskaya, I.Y.; Hammer, G.D.; Schteingart, D.E.; Maturen, K.E.; Worden, F.P. Mebendazole monotherapy and long-term disease control in metastatic adrenocortical carcinoma. *Endocr Pract* **2011**, *17*, e59-62, doi:10.4158/EP10390.CR.

368. Chiang, R.S.; Syed, A.B.; Wright, J.L.; Montgomery, B.; Srinivas, Y. Fenbendazole Enhancing Anti-Tumor Effect: A Case Series. *Clinical Oncology: Case Reports* **2021**, *2021*.

369. Marsboom, R. Toxicologic studies on mebendazole. *Toxicology and Applied Pharmacology* **1973**, *24*, 371-377, doi:10.1016/0041-008X(73)90043-4.

370. Fabian, C.J.; Kimler, B.F.; Hursting, S.D. Omega-3 fatty acids for breast cancer prevention and survivorship. *Breast Cancer Res* **2015**, *17*, 62, doi:10.1186/s13058-015-0571-6.

371. Nindrea, R.D.; Aryandono, T.; Lazuardi, L.; Dwiprahasto, I. Protective Effect of Omega-3 Fatty Acids in Fish Consumption Against Breast Cancer in Asian Patients: A Meta-Analysis. *Asian Pac J Cancer Prev* **2019**, *20*, 327-332, doi:10.31557/APJCP.2019.20.2.327.

372. Zhang, Y.; Sun, Y.; Yu, Q.; Song, S.; Brenna, J.T.; Shen, Y.; Ye, K. Higher ratio of plasma omega-6/omega-3 fatty acids is associated with greater risk of all-cause, cancer, and cardiovascular mortality: a population-based cohort study in UK Biobank. **2023**, 10.1101/2023.01.16.23284631, doi:10.1101/2023.01.16.23284631.

373. Bays, H.E. Safety Considerations with Omega-3 Fatty Acid Therapy. *The American Journal of Cardiology* **2007**, *99*, S35-S43, doi:10.1016/j.amjcard.2006.11.020.

374. Zhang, C.; Sheng, J.; Li, G.; Zhao, L.; Wang, Y.; Yang, W.; Yao, X.; Sun, L.; Zhang, Z.; Cui, R. Effects of Berberine and Its Derivatives on Cancer: A Systems Pharmacology Review. *Frontiers in Pharmacology* **2020**, *10*.

375. Wang, Y.; Liu, Y.; Du, X.; Ma, H.; Yao, J. The Anti-Cancer Mechanisms of Berberine: A Review. *Cancer Manag Res* **2020**, *12*, 695-702, doi:10.2147/CMAR.S242329.

376. Fang, S.; Guo, S.; Du, S.; Cao, Z.; Yang, Y.; Su, X.; Wei, W. Efficacy and safety of berberine in preventing recurrence of colorectal adenomas: A systematic review and meta-analysis. *Journal of Ethnopharmacology* **2022**, *282*, 114617, doi:10.1016/j.jep.2021.114617.

377. Xu, J.; Long, Y.; Ni, L.; Yuan, X.; Yu, N.; Wu, R.; Tao, J.; Zhang, Y. Anticancer effect of berberine based on experimental animal models of various cancers: a systematic review and meta-analysis. *BMC Cancer* **2019**, *19*, 589, doi:10.1186/s12885-019-5791-1.

378. Haginiwa, J.; Harada, M. Pharmacological Studies on Crude Drugs. V. *Yakugaku Zasshi* **1962**, *82*, 726-731, doi:10.1248/yakushi1947.82.5_726.

379. Jiang, W.; Hu, J.-W.; He, X.-R.; Jin, W.-L.; He, X.-Y. Statins: a repurposed drug to fight cancer. *J Exp Clin Cancer Res* **2021**, *40*, 241, doi:10.1186/s13046-021-02041-2.

380. Carter, P.; Vithayathil, M.; Kar, S.; Potluri, R.; Mason, A.M.; Larsson, S.C.; Burgess, S. Predicting the effect of statins on cancer risk using genetic variants from a Mendelian randomization study in the UK Biobank. *Elife* **2020**, *9*, e57191.

381. Yu, O.; Eberg, M.; Benayoun, S.; Aprikian, A.; Batist, G.; Suissa, S.; Azoulay, L. Use of Statins and the Risk of Death in Patients With Prostate Cancer. *JCO* **2014**, *32*, 5-11, doi:10.1200/JCO.2013.49.4757.

382. Manthravadi, S.; Shrestha, A.; Madhusudhana, S. Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis. *International Journal of Cancer* **2016**, *139*, 1281-1288, doi:10.1002/ijc.30185.

383. Ahern, T.P.; Pedersen, L.; Tarp, M.; Cronin-Fenton, D.P.; Garne, J.P.; Silliman, R.A.; Sørensen, H.T.; Lash, T.L. Statin Prescriptions and Breast Cancer Recurrence Risk: A Danish Nationwide Prospective Cohort Study. *J Natl Cancer Inst* **2011**, *103*, 1461-1468, doi:10.1093/jnci/djr291.

384. Lash, T.L.; Riis, A.H.; Ostenfeld, E.B.; Erichsen, R.; Vyberg, M.; Ahern, T.P.; Thorlacius-Ussing, O. Associations of Statin Use With Colorectal Cancer Recurrence and Mortality in a Danish Cohort. *Am J Epidemiol* **2017**, *186*, 679-687, doi:10.1093/aje/kww245.

385. Shao, J.Y.-H.; Lee, F.-P.; Chang, C.-L.; Wu, S.-Y. Statin-Based Palliative Therapy for Hepatocellular Carcinoma. *Medicine (Baltimore)* **2015**, *94*, e1801, doi:10.1097/MD.0000000000001801.

386. Gray, R.T.; Coleman, H.G.; Hughes, C.; Murray, L.J.; Cardwell, C.R. Statin use and survival in colorectal cancer: Results from a population-based cohort study and an updated systematic review and meta-analysis. *Cancer Epidemiol* **2016**, *45*, 71-81, doi:10.1016/j.canep.2016.10.004.

387. Lin, J.J.; Ezer, N.; Sigel, K.; Mhango, G.; Wisnivesky, J.P. The effect of statins on survival in patients with stage IV lung cancer. *Lung Cancer* **2016**, *99*, 137-142, doi:10.1016/j.lungcan.2016.07.006.

388. Elseweidy, M.; Asker, E.-S.; Atteia, H.; Mohamed, S.; Hegazy, S. Atorvastatin and Fenofibrate Modulate Certain Steroidal Hormones, Vitamin D and Bile Acids in Diabetic Dyslipidemic Rats. **2015**, *7*, 426-434.

389. Jiang, W.; Hu, J.-W.; He, X.-R.; Jin, W.-L.; He, X.-Y. Statins: a repurposed drug to fight cancer. *Journal of Experimental & Clinical Cancer Research* **2021**, *40*, 1-33.

390. Baas, J.M.; Krens, L.L.; ten Tije, A.J.; Erdkamp, F.; van Wezel, T.; Morreau, H.; Gelderblom, H.; Guchelaar, H.J. Safety and efficacy of the addition of simvastatin to cetuximab in previously treated KRAS mutant metastatic colorectal cancer patients. *Invest New Drugs* **2015**, *33*, 1242-1247, doi:doi:10.1007/s10637-015-0285-8.

391. PubChem. Simvastatin. Availabe online: https://www.ncbi.nlm.nih.gov/pubmed/ (accessed on

392. Liu, P.; Kumar, I.; Brown, S.; Kannappan, V.; Tawari, P.; Tang, J.; Jiang, W.; Armesilla, A.; Darling, J.; Wang, W. Disulfiram targets cancer stem-like cells and reverses resistance and cross-resistance in acquired paclitaxel-resistant triple-negative breast cancer cells. *British journal of cancer* **2013**, *109*, 1876-1885.

393. Yang, Y.; Zhang, K.; Wang, Y.; Li, M.; Sun, X.; Liang, Z.; Wang, L.; Chen, L.; Yang, H.; Zhu, L. Disulfiram chelated with copper promotes apoptosis in human breast cancer cells by impairing the mitochondria functions. *Scanning* **2016**, *38*, 825-836, doi:https://doi.org/10.1002/sca.21332.

394. PubChem. Disulfiram. Availabe online: https://www.ncbi.nlm.nih.gov/pubmed/ (accessed on

395. Kubecova, M.; Kolostova, K.; Pinterova, D.; Kacprzak, G.; Bobek, V. Cimetidine: an anticancer drug? *Eur J Pharm Sci* **2011**, *42*, 439-444, doi:10.1016/j.ejps.2011.02.004.

396. Tonnesen, H.; Bülow, S.; Fischerman, K.; Hjortrup, A.; Møller Pedersen, V.; Bo Svendsen, L.; Knigge, U.; Damm, P.; Hesselfeldt, P.; Krogh Pedersen, I., et al. Effect of Cimetidine on Survival after gastric cancer. *The Lancet* **1988**, *332*, 990-992, doi:10.1016/S0140-6736(88)90743-X.

397. Deva, S.; Jameson, M. Histamine type 2 receptor antagonists as adjuvant treatment for resected colorectal cancer. *Cochrane Database Syst Rev* **2012**, 10.1002/14651858.CD007814.pub2, CD007814, doi:10.1002/14651858.CD007814.pub2.

398. Brimblecombe, R.W.; Duncan, W.A.M.; Durant, G.J.; Emmett, J.C.; Ganellin, C.R.; Parsons, M.E. Cimetidine—A Non-Thiourea H2-Receptor Antagonist. *J Int Med Res* **1975**, *3*, 86-92, doi:10.1177/030006057500300205.

399. Kleijnen, J.; Knipschild, P. Mistletoe treatment for cancer review of controlled trials in humans. *Phytomedicine* **1994**, *1*, 255-260.

400. John Wasagwa, B.B.L., Biu Abubakar Abdullahi, Luka Joshua, Ngulde Ibrahim Saidu, Onyiche Emmanuel Thank God. Phytochemistry and Toxicity Studies on Aqueous Extracts of Leaf and Stem of Mistletoe (*Science Publishing Group* **2018**, *4*, 1, doi:10.11648/j.ijhnm.20180401.11.

401. Phase I Trial of Intravenous Mistletoe Extract in Advanced Cancer | Cancer Research Communications | American Association for Cancer Research. **2023**, 10.1158/2767-9764.CRC-23-0002, doi:10.1158/2767-9764.CRC-23-0002.

402. Shi, Z.; Tiwari, A.K.; Patel, A.S.; Fu, L.-W.; Chen, Z.-S. Roles of sildenafil in enhancing drug sensitivity in cancer. *Cancer Research* **2011**, *71*, 3735-3738, doi:10.1158/0008-5472.CAN-11-0375.

403. PubChem. Sildenafil.

404. Liu, N.; Yan, L.; Shan, F.; Wang, X.; Qu, N.; Handley, M.K.; Ma, M. Low-dose naltrexone plays antineoplastic role in cervical cancer progression through suppressing PI3K/AKT/mTOR pathway. *Translational Oncology* **2021**, *14*, 101028, doi:https://doi.org/10.1016/j.tranon.2021.101028.

405. WM, L.; AG, D. Naltrexone at low doses (LDN) and its relevance to cancer therapy. *Expert review of anticancer therapy* **2022**, *22*, doi:10.1080/14737140.2022.2037426.

406. L, P.; J, Y. Reduced Pro-Inflammatory Cytokines after Eight Weeks of Low-Dose Naltrexone for Fibromyalgia. *Biomedicines* **2017**, *5*, doi:10.3390/biomedicines5020016.

407. Miskoff, J.A.; Chaudhri, M. Low dose naltrexone and lung cancer: a case report and discussion. *Cureus* **2018**, *10*.

408. Donahue, R.N.; McLaughlin, P.J.; Zagon, I.S. The opioid growth factor (OGF) and low dose naltrexone (LDN) suppress human ovarian cancer progression in mice. *Gynecologic Oncology* **2011**, *122*, 382-388, doi:https://doi.org/10.1016/j.ygyno.2011.04.009.

409. PubChem. Naltrexone. Availabe online: https://www.ncbi.nlm.nih.gov/pubmed/ (accessed on

410. Ghasemi, K.; Ghasemi, K. A Brief look at antitumor effects of doxycycline in the treatment of colorectal cancer and combination therapies. *Eur J Pharmacol* **2022**, *916*, 174593, doi:10.1016/j.ejphar.2021.174593.

411. Tkachenko, E.M.; Grintsov, E.F.; Zupanets, I.A.; Shebeko, S.K. Study of the acute toxicity of the combination of doxycycline with glucosamine hydrochloride. **2014**.

412. Bar-Sela, G.; Cohen, M.; Ben-Arye, E.; Epelbaum, R. The medical use of wheatgrass: review of the gap between basic and clinical applications. *Mini reviews in medicinal chemistry* **2015**, *15*, 1002-1010.

413. Das, P.; Mukhopadhyay, S.; Mandal, S.; Chakraborty, A.; Pal, A.; Sarkar, N.K.; Mukhopadhyay, A. Acute toxicity test of a natural iron chelator and an antioxidant, extracted from Triticum aestivum Linn. (wheat grass). *http://dx.doi.org/10.1080/14786419.2014.901321* **2014**, 901321, doi:901321.

414. Bhardwaj, A.; Sethi, G.; Vadhan-Raj, S.; Bueso-Ramos, C.; Takada, Y.; Gaur, U.; Nair, A.S.; Shishodia, S.; Aggarwal, B.B. Resveratrol inhibits proliferation, induces apoptosis, and overcomes chemoresistance through down-regulation of STAT3 and nuclear factor-kappaB-regulated antiapoptotic and cell survival gene products in human multiple myeloma cells. *Blood* **2007**, *109*, 2293-2302, doi:10.1182/blood-2006-02-003988.

415. Zhang, L.; Wen, X.; Li, M.; Li, S.; Zhao, H. Targeting cancer stem cells and signaling pathways by resveratrol and pterostilbene. *Biofactors* **2018**, *44*, 61-68, doi:10.1002/biof.1398.

416. Ko, J.-H.; Sethi, G.; Um, J.-Y.; Shanmugam, M.K.; Arfuso, F.; Kumar, A.P.; Bishayee, A.; Ahn, K.S. The Role of Resveratrol in Cancer Therapy. *International Journal of Molecular Sciences* **2017**, *18*, 2589, doi:10.3390/ijms18122589.

417. Dimitrov, S.D.; Diderich, R.; Sobanski, T.; Pavlov, T.S.; Chankov, G.V.; Chapkanov, A.S.; Karakolev, Y.H.; Temelkov, S.G.; Vasilev, R.A.; Gerova, K.D., et al. QSAR Toolbox - workflow and major functionalities. *SAR QSAR Environ Res* **2016**, *27*, 203-219, doi:10.1080/1062936X.2015.1136680.

418. Tao, D.L.; Tassi Yunga, S.; Williams, C.D.; McCarty, O.J.T. Aspirin and antiplatelet treatments in cancer. *Blood* **2021**, *137*, 3201-3211, doi:10.1182/blood.2019003977.

419. Corley, D.A.; Kerlikowske, K.; Verma, R.; Buffler, P. Protective association of aspirin/NSAIDs and esophageal cancer: A systematic review and meta-analysis. *Gastroenterology* **2003**, *124*, 47-56, doi:10.1053/gast.2003.50008.

420. Qiao, Y.; Yang, T.; Gan, Y.; Li, W.; Wang, C.; Gong, Y.; Lu, Z. Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. *BMC Cancer* **2018**, *18*, 288, doi:10.1186/s12885-018-4156-5.

421. Bekemeier, H. [Salicylamide and salicylic acid poisoning in cats, in comparison with other animals. I]. *Arzneimittelforschung* **1955**, *5*, 572-575.

422. Amanullah, A.; Upadhyay, A.; Dhiman, R.; Singh, S.; Kumar, A.; Ahirwar, D.K.; Gutti, R.K.; Mishra, A. Development and Challenges of Diclofenac-Based Novel Therapeutics: Targeting Cancer and Complex Diseases. *Cancers* **2022**, *14*, 4385, doi:10.3390/cancers14184385.

423. Forget, P.; Bentin, C.; Machiels, J.P.; Berliere, M.; Coulie, P.G.; De Kock, M. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. *British Journal of Anaesthesia* **2014**, *113*, i82-i87, doi:10.1093/bja/aet464.

424. Singer, K.; Dettmer, K.; Unger, P.; Schönhammer, G.; Renner, K.; Peter, K.; Siska, P.J.; Berneburg, M.; Herr, W.; Oefner, P.J., et al. Topical Diclofenac Reprograms Metabolism and Immune Cell Infiltration in Actinic Keratosis. *Front Oncol* **2019**, *9*, 605, doi:10.3389/fonc.2019.00605.

425. Tao, Y.-L.; Wang, Z.-J.; Han, J.-G.; Wei, P. Inflammatory myofibroblastic tumor successfully treated with chemotherapy and nonsteroidals: A case report. *World J Gastroenterol* **2012**, *18*, 7100-7103, doi:10.3748/wjg.v18.i47.7100.

426. Teshima, M.; Iwae, S.; Hirayama, Y.; Furukawa, T. Nonsteroidal anti-inflammatory drug treatment for desmoid tumor recurrence after surgery. *Otolaryngol Head Neck Surg* **2012**, *147*, 978-979, doi:10.1177/0194599812453561.

427. Lackner, H.; Urban, C.; Benesch, M.; Raith, J.; Moser, A.; Sovinz, P.; Schwinger, W.; Dornbusch, H.J.; Triebl-Roth, K. Multimodal treatment of children with unresectable or recurrent desmoid tumors: an 11-year longitudinal observational study. *J Pediatr Hematol Oncol* **2004**, *26*, 518-522, doi:10.1097/01.mph.0000130219.26284.b3.

428. Lackner, H.; Urban, C.; Kerbl, R.; Schwinger, W.; Beham, A. Noncytotoxic drug therapy in children with unresectable desmoid tumors. *Cancer* **1997**, *80*, 334-340, doi:10.1002/(sici)1097-0142(19970715)80:2<334::aid-cncr22>3.0.co;2-u.

429. Breuer, S.; Maimon, O.; Appelbaum, L.; Peretz, T.; Hubert, A. TL-118-anti-angiogenic treatment in pancreatic cancer: a case report. *Med Oncol* **2013**, *30*, 585, doi:10.1007/s12032-013-0585-9.

430. Schumann, S.; Mann, G.; Wilde, H.; Ploen, U.; Mager, P.P. [Biological effects of 3-substituted acetic acid derivatives of 1,2,4-benzotriazines]. *Pharmazie* **1982**, *37*, 148-149, doi:10.1002/chin.198227233.

431. Majdalawieh, A.F.; Fayyad, M.W.; Nasrallah, G.K. Anti-cancer properties and mechanisms of action of thymoquinone, the major active ingredient of Nigella sativa. *Critical Reviews in Food Science and Nutrition* **2017**, *57*, 3911-3928, doi:10.1080/10408398.2016.1277971.

432. Dogar, M.; Adnan, H.; Akhtar, M.S.; Sheikh, M.A. Preliminary assessment of efficacy of Nigella sativa seeds in acute lymphoblastic leukemia local children. *Pharmacologyonline* **2009**, *2*, 769-777.

433. Zaoui, A.; Cherrah, Y.; Mahassini, N.; Alaoui, K.; Amarouch, H.; Hassar, M. Acute and chronic toxicity of Nigella sativa fixed oil. *Phytomedicine* **2002**, *9*, 69-74, doi:https://doi.org/10.1078/0944-7113-00084.

434. Ayeka, P.A. Potential of Mushroom Compounds as Immunomodulators in Cancer Immunotherapy: A Review. *Evid Based Complement Alternat Med* **2018**, *2018*, 7271509, doi:10.1155/2018/7271509.

435. Cao, Y.; Xu, X.; Liu, S.; Huang, L.; Gu, J. Ganoderma: A Cancer Immunotherapy Review. *Frontiers in Pharmacology* **2018**, *9*, 1217, doi:10.3389/fphar.2018.01217.

436. Jin, X.; Beguerie, J.R.; Sze, D.M.-y.; Chan, G.C.F. <i>Ganoderma lucidum</i> (Reishi mushroom) for cancer treatment. *Cochrane Database of Systematic Reviews* **2012**, 10.1002/14651858.CD007731.pub2, doi:10.1002/14651858.CD007731.pub2.

437. Li, Y.; Zhiyong, X.; Wei, L.; Birong, Z. Study on acute toxicity and genetic toxicity test of Ganoderma Lucidum Spore Powder Capsule. *Tianjin Pharmacy* **2007**, *2*, 14-23.

438. Juarez, M.; Schcolnik-Cabrera, A.; Dueñas-Gonzalez, A. The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug. *Am J Cancer Res* **2018**, *8*, 317-331.

439. Tang, M.; Hu, X.; Wang, Y.; Yao, X.; Zhang, W.; Yu, C.; Cheng, F.; Li, J.; Fang, Q. Ivermectin, a potential anticancer drug derived from an antiparasitic drug. *Pharmacological Research* **2021**, *163*, 105207, doi:10.1016/j.phrs.2020.105207.

440. Ishiguro, T.; Ishiguro, R.H.; Ishiguro, M.; Toki, A.; Terunuma, H. Synergistic Anti-tumor Effect of Dichloroacetate and Ivermectin. *Cureus* **2022**, *14*, e21884, doi:10.7759/cureus.21884.

441. Jones, T.K.; Chu, L.; Mrozik, H.; Slayton, L.; Rafalko, B.; Goldmann, M.L.; Shoop, W.L.; Margiatto, G.; Fisher, M.H. Synthesis and Biological Activity of 4a,4''-Disubstituted Avermectins. *J. Agric. Food Chem.* **1994**, *42*, 1786-1790, doi:10.1021/jf00044a041.

442. Spano, D.; Marshall, J.-C.; Marino, N.; De Martino, D.; Romano, A.; Scoppettuolo, M.N.; Bello, A.M.; Di Dato, V.; Navas, L.; De Vita, G., et al. Dipyridamole prevents triple-negative breast-cancer progression. *Clin Exp Metastasis* **2013**, *30*, 47-68, doi:10.1007/s10585-012-9506-0.

443. Budd, G.T.; Herzog, P.; Bukowski, R.M. Phase I/II trial of dipyridamole, 5-fluorouracil, leukovorin, and mitoxantrone in metastatic breast cancer. *Invest New Drugs* **1994**, *12*, 283-287, doi:10.1007/BF00873042.

444. Kohnoe, S.; Maehara, Y.; Takahashi, I.; Emi, Y.; Baba, H.; Sugimachi, K. Treatment of advanced gastric cancer with 5-fluorouracil and cisplatin in combination with dipyridamole. *Int J Oncol* **1998**, *13*, 1203-1206, doi:10.3892/ijo.13.6.1203.

445. Raschko, J.W.; Synold, T.W.; Chow, W.; Coluzzi, P.; Hamasaki, V.; Leong, L.A.; Margolin, K.A.; Morgan, R.J.; Shibata, S.I.; Somlo, G., et al. A phase I study of carboplatin and etoposide administered in conjunction with dipyridamole, prochlorperazine and cyclosporine A. *Cancer Chemotherapy and Pharmacology* **2000**, *46*, 403-410, doi:10.1007/s002800000142.

446. Takenaka, F.; Takeya, N.; Ishihara, T.; Higuchi, M.; Hayashi, H. Toxicological studies on dipyridamole in the rat. *Arzneimittelforschung* **1972**, *22*, 892-895.

447. Benade, L.; Howard, T.; Burk, D. Synergistic killing of Ehrlich ascites carcinoma cells by ascorbate and 3-amino-1,2,4,-triazole. *Oncology* **1969**, *23*, 33-43, doi:10.1159/000224465.

448. Takahashi, H.; Mizuno, H.; Yanagisawa, A. High-dose intravenous vitamin C improves quality of life in cancer patients. *Personalized Medicine Universe* **2012**, *1*, 49-53, doi:10.1016/j.pmu.2012.05.008.

449. Mikirova, N.; Casciari, J.; Rogers, A.; Taylor, P. Effect of high-dose intravenous vitamin C on inflammation in cancer patients. *Journal of Translational Medicine* **2012**, *10*, 189, doi:10.1186/1479-5876-10-189.

450. PubChem. Ascorbic Acid.

451. Stacpoole, P.W. Therapeutic Targeting of the Pyruvate Dehydrogenase Complex/Pyruvate Dehydrogenase Kinase (PDC/PDK) Axis in Cancer. *J Natl Cancer Inst* **2017**, *109*, doi:10.1093/jnci/djx071.

452. Powell, S.F.; Mazurczak, M.; Dib, E.G.; Bleeker, J.S.; Geeraerts, L.H.; Tinguely, M.; Lohr, M.M.; McGraw, S.C.; Jensen, A.W.; Ellison, C.A., et al. Phase II study of dichloroacetate, an inhibitor of pyruvate dehydrogenase, in combination with chemoradiotherapy for unresected, locally advanced head and neck squamous cell carcinoma. *Invest New Drugs* **2022**, *40*, 622-633, doi:10.1007/s10637-022-01235-5.

453. Limongelli, V.; Bonomi, M.; Marinelli, L.; Gervasio, F.L.; Cavalli, A.; Novellino, E.; Parrinello, M. Molecular basis of cyclooxygenase enzymes (COXs) selective inhibition. *Proceedings of the National Academy of Sciences* **2010**, *107*, 5411-5416.

454. Velasco, G.; Sánchez, C.; Guzmán, M. Anticancer mechanisms of cannabinoids. *Current oncology (Toronto, Ont.)* **2016**, *23*, S23-32, doi:10.3747/co.23.3080.

455. Sarfaraz, S.; Adhami, V.M.; Syed, D.N.; Afaq, F.; Mukhtar, H. Cannabinoids for cancer treatment: progress and promise. *Cancer research* **2008**, *68*, 339-342.

456. RN, P.; RF, T.; RB, F. Acute toxicity of delta-9-tetrahydrocannabinol in rats and mice. *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.)* **1971**, *136*, doi:10.3181/00379727-136-35241.

457. *NIDA Research Monograph*; 2023.

458. Guggisberg, J.; Schumacher, M.; Gilmore, G.; Zylla, D.M. Cannabis as an Anticancer Agent: A Review of Clinical Data and Assessment of Case Reports. *https://home.liebertpub.com/can* **2022**, 10.1089/can.2021.0045, doi:10.1089/can.2021.0045.

459. Lian, X.; Wang, G.; Zhou, H.; Zheng, Z.; Fu, Y.; Cai, L. Anticancer properties of fenofibrate: a repurposing use. *Journal of Cancer* **2018**, *9*, 1527.

460. Kumar, M.; Patidar, S.; Singh, R.; Dhiman, V. Fenofibrate inhibit the development of malaria in Plasmodium berghei-infected mice. *World Journal of Pharmaceutical Sciences* **2014**, 1273-1276.

461. Chang, C.; Zhao, W.; Xie, B.; Deng, Y.; Han, T.; Cui, Y.; Dai, Y.; Zhang, Z.; Gao, J.; Guo, H. Pao pereira extract suppresses castration-resistant prostate cancer cell growth, survival, and invasion through inhibition of NFκB signaling. *Integrative Cancer Therapies* **2014**, *13*, 249-258.

462. Bemis, D.L.; Capodice, J.L.; Desai, M.; Katz, A.E.; Buttyan, R. beta-carboline alkaloid-enriched extract from the amazonian rain forest tree pao pereira suppresses prostate cancer cells. *Journal of the Society for Integrative Oncology* **2009**, *7*, 59-65.

463. Moser, J.C.; Salvador, E.; Deniz, K.; Swanson, K.; Tuszynski, J.; Carlson, K.W.; Karanam, N.K.; Patel, C.B.; Story, M.; Lou, E., et al. The Mechanisms of Action of Tumor Treating Fields. *Cancer Research* **2022**, *82*, 3650-3658, doi:10.1158/0008-5472.CAN-22-0887.

464. Juarranz, Á.; Jaén, P.; Sanz-Rodríguez, F.; Cuevas, J.; González, S. Photodynamic therapy of cancer. Basic principles and applications. *Clinical and Translational Oncology* **2008**, *10*, 148-154, doi:10.1007/s12094-008-0172-2.

465. Moen, I.; Stuhr, L.E.B. Hyperbaric oxygen therapy and cancer--a review. *Target Oncol* **2012**, *7*, 233-242, doi:10.1007/s11523-012-0233-x.

466. Manning, E.P. Central Nervous System Oxygen Toxicity and Hyperbaric Oxygen Seizures. **2016**, info:doi/10.3357/AMHP.4463.2016, doi:info:doi/10.3357/AMHP.4463.2016.

467. Gonzalez, R.P.; Leyva, A.; Moraes, M.O. Shark cartilage as source of antiangiogenic compounds: from basic to clinical research. *Biological and Pharmaceutical Bulletin* **2001**, *24*, 1097-1101.

468. Miller, D.R.; Anderson, G.T.; Stark, J.J.; Granick, J.L.; Richardson, D. Phase I/II trial of the safety and efficacy of shark cartilage in the treatment of advanced cancer. *https://doi.org/10.1200/JCO.1998.16.11.3649* **2016**, 9817287, doi:9817287.

469. Mondo, K.; Hammerschlag, N.; Basile, M.; Pablo, J.; Banack, S.A.; Mash, D.C. Cyanobacterial Neurotoxin β-N-Methylamino-L-alanine (BMAA) in Shark Fins. *Marine Drugs* **2012**, *10*, 509-520, doi:10.3390/md10020509.

470. Liczbiński, P.; Bukowska, B. Molecular mechanism of amygdalin action in vitro: review of the latest research. *Immunopharmacology and Immunotoxicology* **2018**, *40*, 212-218, doi:10.1080/08923973.2018.1441301.

471. Shi, J.; Chen, Q.; Xu, M.; Xia, Q.; Zheng, T.; Teng, J.; Li, M.; Fan, L. Recent updates and future perspectives about amygdalin as a potential anticancer agent: A review. *Cancer Medicine* **2019**, *8*, 3004-3011, doi:https://doi.org/10.1002/cam4.2197.

472. Adewusi, S.R.A.; Oke, O.L. On the metabolism of amygdalin. 1. The LD50 and biochemical changes in rats. *https://doi.org/10.1139/y85-177* **2011**, 10.1139/y85-177, doi:10.1139/y85-177.