THE ANTICANCER MECHANISMS OF ACTION OF KEY REPURPOSED MEDICATIONS AND NATURAL COMPOUNDS

In the evolving landscape of oncology, the repurposing of medications and exploration of natural compounds have emerged as promising avenues for cancer treatment. This paper delves into the multifaceted mechanisms by which certain repurposed medications, including auranofin, disulfiram, and others, along with natural compounds like docosahexaenoic acid, mannose, and others, manifest potent anticancer activities. By elucidating the biochemical pathways and cellular interactions these agents modulate, we aim to highlight their potential in contributing to more effective and nuanced cancer therapies.

Aprepitant:

Aprepitant is a medication used to prevent chemotherapy-induced nausea and vomiting. It has been found to exhibit several anti-cancer mechanisms:

1. Antiproliferative effects: Aprepitant exerts antiproliferative effects in various cancer cell lines by inhibiting the mitogenic actions of the substance P/neurokinin-1 receptor (SP/NK-1R) pathway. This is highlighted by its ability to inhibit cell proliferation in a dose-dependent manner across multiple cancer types.
2. Induction of apoptosis: Aprepitant promotes apoptosis by interfering with multiple cellular pathways. It favors calcium flux from the endoplasmic reticulum into mitochondria, increasing the level of mitochondrial reactive oxygen species, which are crucial for the apoptotic process. It also promotes the activation of caspase-dependent apoptotic pathways.
3. Cell cycle arrest: It can induce G2/M phase cell-cycle arrest in cancer cells, disrupting the normal cell cycle and preventing cancer cell proliferation.
4. Anti-angiogenic effects: Aprepitant has anti-angiogenic properties, which it achieves by inhibiting the production of vascular endothelial growth factors that are critical for tumor angiogenesis.
5. Antimetastatic actions: It inhibits the migration and invasion of tumor cells, contributing to its antimetastatic effects. This is particularly important for reducing the spread of cancer to other parts of the body.
6. Regulation of apoptosis-associated genes: Aprepitant affects the expression of key apoptotic genes, increasing the expression of pro-apoptotic genes (e.g., Bax, Bid, Bad) and decreasing the expression of anti-apoptotic genes (e.g., Bcl-2), thus promoting apoptosis in cancer cells.
7. Impact on cellular signaling pathways: It modulates several critical signaling pathways including the Akt/PI3K pathway, the Wnt/β-catenin signaling path-

way, and the mTOR signaling axis, all of which are crucial in regulating cell growth, survival, and metastasis.

8. Inhibition of the SP/NK-1R system: By blocking the SP/NK-1R system, Aprepitant reduces the proliferative and survival signals in cancer cells mediated through this pathway.
9. Cancer stem cells: Aprepitant has demonstrated effects on cancer stem cells by influencing key signaling pathways that are crucial for stem cell maintenance and differentiation. Specifically, it has been shown to block the canonical Wnt pathway, leading to a downregulation of significant stemness markers such as LGR5, AXIN2, OCT4, NANOG, SOX2, CD13, and AFP in cancer cells. These pathways and markers are instrumental in maintaining the properties of cancer stem cells, including their renewal and differentiation capabilities.
10. Quality-of-life: By modulating the substance P/neurokinin-1 receptor (SP/NK-1R) system, aprepitant has been found to have anxiolytic, antidepressant, and analgesic properties. These are crucial, as they contribute to reduced anxiety and depression levels in patients. Additionally, aprepitant offers significant pain relief. Its role in controlling chemotherapy-induced nausea and vomiting further consolidates its beneficial impact on patient well-being.

These mechanisms contribute to the anti-cancer effects of aprepitant across a range of tumor types, making it a potent agent in the therapeutic arsenal against cancer. Additionally, aprepitant may significantly enhance the quality of life of cancer patients.

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Auranofin:

A gold-containing anti-inflammatory drug used to treat rheumatoid arthritis, auranofin exhibits diverse anticancer mechanisms across various cancer types:

1. Cell cycle arrest and apoptosis induction: In multiple myeloma, auranofin induces cell cycle arrest and apoptosis, reduces Mcl-1 expression, and down-regulates NF-κß activity.
2. Oxidative stress induction: It increases reactive oxygen species (ROS) levels, leading to DNA damage and caspase-independent apoptosis, particularly in cells dependent on the Trx1 system.
3. PI3K/AKT/mTOR pathway inhibition: Auranofin inhibits this pathway, essential for cell proliferation, apoptosis, and angiogenesis, affecting tumor growth and metastasis.
4. Protein homeostasis disruption: It inhibits proteasome and deubiquitinases (dubs), inducing apoptosis in liver hepatocellular and breast cancer cells.
5. FOXO3-dependent apoptosis: In ovarian cancer cells lacking p53, auranofin triggers apoptosis through FOXO3 activation, indicating a p53-independent pathway.
6. IKK-β inhibition and NF-κß signaling modulation: Downregulates IKK-β, reducing NF-κß signaling and promoting apoptosis via FOXO3 nuclear translocation.
7. Mitochondrial dysfunction: Leads to loss of mitochondrial membrane potential, resulting in cell death through apoptosis or necrosis.

These actions demonstrate auranofin's potent anticancer activity through multiple pathways, underscoring its potential as an anticancer agent.

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Disulfiram:

Disulfiram (DSF) is an old drug originally used to treat alcoholism that has shown potential in cancer treatment due to its various anti-cancer mechanisms:

1. Induction of oxidative stress and apoptosis: Disulfiram, especially when combined with copper (DSF/Cu), induces reactive oxygen species (ROS)

generation, leading to oxidative stress and apoptosis in cancer cells. This mechanism involves the activation of the JNK and p38 MAPK pathways and can result in cell death through the intrinsic apoptotic pathway.
2. Inhibition of proteasome activity: Disulfiram has been shown to inhibit the proteasome activity in cancer cells, leading to the accumulation of misfolded proteins and inducing cell stress and apoptosis.
3. Targeting cancer stem cells (CSCs): Disulfiram affects the regenerative capacity of tumors by targeting cancer stem cells, particularly those marked by high aldehyde dehydrogenase (ALDH) activity. It suppresses the proliferation of CSCs and enhances the efficacy of radiotherapy and chemotherapy.
4. Interference with NF-κß signaling: Disulfiram inhibits the NF-κß signaling pathway, which is involved in promoting cancer cell survival and chemoresistance, thereby enhancing the apoptotic response to treatment.
5. Disruption of tumor energy metabolism: By inhibiting key metabolic enzymes like ALDH1L1 and PKM2, disulfiram disrupts the energy metabolism in cancer cells, leading to ATP depletion and hampering tumor growth and survival.
6. Modification of the tumor microenvironment: Disulfiram can alter the tumor microenvironment, affecting tumor immunity and potentially reducing the protective niche for cancer cells.
7. Enhancement of chemotherapeutic effects: Disulfiram can enhance the cytotoxic effects of conventional chemotherapeutic agents, such as paclitaxel, through synergistic mechanisms, including increased ROS production and apoptosis.
8. Targeting NPL4 and inducing proteotoxic stress: Disulfiram binds to and inhibits the function of the NPL4 protein, leading to proteotoxic stress and cell death in cancer cells.
9. Downregulation of key survival pathways: Including the Akt signaling pathway, disulfiram leads to reduced survival signaling in cancer cells.

These mechanisms underline the multifaceted action of disulfiram as an anticancer agent, involving direct cytotoxic effects, modulation of cellular signaling pathways, impact on cancer stem cells, and interference with the metabolic and immune contexts of tumors.

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Docosahexaenoic acid:

An omega-3 fatty acid found in algae and cold-water, fatty fish, such as salmon, docosahexaenoic acid (DHA) possesses numerous anticancer properties:

1. Enhancement of radiosensitivity: DHA integrates into tumor cell membranes, increasing their sensitivity to radiation and chemotherapy by enhancing reactive oxygen species (ROS) generation.
2. Apoptosis induction: Triggers apoptosis through various pathways, including MAPK activation, mitochondrial ROS overproduction, caspase-8 activation, and survivin downregulation.
3. Cell cycle arrest: Induces cell cycle arrest by affecting regulators like p53 and cyclin E, suppressing cancer cell proliferation.
4. Inhibition of cancer cell proliferation: Downregulates survival pathways and affects cellular metabolism to inhibit cancer cell growth.
5. Ferroptosis induction: Promotes ferroptosis by increasing intracellular lipid peroxidation through lipoxygenase-dependent and independent pathways.
6. Wnt/β-catenin signaling inhibition: Disrupts this pathway, crucial for cancer cell proliferation and growth.
7. Reduction of angiogenesis and invasion: Decreases expression of pro-angiogenic factors and enzymes like COX-2 and matrix metalloproteinases, suppressing tumor growth and metastasis.
8. Selective cytotoxicity and chemosensitivity enhancement: Exhibits selective cytotoxicity to cancer cells and increases their sensitivity to chemotherapy.
9. Gene expression and signal transduction regulation: Affects genes and proteins involved in cancer cell survival, proliferation, and apoptosis, like PPARγ, RXRα, NF-κß, and Bcl-2 family proteins, modifying key signaling pathways.
10. DNA damage and repair modulation: Induces oxidative DNA damage leading to apoptosis.

11. Prevention of inflammation-induced carcinogenesis: Prevents carcinogenesis by resolving inflammation, as seen with Lipoxin A4 (LXA4) suppressing colorectal cancer development.
12. Enhanced clearance of tumor cell debris: In combination with chemotherapy or targeted therapy, resolvins from DHA block the tumor-stimulatory activity of therapy-generated debris, inducing tumor regression.
13. Modulation of tumor microenvironment: Counteracts pro-tumorigenic properties of tumor-associated macrophages (TAMs) and fosters an effective anti-tumor immune response.

These findings illustrate the multi-targeted anti-cancer effects of DHA, operating through diverse mechanisms including direct cytotoxicity, modulation of cellular signaling pathways, and affecting the cell's microenvironment and responses to therapy.

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High-ozonide ozonated oil:

The anticancer mechanisms of high-ozonide ozonated oil (HOO) are as follows:

1. Scavenging of antioxidants from cancer cells: HOO depletes cancer cells of antioxidants, making them more sensitive to chemo/radiotherapies and overcoming resistance.
2. Re-activation of intrinsic apoptosis: HOO oxidizes mitochondrial membranes in cancer cells, triggering the release of cytochrome c and calcium, leading to apoptosis. Cancer cells are more sensitive to this due to inactive mitochondria.
3. Inhibition of tumor-associated macrophage activation: HOO inhibits the oxidative burst and inflammatory cytokine release from macrophages that typically support tumor growth.
4. Increase of oxygen availability in tumor tissue: HOO releases oxygen species inside cancer tissue, counteracting the hypoxic environment that triggers angiogenesis and metastasis.
5. Competition with mitochondrial fat oxidation pathway: HOO may compete with fatty acid oxidation, which provides energy to cancer cells. Its catabolism leads to oxidative stress, mitochondrial damage, and apoptosis.
6. Targeting cancer stem cells: HOO depletes the high antioxidant levels in cancer stem cells, reversing their chemo/radioresistance.

7. Anti-inflammatory effects at the systemic level: HOO induces anti-inflammatory effects without immunosuppression by inhibiting macrophage oxidative burst.

In summary, the oxidative stress induced by HOO selectively targets vulnerabilities of cancer cells related to their mitochondria, stem cells, and supporting tumor microenvironment. This allows HOO to complement and potentiate standard chemo/radiotherapies.

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Mannose:

A simple sugar found in many fruits; mannose has demonstrated a variety of anti-cancer mechanisms:

1. Growth retardation and enhanced chemotherapy: Mannose causes growth retardation in tumor types and enhances cell death in response to chemotherapy, affecting glucose metabolism and anti-apoptotic protein levels.
2. Interference with glucose metabolism: It disrupts glucose metabolism in cancer cells, particularly affecting glycolysis and the pentose phosphate pathway.
3. Enhanced chemoradiotherapy in glioblastoma: Mannose synergizes with chemoradiotherapy, affecting the HIF-1 signaling pathway to improve treatment efficacy in glioblastoma.
4. Increased sensitivity to carboplatin in lung adenocarcinoma: It enhances the sensitivity to carboplatin, inhibits cell proliferation and migration, and promotes apoptosis.
5. Degradation of IDH2 in breast cancer: Mannose promotes IDH2 protein degradation via the ubiquitination-proteasome pathway, specifically upregulating the E3 ligase RNF185, leading to reduced NADPH production and suppressed cell proliferation.
6. Enhancement of immunotherapy and radiotherapy in TNBC: Mannose degrades PD-L1, leading to increased T cell activation and killing of tumor cells, making TNBC more sensitive to treatments and extending the lifespan of tumor-bearing mice.

These mechanisms highlight mannose's multifaceted role in cancer therapy, offering potential for its use in treating various cancer types by targeting specific cellular processes and pathways.

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Niclosamide:

Niclosamide is a compound initially approved for use as an anthelminthic medication to treat parasitic infections, particularly those caused by tapeworms. Over time, its potential as an anti-cancer agent has garnered attention. Here are some of the anti-cancer mechanisms of niclosamide:

1. Selective toxicity against p53-deficient cells: Niclosamide preferentially impairs the growth of p53-deficient cells and p53 mutant patient-derived ovarian xenografts, highlighting its targeted action against cancer cells with specific genetic vulnerabilities.
2. Mitochondrial uncoupling and energy metabolism interference: It induces mitochondrial uncoupling, affects mitochondrial function, and disrupts energy metabolism in cancer cells, leading to metabolic stress, cell death through apoptosis, and autophagy.
3. Induction of apoptosis and cell cycle arrest: Niclosamide triggers apoptosis in cancer cells, disrupts cell cycle progression, and enhances cleavage of caspase-9, caspase-3, and PARP1, contributing to the inhibition of tumor cell growth.
4. Alteration of metabolome profile and arachidonic acid accumulation: It alters the metabolic landscape, particularly leading to the accumulation of arachidonic acid in p53-deficient cells, which is implicated in apoptosis.
5. Perturbation of Ca^{2+} homeostasis: By triggering intracellular calcium fluxes, niclosamide affects calcium-dependent processes, leading to changes in cell signaling and metabolism.
6. Inhibition of various signaling pathways: Niclosamide downregulates critical cancer signaling pathways, including NF-κB, Wnt/β-catenin, Notch, ROS, mTORC1, STAT3, and HIF-1α, suppressing cancer cell energy metabolism, proliferation, growth, and survival.
7. Targeting cancer stem cells: Niclosamide targets cancer stem cells, addressing the challenges of tumor recurrence and metastasis.
8. Inhibition of tumor growth and metastasis: It exhibits anti-metastatic properties, inhibiting cancer cell migration, invasion, and overall tumor growth.

9. Enhancing chemo and radio sensitivity: Niclosamide improves the sensitivity of cancer cells to chemotherapy and radiotherapy, making it a valuable adjunct in cancer treatment.
10. Synergistic effects with cancer therapies: Demonstrating synergy with existing cancer treatments, niclosamide can potentiate the therapeutic effects against cancer.
11. Modulation of epigenetic regulation: It influences epigenetic mechanisms, altering gene expression related to cancer survival and resistance.
12. Altering tumor microenvironment: Niclosamide may improve the therapeutic response by modulating the tumor microenvironment and affecting the cancer's immune evasion capabilities.
13. Induction of lipid oxygenation genes in wild-type p53 cells: In cells with functional p53, niclosamide induces genes involved in lipid metabolism, which helps in counteracting the metabolic stress imposed by the drug.
14. Elevation of reactive oxygen species (ROS): Elevates ROS levels in cancer cells, which contributes to cell stress and death.
15. Inhibition of glutathione synthase (GS): Inhibits GS, reducing glutathione levels and increasing oxidative stress.
16. Downregulation of nuclear factor of activated T-cells (NFAT) activity: Decreases NFAT activity, impacting cell growth and viability.

The anti-cancer effects of niclosamide span various types of cancer and involve a multifaceted approach by targeting multiple pathways and processes critical for cancer development and progression.

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Piperlongumine:

Piperlongumine (PL) is an alkaloid amide derived from the roots of Piperaceae plants like long pepper and peppercorn. It exhibits anti-cancer properties by inhibiting tumor growth and metastasis. The anti-cancer mechanisms of piperlongumine are varied and include:

1. Induction of reactive oxygen species (ROS): Piperlongumine increases ROS levels, causing cellular stress and damage. This effect is critical for its ability to induce apoptosis and enhance radiosensitivity in cancer cells.
2. DNA damage and repair inhibition: It causes DNA damage, primarily through ROS-mediated mechanisms, and hampers the repair processes, leading to enhanced cytotoxicity.
3. Cell cycle arrest: Piperlongumine induces G2/M phase arrest, disrupting the ability of cancer cells to divide and proliferate.
4. Promotion of apoptosis: Beyond increasing ROS, it directly triggers apoptotic pathways within cancer cells, contributing to its anti-cancer efficacy.
5. Inhibition of cell proliferation: By downregulating cell cycle-associated proteins and inhibiting crucial signaling pathways like Akt, piperlongumine decreases the proliferation of cancer cells.
6. Modulation of signaling pathways: Affects various cellular signaling pathways involved in cancer progression, including Akt/mTOR, NF-κß, and JAK/STAT3.
7. Inhibition of nuclear factor (NF)-κB: Reduces expression of genes involved in survival, proliferation, and metastasis of cancer cells by inhibiting the NF-κß signaling pathway.
8. Dual inhibition of antioxidant systems: Specifically targets the glutathione and thioredoxin systems, leading to increased ROS production and contributing to its cytotoxic and radiosensitizing effects.
9. Enhanced radiosensitivity: Improves the sensitivity of cancer cells to radiation therapy, linked to increased ROS production, DNA damage, and cell cycle arrest.
10. Inhibition of cellular respiration: Decreases oxygen consumption in cancer cells, which is considered an approach to combat hypoxic radioresistance.

11. Selective cytotoxicity and targeting specific cancer cell mechanisms: Selectively kills cancer cells, including those resistant to other forms of chemotherapy, sparing normal cells.
12. Chemoresistance and radioresistance inhibition: Overcomes resistance mechanisms in cancer cells, enhancing the efficacy of conventional cancer treatments.
13. Autophagy induction: Triggers autophagy through ROS-p38 pathway, contributing to cell death in cancer cells.
14. In vivo effectiveness: Demonstrates enhanced tumor response to radiation and increased survival in tumor-bearing animal models, validating its potential for clinical application.

This list encompasses the multifaceted mechanisms through which piperlongumine exerts its anti-cancer effects, including inducing oxidative stress, damaging DNA, affecting cell cycle and signaling pathways, enhancing radiosensitivity, and selectively targeting cancer cells.

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Probiotics & prebiotics:

The health of the gut microbiome plays a critical and often overlooked role in the treatment and prevention of cancer. Here's how:

1. Role of gut microbiota in cancer pathophysiology: The gut microbiota is significant in various aspects of human health, including its relation to cancer development and prevention, highlighting the multifactorial nature of cancer pathophysiology.
2. Immunomodulation and cancer prevention: Prebiotics and probiotics play a crucial role in cancer prevention through immunomodulatory effects, influencing the growth of beneficial microbes that exert oncostatic effects via mechanisms like recruitment of cytotoxic T cells and natural killer cells, and promoting apoptosis in the tumor microenvironment.

3. Dysbiosis and carcinogenesis: Dysbiosis, or the imbalance of gut microbial communities, is linked to carcinogenesis and metabolic disorders, emphasizing the importance of maintaining a balanced gut microbiota for cancer prevention.
4. Microbiota's oncostatic properties: Probiotics are highlighted for their potential oncostatic properties, mediating anti-cancer effects through immunomodulation and direct actions against tumor growth and progression.
5. Potential in adjuvant cancer therapy: Probiotics and their metabolic products are considered for use as adjuvants in cancer therapy, enhancing the effectiveness of conventional treatments by improving immune surveillance and exerting direct anti-tumor activities.
6. Systemic immune response and cancer: The systemic effects of the microbiota on immune response, including the promotion of inflammatory and immune-regulatory pathways, have implications for cancer development and the effectiveness of cancer immunotherapies.

These findings underscore the significant impact of the gut microbiota on cancer, illustrating its potential in cancer prevention, the modulation of the immune response to tumors, and the enhancement of therapeutic outcomes.

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In conclusion, the investigation of repurposed medications and natural compounds in cancer therapy represents a burgeoning field that harnesses the untapped potential of existing drugs and natural agents can be targeted to combat cancer. The comprehensive analysis of the compounds presented here underscores the necessity for continued research to fully unravel the therapeutic spectrum they provide, paving the way for novel strategies in cancer management.