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Review Paper

Adjuvant Therapies for the Mitigation of Chemotherapy-Induced Toxicities: APIs, Formulation Strategies, and Regulatory Perspectives

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ABSTRACT

While chemotherapy is an essential aspect of cancer treatment, its effectiveness is often affected by the dose-limiting toxicities associated with its use which affect patient adherence and quality of life. The current and developing adjuvant strategies aimed at reducing the chemotherapy-associated toxicities will be examined in detail in this review. These include the use of pharmacological agents like the established adjuvants antiemetics, granulocyte colony-stimulating factors, palifermin, duloxetine, and dexrazoxane as well as new adjuvants, which are being explored to reduce toxicity and improve the overall experience for patients receiving chemotherapy. In addition, the review provides updates on the various advanced drug-delivery systems currently being used to maximize drug-targeting potential and reduce toxicity. These include liposomal, PEGylated, nanocarrier, self-nanoemulsifying, and mucoadhesive technologies, which have various potential advantages over traditional drug-delivery forms. The increasing number of nutraceuticals (e.g., curcumin, ginger, omega-3 fatty acids, probiotics, melatonin) is also discussed in relation to their bioavailability-enhancing formulations. Finally, the latest evidence-based non-pharmacological approaches (i.e., exercise, photobiomodulation, cryotherapy, acupuncture, and scalp cooling) that are being utilized to support the management of chemotherapy-associated toxicities are presented along with regulatory guidelines from the FDA, EMA, and WHO pertaining to the use of complex formulations, biosimilars, and nanomedicines. Together, these newly developed standards of care will allow for a more precise, patient-centered approach to the treatment of cancer and to provide the best opportunity to maintain both therapeutic efficacy and quality of life while undergoing chemotherapy.

INTRODUCTION

Cancer treatment commonly utilizes chemotherapy as a primary method either alone or with the help of other methods. A major drawback of chemotherapy is that it creates toxicity against all cells of your body due to its non-selectiveness;

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this results in dose limiting toxicities, which may be experienced through nausea/vomiting, cardiotoxicity, neuropathy or myelosuppression. These side effects add up to creating substantial financial, psychological, and physical barriers for cancer patients. [1, 2] Modern approaches to supportive cancer care are beginning to focus on proactive, evidence-based strategies rather than traditional reactionary methods to minimize these side effects. Chemotherapy induced nausea/vomiting occurs in 70-80% of patients without prophylactic medication management in place; and febrile neutropenia and peripheral neuropathy are additional reasons for poor treatment outcomes. Examples of some of the major advancements that have been introduced to supportive oncology therapeutic options include pharmacologic agents (e.g., antiemetics; G-CSF; dexrazoxane; duloxetine) that have all become part of globally accepted clinical standards of treatment. [3,4,5] Advanced drug delivery innovations such as liposomes and nanoparticles also contribute to increased safety/accuracy during administration of chemotherapy drugs. While nutraceuticals (e.g., curcumin; probiotics) have demonstrated positive outcomes regarding supportive oncological treatment, additional validation studies are necessary prior to including nutraceuticals in global treatment guidelines. Overall this literature review will highlight a systematic approach using pharmacologic (drug), nutraceutical (nutrition-based), and formulation methods of intervention in order to enhance supportive cancer care. [6,7]

2. Classification of Chemotherapy and Its Side Effects

The same cytotoxic mechanism that enables chemotherapy to destroy malignant cells also accounts for its deleterious effects on normal tissues, particularly those with rapid turnover rates. This unintended injury manifests as a broad range of toxicities that can limit dosing, interrupt treatment schedules, and degrade patients' quality of life. The following subsections categorize the principal adverse effects of chemotherapy, outlining their clinical implications and preventive strategies.[8]

Table 1. Common Cancers and Their Chemotherapy Regimens

Cancer Type	Chemotherapy Drugs (APIs)	Common Side Effects
Breast Cancer	Doxorubicin (Adriamycin), Cyclophosphamide, Paclitaxel, Docetaxel, Capecitabine (Xeloda)	Nausea, vomiting, hair loss, mouth sores, fatigue, heart damage, infertility, neuropathy.
Lung Cancer	Cisplatin, Carboplatin, Paclitaxel, Docetaxel, Gemcitabine, Etoposide	Nausea, vomiting, hair loss, fatigue, nerve damage, kidney damage, lung toxicity.
Colorectal Cancer	5-Fluorouracil (5-FU), Leucovorin, Oxaliplatin, Irinotecan, Capecitabine	Nausea, vomiting, diarrhea, mouth sores, fatigue, neuropathy, risk of infection.
Leukemia	Cytarabine, Daunorubicin, Idarubicin, Cyclophosphamide, Methotrexate	Nausea, vomiting, hair loss, mouth sores, fatigue, increased risk of infection, bleeding, anemia
Lymphoma	Cyclophosphamide, Doxorubicin (Adriamycin), Vincristine (Oncovin), Prednisone, Rituximab (R-CHOP)	Nausea, vomiting, hair loss, mouth sores, fatigue, increased risk of infection, bleeding, anemia.

Ovarian Cancer	Carboplatin, Paclitaxel, Doxorubicin, Cyclophosphamide, Topotecan	Nausea, vomiting, hair loss, mouth sores, fatigue, nerve damage, and kidney damage.
Testicular Cancer	Bleomycin, Etoposide, Cisplatin (BEP regimen)	Nausea, vomiting, hair loss, mouth sores, fatigue, lung toxicity (bleomycin), nerve damage (cisplatin)
Bladder Cancer	Gemcitabine, Cisplatin, Methotrexate, Vinblastine, Doxorubicin	Nausea, vomiting, hair loss, mouth sores, fatigue, kidney damage, bladder irritation.
Endometrial (Womb) Cancer	Doxorubicin, Paclitaxel, Carboplatin, Cisplatin, Docetaxel	Nausea, vomiting, hair loss, mouth sores, fatigue, nerve damage, and kidney damage.
Pancreatic Cancer	Gemcitabine, Nab-paclitaxel, 5-Fluorouracil (5-FU), Oxaliplatin	Nausea, vomiting, diarrhea, mouth sores, fatigue, neuropathy, risk of infection.

3.pharmacological Adjuvant Therapies and Their Role in Chemotherapy Toxicity

Chemotherapy-induced toxicities continue to represent a major challenge for clinicians and patients alike, frequently restricting dose intensity and diminishing quality of life. Pharmacologic adjuvant therapies—ranging from receptor antagonists to cytoprotective agents—form the backbone of strategies to mitigate these adverse effects.[9] Each class targets a specific biological mechanism to preserve normal tissue integrity while sustaining anticancer efficacy. The following subsections summarize key categories of pharmacologic adjuvants, outlining their mechanisms, evidence base, and clinical applications. [10]

Table 2: Adjuvant API used in chemotherapy

Type of Adjuvants	Treatment (API)	Formulation	Mechanism
Antiemetic Adjuvants	Ondansetron	Oral / IV	5-HT_3 receptor antagonist
Antiemetic Adjuvants	Aprepitant	Oral	NK_1 receptor antagonist
Antiemetic Adjuvants	Dexamethasone	Oral / IV	Corticosteroid
Antiemetic Adjuvants	Lorazepam	Oral / IV	Benzodiazepine (sedative)
Neuropathy Adjuvants	Duloxetine	Oral	SNRI (serotonin-norepinephrine reuptake inhibitor)
Mucositis-Protective Adjuvants	Gabapentin	Oral	Anticonvulsant (neuropathic pain modulation)
Mucositis-Protective Adjuvants	Cryotherapy	Topical (oral cooling)	Local cooling reduced mucosal exposure/injury
Mucositis-Protective Adjuvants	Palifermin	IV	Keratinocyte growth factor mucosal regeneration
Mucositis-Protective Adjuvants	Morphine mouthwash	Topical	Opioid analgesic (topical pain control)
Cardiotoxicity Adjuvants	Dexrazoxane	IV	Iron chelation/cardioprotection of anthracyclines

Cardiotoxicity Adjuvants	ACE inhibitors	Oral	RAAS inhibition — cardioprotective/afterload reduction
Cardiotoxicity Adjuvants	Beta-blockers	Oral	Sympathetic blockade — cardioprotective

4. Natural and Nutraceutical Adjuvant Therapies

The rising interest in natural and nutraceutical adjuvants reflects a growing movement toward integrative oncology—an approach that complements pharmacologic treatments with dietary and botanical interventions supported by emerging evidence. These agents often exert multifaceted effects, including antioxidant, anti-inflammatory, immunomodulatory, and cytoprotective actions, which help the body better tolerate chemotherapy. While pharmacologic adjuvants remain the mainstay of supportive care, nutraceuticals may provide synergistic benefits that enhance recovery, resilience, and overall well-being [11,12] However, consistent clinical translation depends on standardized formulations, improved bioavailability, and rigorous validation through controlled studies. The following subsections outline prominent nutraceutical candidates and summarize key findings regarding their mechanisms and therapeutic potential.

Table 3: Natural / Nutraceutical Adjuvants for Chemotherapy-Induced Toxicities

Agent	Key Benefits	Mechanism
Ginger (Zingiber officinale)	Reduces nausea & vomiting (CINV)	Modulates the 5-HT_3 pathway, anti-inflammatory
Curcumin (Turmeric)	Reduces inflammation, fatigue, and mucositis	Antioxidant, NF-B modulation
Probiotics (Lactobacillus, Bifidobacterium)	Reduces diarrhea, GI toxicity	Restores gut microbiota, mucosal protection
Omega-3 fatty acids (EPA/DHA)	Improves appetite, reduces cachexia	Anti-inflammatory, modulates cytokines
Melatonin	Improves sleep and fatigue	Circadian rhythm regulation
Honey	Reduces oral mucositis	Antimicrobial, promotes mucosal healing
Glutamine	Supports intestinal repair	Substrate for enterocytes
Cannabinoids (THC/CBD)	Reduces nausea, improves appetite	Endocannabinoid receptor modulation
Green tea polyphenols (EGCG)	Antioxidant, cytoprotective	Antioxidant modulates signaling

5. Non-Pharmacological Adjuvant Therapies

In recent years, non-pharmacological adjuvant therapies have become integral components of comprehensive cancer care. Rather than addressing toxicity through drugs alone, these interventions emphasize physical, psychological, and behavioral well-being, providing multidimensional support throughout chemotherapy. They reduce symptom burden, enhance resilience, and improve overall quality of life. Increasing inclusion of these modalities in global oncology guidelines highlights a paradigm shift toward holistic and patient-centered supportive care. [13]

Table 4: Non-Pharmacological Adjuvant Therapies for side effects

Therapy / Intervention	Side Effect / Toxicity	Mode of Application	Mechanism and Rationale
Acupuncture / Acupressure	CINV	P6 point stimulation	Regulates autonomic & serotonin pathways

Relaxation / Guided Imagery		Behavioral therapy	Reduces anxiety & nausea perception
Cryotherapy (Cold Gloves/Socks)	CIPN	During infusion	Vasoconstriction limits nerve drug exposure
Exercise / Physical Training		Aerobic & resistance	Enhances circulation, reduces inflammation
Acupuncture		Auricular / body points	Neurotrophic & anti-inflammatory
PBM Therapy (Low-Level Laser)	Oral Mucositis	Intraoral laser	Promotes epithelial healing & reduces pain
Oral Cryotherapy		Ice rinse	Reduces mucosal cytotoxic exposure
Honey / Mouth Rinse		Topical	Antimicrobial & mucosal repair
Exercise	Fatigue / Cognitive Dysfunction	Supervised program	Improves mitochondrial function
Mindfulness / Yoga / Meditation		Behavioral	Reduces cortisol & fatigue
Scalp Cooling	Alopecia	During chemotherapy	Decreases follicular drug uptake
Aerobic Exercise	Cardiotoxicity	Supervised rehab	Improves cardiac output & antioxidant defense
CBT	Emotional Distress / Anxiety	Psychotherapy	Cognitive reframing reduces distress
Massage / Reflexology	Pain / QoL	Manual therapy	Reduces tension & pain perception

6. Formulation Strategies and APIs

Recent advances in formulation science have reshaped how chemotherapy and adjuvant agents are designed and delivered, fundamentally improving their safety and efficacy profiles. The primary objective is to refine drug delivery by enhancing tumor selectivity, reducing systemic exposure, and increasing patient tolerability. These innovations—spanning nanotechnology, biopharmaceutics, and targeted delivery—reflect a broader shift toward precision-based supportive oncology.

6.1 Liposomal and PEGylated Formulations

Liposomal and PEGylated systems have transformed chemotherapeutic delivery by optimizing pharmacokinetics and biodistribution. Encapsulation of cytotoxic agents within lipid vesicles or polymeric coatings reduces plasma peaks and minimizes exposure to healthy tissue.[14] Pegylated liposomal doxorubicin (PLD) is a notable example that significantly lessens anthracycline-related cardiotoxicity while maintaining antitumor potency. The polyethylene glycol (PEG) layer extends circulation time and promotes preferential tumor accumulation via the enhanced permeability and retention (EPR) effect. Similar liposomal versions of cisplatin and paclitaxel also demonstrate reduced nephrotoxicity and neurotoxicity compared to their conventional forms.[15]

6.2 Nanocarriers and Targeted Drug Delivery

Nanocarriers—including polymeric nanoparticles, micelles, dendrimers, and solid lipid nanoparticles—enable controlled drug release and improved solubility.[16] Their tunable size, charge, and surface ligands allow precise tumor targeting

while sparing healthy tissues. For instance, PLGA-based nanoparticles co-encapsulating chemotherapeutic and protective agents have shown reduced oxidative stress and lower organ toxicity. Stimuli-responsive nanocarriers—triggered by pH, temperature, or redox gradients—further enhance site-specific release and reduce collateral damage. [17]

6.3 Self-Emulsifying and Nanoemulsion Systems

Poorly water-soluble active pharmaceutical ingredients (APIs), such as curcumin or resveratrol, often suffer from erratic absorption. Self-nanoemulsifying (SNEDDS) and self-microemulsifying (SMEDDS) systems address this by spontaneously forming fine emulsions upon contact with gastrointestinal fluids, greatly improving dissolution and absorption. [18] These systems can also co-encapsulate synergistic agents, amplifying therapeutic efficacy while minimizing toxicity. [19]

6.4 Mucoadhesive and Localized Delivery Systems

Mucoadhesive drug delivery platforms are particularly promising for localized prevention of mucositis and gastrointestinal injury. By adhering to mucosal tissues, polymer-based films or gels sustain drug release at the target site. Chitosan- and carbopol-based systems delivering agents like honey, glutamine, or curcumin have shown significant improvement in mucosal protection and comfort. [20] These systems exemplify how targeted local delivery minimizes systemic exposure while enhancing therapeutic effect. [21]

6.5 Prodrug and Controlled-Release Strategies

Prodrug technologies modify active compounds into inactive precursors that become therapeutically active after enzymatic conversion in vivo, improving selectivity and minimizing systemic toxicity. Controlled-release systems—such as hydrogels, microspheres, or biodegradable implants—maintain steady drug levels, preventing the concentration spikes that often precipitate adverse reactions. [22] These approaches are particularly effective for agents with narrow therapeutic windows or dose-dependent toxicities.

6.6 Biosimilars and Biobetters

Biosimilars—highly similar versions of biologic drugs—have significantly increased global access to key supportive therapies such as G-CSFs and erythropoiesis-stimulating agents (ESAs). Comparative studies demonstrate equivalent efficacy, safety, and immunogenicity to original biologics [23,24]. Biobetters, or next-generation biologics, incorporate molecular improvements that extend half-life, reduce immunogenic potential, or enhance receptor affinity, representing a new frontier in adjuvant pharmacotherapy. [25] Harmonized guidelines from the FDA, EMA, and WHO ensure consistent evaluation of these complex biologics. [26]

6.7 Nanopharmaceuticals and Regulatory Integration

Nanopharmaceuticals—including liposomal, polymeric, and metallic nanoparticle formulations—occupy a rapidly evolving regulatory landscape. Agencies such as the FDA, EMA, and WHO now mandate detailed physicochemical characterization covering particle size, charge, release kinetics, and stability. [27] Recent guidance from the EMA (2024) and MHRA (2025) emphasizes the use of standardized analytical and comparability frameworks for nano-enabled formulations. [28] The integration of Quality by Design (QbD) and risk-based assessment models ensures reproducible manufacturing and safety compliance. [29, 30]

6.8 Synergistic Formulation Approaches

Recent innovations increasingly focus on dual-delivery systems that combine cytotoxic and

protective agents within a single nanocarrier. For example, co-encapsulation of doxorubicin with curcumin or cisplatin with resveratrol within nanoparticles has been shown to decrease cardiotoxicity and nephrotoxicity without compromising antitumor efficacy. [31,32] These intelligent platforms exemplify how drug delivery can evolve from passive transport to dynamic, toxicity-mitigating systems.

6.9 Clinical and Translational Implications

Advances in formulation technology are redefining adjuvant therapy by transitioning from reactive symptom management to proactive toxicity prevention. The success of these technologies, however, relies on interdisciplinary collaboration among oncologists, formulation scientists, and regulatory authorities. Key challenges remain—scaling production, ensuring affordability, and maintaining long-term safety oversight. [33,34] As these innovations mature, they promise to bridge the gap between laboratory research and real-world oncology practice, laying the foundation for precision-driven supportive care.

7. Regulatory & Safety Considerations

The translation of adjuvant therapies from laboratory innovation to clinical practice depends on robust regulatory oversight and continuous safety evaluation. Agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the World Health Organization (WHO) provide structured frameworks to ensure product quality, efficacy, and patient protection throughout the entire product lifecycle. As oncology embraces increasingly complex modalities—such as nanomedicines, liposomal systems, biosimilars, and nutraceutical-pharmaceutical hybrids—regulatory science must evolve to balance innovation with safety. [35]

Table 5: International Regulatory Guidelines Relevant to Adjuvants and Advanced Formulation

Guideline / Authority	Year	Scope / Title	Key Points	Relevance
U.S. FDA — CINV: Developing Drugs for Prevention (Draft) [37]	2021	Clinical guidance for antiemetic drug development.	Defines trial design, endpoints, and PROs for acute/delayed CINV.	Useful for supportive/adjuvant therapy trials.
U.S. FDA — Liposome Drug Products: CMC, PK/BA, Labeling [38]	2018	Liposomal formulation standards.	Details CMC, particle size, release, stability, PK/BA.	Key for liposomal adjuvants and nanoformulations.
EMA — Reflection Paper on IV Liposomal Products (Rev. 2) [38]	2013	Data needs for liposomal comparability.	Focuses on characterization, PK bridging, biodistribution.	Supports EU submissions for reformulated adjuvants.
EMA — Nanomedicine Guidelines Hub [39]	Ongoing	Regulatory framework for nanomedicines.	Covers immunogenicity, ADME, CQAs, validation.	Applies to nanocarrier-based adjuvants.

ICH — Q8, Q9, Q10, Q2(R2), Q14 [40,41]	2005–2023	Global quality and lifecycle standards.	QbD, risk management, analytical validation.	Ensures CMC quality for adjuvant formulations.
WHO — Biosimilar Evaluation Guidelines [42]	2022	Framework for biosimilar products.	Defines analytical, clinical similarity, immunogenicity.	Relevant for biologic adjuvants and supportive agents.
MHRA (UK) — Decision Tree for Nanotech Products [43]	2024–2025	Classification of nano/drug-device systems.	Clarifies product type, ICH route, advice pathway.	Helps with hybrid or device-integrated adjuvants.
CDSCO / DBT / ISNM (India) — Nanopharma Guidelines [44]	2019	National standards for nanopharmaceuticals.	Defines testing, stability, in-vivo, toxicity per ICH/EMA.	Key for Indian nanocarrier adjuvant development.

CONCLUSION

Chemotherapeutically induced toxicities management has changed and progressed into a multidimensional, evidence based discipline that includes pharmacology, formulation science, and holistic care, while helping to provide patients with both a good chance at survival and a good quality of life. Pharmacological adjuvants such as antiemetics, G-CSFs, palifermin, duloxetine, and dexrazoxane are now central to the prevention of toxicities caused by chemotherapy, and are included in both Canadian and World Health Organisation guidelines. Advances in drug delivery systems (liposomal and nano-based formulations) have improved the safety and tolerability of the drugs and biosimilars have improved the accessibility. Nutraceuticals (curcumin and probiotics) are clinically proven to be of potential benefit but require more validation studies. Non-pharmacological interventions (i.e., exercise and cognitive therapies) will further assist in improving the overall wellbeing of patients receiving chemotherapy. There are strong regulatory agencies that will enforce the safety and efficacy of the preventive treatments. In the future, there will be an even greater focus on providing precision-guided supportive oncology using biomarkers, artificial intelligence derived dosing, and integrative therapeutic systems to allow for the delivery of cancer care that is truly patient-centered and individualized.

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