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ORIGINAL RESEARCH

THE GLOBAL CHALLENGE OF CHEMOTHERAPY TOXICITY: RETHINKING SUPPORTIVE CARE IN MODERN ONCOLOGY

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ABSTRACT

Chemotherapy remains a central component of cancer treatment, yet its therapeutic efficacy is frequently overshadowed by a broad spectrum of systemic toxicities that severely compromise patient quality of life. This adverse effect – ranging from nausea, vomiting, and anorexia to mucositis, diarrhea, fatigue, and alopecia, are driven by complex molecular and cellular mechanisms that extend far beyond the direct cytotoxicity to malignant cells. Emerging evidence highlights the role of inflammatory cytokine cascades, oxidative stress, neurotransmitter imbalance, mitochondrial dysfunction, and epithelial barrier disruption in mediating these side effects. For instance, serotonin release and 5-HT_3 receptor activation underlie chemotherapy induced emesis, while hypothalamic dysregulation contributes to anorexia. Mucositis results from ROS mediated NF-κB activation and epithelial apoptosis, whereas diarrhea is linked to SN-38 induced enterocyte damage, tight junction disruption, and microbiome imbalance. Fatigue stems from altered HPA axis signalling and mitochondrial energy deficits, while alopecia arises from p53 mediated apoptosis in hair follicle keratinocytes. Understanding these multifaceted mechanisms provides a foundation for the development of targeted adjunct therapies, particularly those driven from biocompatible and multifunctional natural agents. This review presents an integrated molecular perspective on chemotherapy induced toxicities and explores innovative strategies for their prevention and management.

Keywords: Chemotherapy, toxicity, Nausea and vomiting, Anorexia, P53 pathway, Oncology, Inflammatory cytokines

INTRODUCTION

significant challenges to healthcare systems globally. Despite the considerable progress made in prevention, early detection, and treatment modalities, cancer continues to account for substantial morbidity and mortality[1]. According to the World Health Organization (WHO), over 19 milllion new cancer cases are diagnosed annually, and this number is expected to rise in the coming decades due to aging populations, lifestyle changes, and environmental exposures. While advances in immunotherapy, targeted therapy, and precision medicine have revolutionized oncologic care, chemotherapy remains a cornerstone of cancer treatment, especially in settings where advanced or metastatic disease precludes localized interventions[2].

Chemotherapy refers to the systemic administration of cytotoxic agents that are designed to kill or inhibit the proliferation of rapidly dividing cells. The rationale behind its use stems from the high mitotic activity that characterizes most malignancies[3]. Agents such as alkylating compounds, antimetabolites, topoisomerase

inhibitors, and mitotic spindle poisons have been staples in oncologic pharmacology for decades. These drugs interfere with various stages of the cell cycle, therby arresting tumor growth or inducing apoptosis in neoplastic cells. However, the lack of specificity toward malignant cells remains chemotherapy's greatest shortcoming[4]. Normal cells that also possess high proliferative rates- such as those in the bone marrow, gastrointestinal tract, hair follicles, and reproductive organs- become inadvertent targets, leading to the well documented toxicities associated with chemotherapy[5].

The toxicity profile of chemotherapeutic drugs is broad and varies depending on the class of agent, dose, duration of treatment, and individual patient susceptibility. Acute side effects include nausea, vomiting, mucositis, diarrhea, and myelosuppression, which can culminate in anaemia, leukopenia and thrombocytopenia. These hematologic toxicities, in turn, increase the risk of infection, bleeding, and fatigue. Furthermore, alopecia, skin rashes, and altered taste perception can significantly affect body image and self-esteem. Long term and late effects are of particular concern for cancer survivors and may include cardiotoxicity, neurotoxicity, nephrotoxicity, pulmonary fibrosis, secondary malignancies, infertility, and cognitive impairments often described as "chemo brain". Each of these sequelae carries profound implications for quality of life and functional independence[6].

The paradox of chemotherapy lies in its duality- it is both life saving and life altering. While it remains indispensable in many cancer treatment protocols, its impact extends far beyond tumor cytoreduction. The physiological toll is often compounded by psychological distress, including anxiety, depression, and post-traumatic stress. Social isolation and financial toxicity are also frequently reported, particularly in low- and middle-income countries where health insurance coverage and access to supportive care may be limited[7]. Caregivers, too, bear a significant emotional and physical burden, further underscoring the ripple effects of cancer treatment. In this context, the quality of survivorship has become an essential metric alongside traditional outcomes such as progression free and overall survival. Over the years, numerous strategies have been employed to ameliorate chemotherapy associated toxicity. These include the development of supportive medications such as antiemetics (e.g., 5HT3 receptor antagonists), growth factors (e.g., G-CSF), and cytoprotective agents (e.g., dexrazoxane for anthracycline- induced cardiotoxicity). Advances in pharmacogenomics have allowed for more personalized dosing regiments, aiming to minimize toxicity without compromising efficacy. However, these approaches are often reactive rather than preventive and may not sufficiently address the multifactorial nature of chemotherapy induced damage[8].

In light of these challenges, nanotechnology and targeted drug delivery systems have emerged as promising alternatives or adjuncts to traditional chemotherapy. By encapsulating chemotherapeutic agents in nanoparticles or conjugating them with ligands that recognize tumor-specific antigens, it is possible to increase drug accumulation in tumor tissues whiles sparing normal cells[3,9]. This selective delivery can reduce systemic exposure, thereby minimizing off-target effects. Furthermore, such platforms can be engineered to release their payload in response to specific stimuli in the tumor microenvironment, such as pH, enzymes, or temperature. Several nanocarrier systems – including liposomes, dendrimers, micelles, and polymeric nanoparticles- are currently under investigation or have received regulatory approval, marking a paradigm shift in the way chemotherapeutics are administered[10]. Phytochemicals and natural compounds are also gaining attention for their potential to modulate the toxic effects of chemotherapy. Substances such as curcumin, resveratrol, quercetin, and thymoquinone exhibit antioxidant, anti-inflammatory, and cytoprotective properties. These agents may enhance the therapeutic index of chemotherapy by sensitizing tumor cells to its effects while simultaneously protecting normal cells from collateral damage. Some compounds even possess intrinsic anticancer activity and can be used in combination with conventional drugs to achieve a synergistic effect. This has paved the way for the exploration of integrative oncology, which seeks to harmonize conventional and complementary therapies for a more holistic approach to cancer care[11].

An emerging area of focus involves the tumor microenvironment (TME), which plays a critical role in cancer progression, metastasis, and response to therapy. The TME comprises not only cancer cells but also stromal cells, immune cells, extracellular matrix components, and signalling molecules. Chemotherapy can inadvertently remodel the TME, sometimes enhancing the invasive or drug-resistant properties of residual cancer cells. Strategies that concurrently target the TME- such as inhibiting angiogenesis, modulating immune checkpoints, or reprograming cancer associated fibroblasts-may improve therapeutic outcomes and reduce recurrence rates. Understanding these intricate cellular interactions is vital for designing next generation chemotherapeutic regiments with improved efficacy and tolerability[12].

Moreover, the psychosocial and supportive care dimension of chemotherapy is garnering increased recognition. Effective communication between clinicians and patients, adequate symptom management, nutritional support, psychological counselling, and palliative care are all crucial for enhancing the overall treatment experience. Patient reported outcome measures (PROMs) are increasingly being integrated into clinical trials and

routine practice to capture the subjective experience of chemotherapy, ensuring that therapeutic decisions are aligned with patient preferences and values. Thus, chemotherapy continues to be a mainstay of cancer treatment, offering hope and extended survival for millions of patients worldwide. However, its use is marred by a host of adverse effects that compromise patient well being and can lead to treatment delays or discontinuation. Addressing these challenges requires a multifaced approach, including innovations in drug design and delivery, incorporation of complementary therapies, improved understanding of the tumor microenvironment, and enhanced supportive care, As the field of oncology moves toward more precise and personalized interventions, the goal must be not only to prolong life but to preserve its quality, ensuring that the fight against cancer does not come at the cost of the patient's dignity, functionality, and overall health[13].

The following table outlines the major side effects induced by chemotherapy, emphasizing the specific molecular mechanisms involved such as neurotransmitter activation, inflammatory cytokine release, oxidative stress and apoptosis. These representative chemotherapeutic agents are also known to trigger each and or the entire symptom as mentioned in the table. A mechanistic understanding of these toxicities is critical for guiding the development of effective, multi-targeted supportive care interventions to mitigate patient burden and enhance treatment adherence (Table 1).

Table 1. Chemotherapy Induced Side effects: Molecular mechanisms and Representative drugs

Symptom	Molecular Mechanism	Example Drug
Nausea/Vomiting	5-HT_3 receptor stimulation via serotonin → CTZ activation	Cisplatin[13]
Anorexia	Cytokine-induced hypothalamic and dopaminergic disruption	Doxorubicin[14]
Mucositis	ROS → NF-κB → cytokines/MMPs → mucosal damage	5-Fluorouracil[15]
Diarrhea	Enterocyte loss, microbiome shift, COX-2/IL-6 upregulation	Irinotecan[16]
Fatigue	Mitochondrial dysfunction + HPA axis/cytokine imbalance	Paclitaxel[1,17]
Alopecia	p53-mediated apoptosis of hair follicle keratinocytes	Cyclophosphamide[18]

2.Molecular Mechanism of the Chemotherapeutic induced side effects

2.1 Nausea and Vomiting: A Molecular Mechanistic Perspective in Chemotherapy

Nausea and vomiting are among the most distressing and commonly reported adverse effects associated with chemotherapy. These symptoms result from a complex interplay of peripheral and central nervous system mechanisms, primarily mediated by the stimulation of neurochemical receptors and signalling pathways in response to cytotoxic insult[19]. The emetogenic potential of chemotherapeutic agents particularity drugs like cisplatin is attributed to their ability to damage gastrointestinal tissues and induce neurochemical cacades that ultimately activate the vomiting center in the brainstem. The process begins in the gastrointestinal (GI) mucosa, where chemotherapeutic agents such as cisplatin induce cellular stress and damage. Specifically, they act on enterochromaffin cells, specialized epithelial cells found in

the lining of the small intestine, which contain large quantities of serotonin (5-hydroxytryptamine or 5-HT) stored in secretory granules. Upon damage or stimulation, these cells release 5-HT into the surrounding tissue and bloodstream (Figure 1)[20].

The released 5-HT binds to 5-HT3 receptors, which are ligand gated ion channels located on the terminals of vagal afferent neurons that project to the brainstem. Activation of these receptors causes neuronal depolarization and the initiation of action potentials that travel along the vagus nerve to the nucleus tractus solitarius (NTS) and area postrema, the latter of which contains the chemoreceptor trigger zone (CTZ). The CTZ is one of the few areas in the brain without a well-developed blood brain barrier, making it highly sensitive to circulating emetogenic substances, including chemotherapeutic agents and their metabolites. Once the CTZ is activated, it communicates with the central pattern generator (CPG) in the medulla oblongata, integrating multiple afferent inputs. This leads to coordinated efferent signals that stimulate the somatic and autonomic systems responsible for the vomiting reflex. Importantly, the CTZ and NTS contain multiple nueroreceptors that modulate this process, including dopaminergic D_2 rceptors, neurokinin-1 (NK-1) receptors, and muscarinic and histaminergic receptors[21,22].

Chemotherapy induced nausea and vomiting (CINV) can be divided into acute and delayed phases. Acute CINV occurs within the first 24 hours of chemotherapy and is predominantly mediated by the 5-HT_3 pathway, while delayed CINV, which occurs 24-72 hours later, is more associated with substance P and activation of NK-1 receptors. This biphasic response underscores the need for combination antiemetic therapies, often involving 5-HT_3 receptor antagonists (e.g., ondansetron), NK-1 receptor antagonists 9e.g., aprepitant), and dopamine antagonists (e.g., metoclopramide). Among all chemotherapeutic agents, cisplatin is considered the most emetogenic, with nearly 90% of patients experiencing significant nausea and vomiting without prophylactic antiemetic therapy. Cisplatin's high emetogenicity is due to its potent activation of enterochromaffin cells and subsequent massive serotonin release. Overall, the pathophysiology of chemotherapy induced nausea and vomiting is rooted in the serotonergic activation of vagal afferents, central dopaminergic and neurokinin pathways, and integrated reflex control by the brainstem. Understanding these pathways has led to the development of targeted pharmacological interventions that have dramatically improved patient outcomes, yet the complexity and multifactorial nature of CINV still present significant challenges in cancer care[23,24].

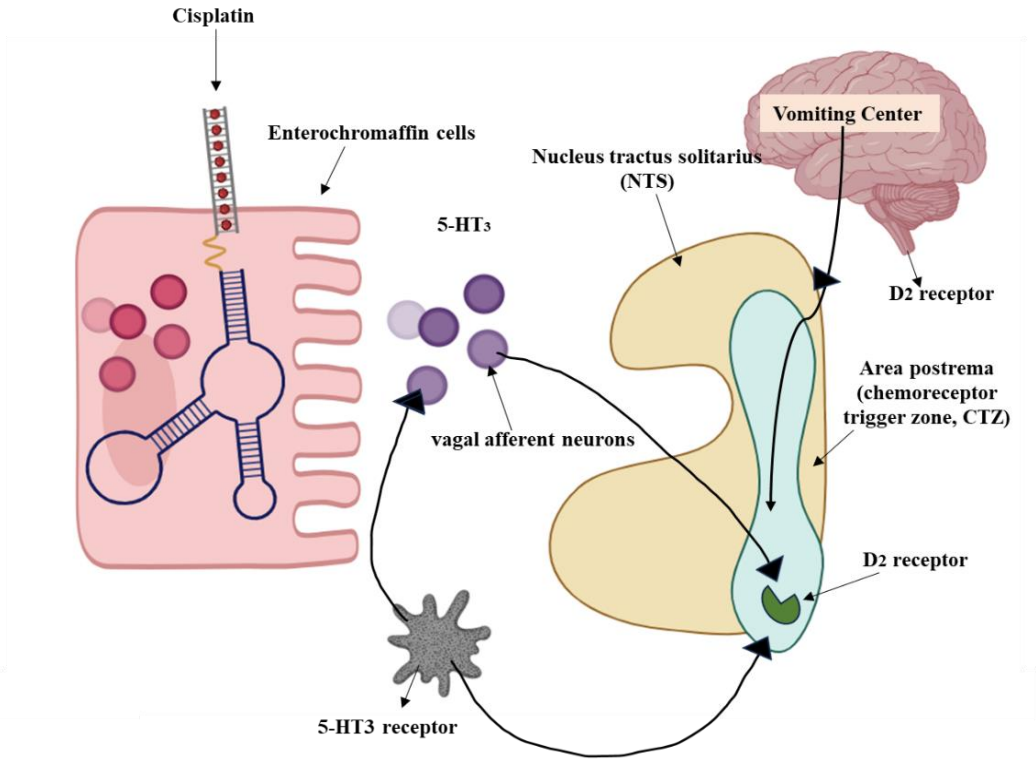

Figure 1: Molecular Mechanism of Chemotherapy Induced Nausea and Vomiting

Cisplatin induced damage to gastrointestinal epithelial cells stimulates enterochromaffin cells to release serotonin (5-HT). Serotonin activates 5-HT_3 receptors on vagal afferent nerves, transmitting signals to the nucleus tractus solitarius (NTS) and the chemoreceptor trigger zone (CTZ) in the medulla oblongata. The CTZ integrates these inputs and activates the vomiting center via dopaminergic (D_2) and neurokinin-1 (NK-1) receptors, resulting in the emetic reflex. The actute phase is primarily 5 HT_3 mediated, while the delayed phase involves NK-1 receptor activation.

2.2 Anorexia (Loss of Appetite): Molecular Mechanisms in Chemotherapy

Anorexia, or the pathological loss of appetite, is a prevalent and debilitating side effect of chemotherapy. It contributes significantly to cancer cachexia, impaired immune response, delayed healing, and reduced quality of life. While often perceived as a simple reduction in food intake, chemotherapy induced anorexia is a complex neuroimmunology disorder orchestrated by the interaction between pro-inflammatory cytokines, neuroendocrine dysregulation, and neurotransmitter imbalances within the brain, especially the hypothalamus and mesolimbic system[25].

The hypothalamus plays a central role in appetite regulation by integrating peripheral signas related to energy status and coordinating hormonal and neural inputs. Under normal conditions, orexigenic (appetite stimulating) signals such as neuropeptide Y (NPY) and agouti related peptide (AgRP) stimulate food intake. In contrast, anorexigenic (appetite suppressing) signals like pro-opiomelanocortin (POMC) and leptin reduce appetite. Ghrelin, a hormone secreted by the stomach, activates NPY/AgRP neurons, promoting hunger[26].

Chemotherapy disrupts this tightly regulated system primarily through the elevation of systemic pro-inflammatory cytokines, including tumor necrosis factor -alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These cytokines are released in response to cellular damage and oxidative stress induced by cytotoxic drugs like doxorubicin, and they easily cross the blood brain barrier (BBB) or signal via vagal afferents to the hypothalamus. Once in the brain, these cytokines inhibit the expression and activity of NPY, thereby suppressing orexigenic signals. Simultaneously, they enhance the leptin like anorexigenic pathways, even in the absence of actual leptin increase. For example, IL-1β inhibits food intake by increasing POMC activity melanocortin signalling through MC4R receptors [27].

Beyond the hypothalamus, chemotherapy induced anorexia also involves the mesolimbic dopamine system, which governs the reward value of food. This pathway includes key region like the ventral tegmental area (VTA) and the nucleus acumens (NAc). Dopamine release in this circuit is essential for the motivation to eat. Chemotherapeutic drugs and inflammatory cytokines disrupt dopaminergic neurotransmission by impairing dopamine synthesis (Via tyrosine hydroxylase inhibition) and altering dopamine receptor sensitivity. The resulting anhedonia (inability to feel pleasure) diminishes the hedonic drive to eat, even when energy reserves are low[28].

Moreover, peripheral signals like gastric emptying delays and altered taste/smell perception, both mediated by cytokines effects and direct mucosal toxicity, further reduce the appeal and anticipation of eating. Chemotherapy also affects the vagal signaling to the brainstem, altering satiety thresholds and reinforcing early satiation. An illustrative example is doxorubicin, which increases circulating levels of TNF-α and IL-6, both centrally implicated in anorexia. Animal models treated with doxorubicin show profound reductions in food intake accompanied by hypothalamic downregulation of NPY and ghrelin receptors and reduced dopaminergic tone in the NAc. Ultimately, chemotherapy induced anorexia is a multifaced condition mediated by inflammatory, neuroendocrine, and neurochemical alterations. The cytokine driven suppression of orexigenic pathways, enhancement of anorexigenic signalling, and blunting of reward mechanisms together contribute to a profound and persistent loss of appetite, often resistant to standard nutritional support. Understanding these mechanisms paves the way for targeted interventions, such as ghrelin agonists, anti-inflammatory agents, and dopamine modulators, to compact anorexia and improve patient wellbeing during cancer therapy (Figure 2)[29].

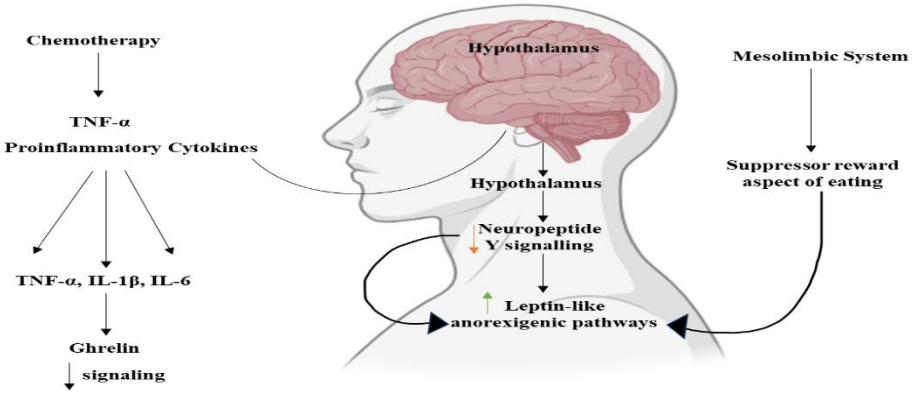

Figure 2. Molecular mechanism of chemotherapy induced Anorexia.

Chemotherapy elevates systemic pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), which disrupt hypothalamic appetite regulation. These cytokines suppress orexigenic signals and enhance anorexigenic pathways. Ghrelin signalling is impaired, further reducing hunger drive. Additionally, cytokines and chemotherapeutic agents disrupt dopaminergic signalling in the mesolimbic system, diminishing reward perception and motivation to eat. Altered vagal input, taste perception, and gastric motility also contribute to appetite suppression.

2.3 Mucositis: Molecular Mechanisms of Chemotherapy Induced Mucosal Injury

Mucositis is a severe and painful inflammatory condition of the mucous membranes lining the gastrointestinal (GI) tract, especially affecting the oral cavity. It is a common and dose limiting side effect of cytotoxic chemotherapy, particularly with agents like 5-flurouracil (5-FU). Clinically, mucositis manifests as erythema, ulceration, pain, dysphagia, and increased risk of systemic infections due to barrier breakdown. At the molecular level, mucositis arises from a series of interconnected biological events, beginning with epithelial stem cell damage and culminating in inflammatory amplification, tissue breakdown, and ulceration[30].

Chemotherapeutic agents such as 5-FU target rapidly proliferating cells, which include not only tumor cells but also the basal epithelial progenitor cells in the mucosal lining. These cells are essential for continuous mucosal regeneration. Damage to these cells initiates the first phase of mucositis-epithelial injury. DNA damage caused by chemotherapy induces a cascade of oxidative stress, with the overproduction of reactive oxygen species (ROS) within mucosal tissues. ROS play a dual role: while they directly damage cellular structures (lipids, proteins , DNA), they also serve as secondary messengers that activate downstream signaling pathways, most notably nuclear factor kappa B (NF-κB). NF-κB is a redox sensitive transcription factor that translocates into the nucleus upon activation and binds to promoter regions of genes involved in inflammation and cell death[31].

This leads to the second phase – upregulation of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin -6 (IL-6). These cytokines create a positive feedback loop by further activating NF-κB and recruiting immune cells like neutrophils and macrophages into the mucosal tissue. The resulting inflammatory amplification promotes the release of matrix metalloproteinases (MMPs), particularly MMP-1 and MMP-9, which degrade the extracellular matrix and basal membrane components, destabilizing the mucosal structure[32].

Simultaneously, apoptosis of mucosal epithelial cells is triggered through both intrinsic (mitochondrial) and extrinsic (death receptor) pathways. ROS cause mitochondrial dysfunction and cytochrome c release, activating caspase-9 and downstream executioner caspases, while TNF-α binds to TNFR1, initiating FADD dependent caspase 8 activation. Together, these lead to widespread epithelial cell death and sloughing of the mucosal surface.

The third phase is characterized by ulceration, where the mucosal integrity is lost, exposing underlying submucosa to mechanical injury and microbial invasion. Bactrial components like lipopolysaccharide (LPS) further exacerbate inflammation by engaging Toll-like receptors on immune and epithelial cells, sustaining NF-κB activity and cytokine production. A prominent example eis 5-fluorouracil (5-FU), which interferes with thymidylate synthase and incorporates into RNA/DNA, leading to cell cycle arrest and apoptosis in epithelial stem cells. In preclinical models, 5-FU has been shown to increase ROS levels and activates NF-κB, resulting in significant upregulation of TNF-α, IL-1β, MMPs, directly correlating with ulcer severity.Taken together, chemotherapy induced mucositis is a multi phase pathological process involving epithelial stem cell damage, oxidative stress, NF-κB mediated inflammation, matrix degradation, and apoptosis. The breakdown of the mucosal barrier not only causes significant morbidity but also compromises nutrition, drug delivery, and infection control. Understanding these molecular underpinnings has paved the way for targeted interventions, including antioxidants, NF-κB inhibitors, cytokine blockers, and growth factors like palifermin, aimed at preventing or mitigating mucosal damage in cancer patients[33] (Figure 3).

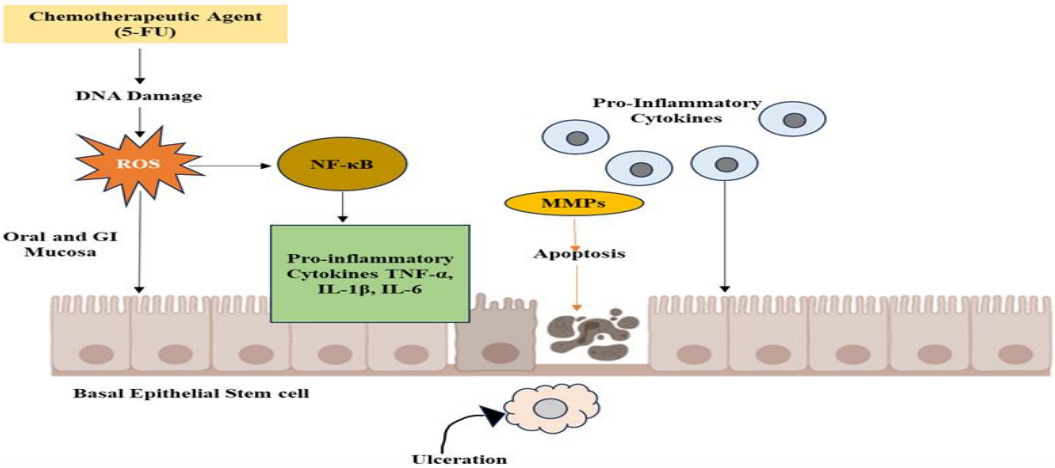

Figure 3. Molecular Mechanism of Chemotherapy Induced Mucositis

Chemotherapy agents like 5-fluorouracil (5-FU) damage basal epithelial cells, intitaiting oxidative stress and generation of reactive oxygen species (ROS0. ROS activate NF-κB, leading to the upregulation of pro-inflammatory cytokines and matrix metalloproteinases , which degrade the extracellular matrix. Apoptosis is triggered via both mitochondrial and extrinsic pathways. Barrier breakdown results in ulceration and microbial invasion, sustaining inflammation and worsening mucosal injury.

2.4 Chemotherapy Induced Diarrhea: Molecular Mechanism of Gastrointestinal Toxicity

Diarrhea is a common and potentially severe gastrointestinal side effect of many chemotherapeutic agents. It results from complex disruptions in intestinal epithelial integrity, inflammation, secretory function, and microbiome balance, leading to increased fluid secretion and reduced absorption. Among chemotherapeutic agents, irinotecan is notorious for causing severe, often delayed onset diarrhea, primarily due to its active metabolite SN-38. The molecular mechanisms behind chemotherapy induced diarrhea involve DNA damage, inflammatory signalling. Tight junction disruption, and microbiota alterations.At the core of this toxicity is epithelial cell damage. Chemotherapy targets rapidly dividing cells, including the intestinal crypt stem cells responsible for regenerating the epithelial lining. DNA damage induced by drugs such as irinotecan, 5-fluorouracil, and methotrexate causes apoptosis of enterocytes. This leads to villous atrophy, decreased absorptive surface area, and malabsorption of water and nutrients, which are primary contributors to diarrhea[34].

Irinotecan is converted in the liver to its active metabolite SN-38, which is responsible for both anti-tumor efficacy and gastrointestinal toxicity. SN-38 exerts its effects by inhibiting topoisomerase I, leading to accumulation of DNA strand breaks, activation of P53, and apoptosis of intestinal epithelial cells. SN-38 is detoxified in the liver via glucuronidation, but it can be reactivated in the gut by bacterial β-glucuronidase enzymes, leading to prolonged exposure of the intestinal mucosa to SN-38, resulting in epithelial injury and inflammation. This epithelial damage leads to the release of pro-inflammatory cytokines, particularly interleukin-6 and TNF-α. These cytokines activate downstream pathways such as the cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2) axis, which promotes inflammation, vasodilation, and chloride secretion, therby enhancing intestinal fluid loss. IL-6 also activates STAT3, contributing to mucosal inflammation and impaired mucosal regeneration.

In addition to inflammatory cytokines, epithelial barrier dysfunction is exacerbated by disruption of tight junction proteins, such as claudins, occludins, and zonula occludens-1 (ZO-1). Chemotherapy induced ROS and cytokines lead to the internalization or degradation of these proteins, increasing paracellular permeability. The compromised barrier permits luminal antigens and bacteria to infiltrate the mucosa, further amplifying inflammation and contributing to secretory diarrhea. Furthermore, chemotherapy induces gut microbiome dysbiosis, characterized by a reduction in commensal bacteria and overgrowth of pathogenic strains. These microbial changes enhance mucosal inflammation and reduce production of short chain fatty acids (SCFAs) like butyrate, which are essential foe enterocyte health and water reabsorption. In irinotecan treated models, pathogenic bacteria with β glucuronidase activity increase reactivation of SN-38G, creating a toxic positive feedback loop (Figure 4).

In the delated phase of irinotecan induced diarrhea, which occurs 2-10 days post treatment, the main pathological event is epithelial apoptosis, sustained inflammation, and impaired regenerative capacity. In severe cases, this can progress to life threatening colitis or dehydration, necessitating dose reduction or treatment discontinuation. Utimately, chemotherapy induced diarrhea is a multifactorial process involving enterocyte apoptosis, inflammatory cytokine release, barrier dysfunction, and microbiome disturbances. Irinotecan exemplifies this toxicity through its SN-38 metabolite and its interaction with the microbiota. Understanding these molecular mechanisms has led to the development of preventive and therapeutic strategies, including probiotics, COX-2 inhibitors, IL-6 blockers, and β-glucuronidase inhibitors, aimed at mitigating intestinal injury and improving patient outcomes during chemotherapy[35].

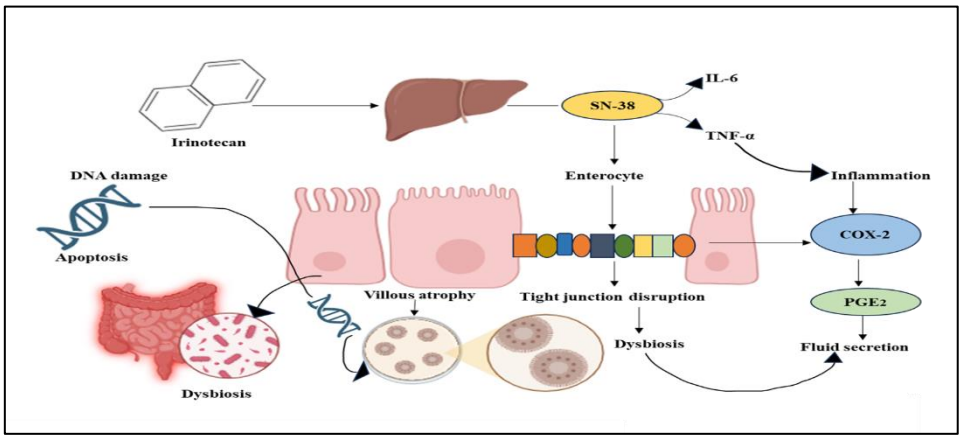

Figure 4. Molecular Mechanism of chemotherapy Induced Diarrhea

Irinotecan is metabolized to SN-38, which induces DNA damage and apoptosis in intestinal epithelial cells, leading to villous atropy and malabsorbtion. SN-38 also promotes the release of pro-inflammatory cytokines and activates the COX-2/PGE2 pathway, enhancing intestinal secretion. Disruption of tight junction proteins increases epithelial permeability. Gut dysbiosis and bacterial β-glucuronidase mediated reactivation of SN-38G amplify mucosal injury, resulting in delayed onset secretory diarrhea.

2.5 Chemotherapy – Induced Fatigue: Molecular Mechanisms of Energy Dysregulation

Fatigue is one of the most common and distressing symptoms experienced by cancer patients undergoing chemotherapy. It is characterized by a persistent sense of physical, emotional, and cognitive tiredness that s not relieved by rest and significantly impairs daily functioning. Unlike normal tiredness, chemotherapy-induced fatigue is rooted in cellular and molecular disturbances that affect energy production, inflammatory regulation, endocrine balance, and neurotransmitter signaling.

At the cellular level, chemotherapy leads to mitochondrial dysfunction, which ia a major contributor to fatigue. Mitochondria are the primary site of adenosine triphosphate (ATP) production through oxidative phosphorylation. Chemotherapuetic agents such as paclitaxel and doxorubicin generate reactive oxygen species (ROS) as byproducts of their action on rapidly dividing cells. These ROS cause oxdative damage to mitochondrial membranes, enzymes, and mitochondrial DNA (mt DNA), impairing the fuction of the electron transport chain (ETC). The inhibition of ETC complexes leads to reduced ATP synthesis and energy deficit at the cellular level, particularly in high demand tissues like skeletal muscle and the central nervous system. The resulting bioenergetic failure directly contributes to the feeling of physical exhaustion[36].

Simultaneously, chemotherapy induces chronic systemic inflammation, a process that amplifies fatigue through immune endocrine dysregulation. Cytotoxic agents trigger the release of pro-inflammatory cytokines, including interleukin-6, TNF-α, interleukin-1 beta. The cytokines can cross the blood brain barrier or signal through vagal afferent pathways, activating microglial cells in the central nervous system. The resulting neuroinflammation disrupts normal neuronal activity, particularly in the hypothalamic pituitary adrenal (HPA) axis[37].

The HPA axis is central to maintain circadian rhythms, stress response, and cortisol homeostasis. Chemotherapy induced cytokines interfere with the hypothalamic secretion of corticotropin releasing hormone (CRH) and arginine vasopression (AVP), leading to impaired release of adrenocorticotropic hormone (ACTH) and subsequent adrenal cortisol production. Disruption of this axis causes flattering of the diurnal cortisol rhythm, which is strongly associated with central fatigue, mood disturbances, and sleep disorders[38].

Neurotransmitter imbalance further exacerbates fatigue. Chemotherapy affects central neurotransmission, particularly involving serotonin (5-HT), dopamine (DA), and norepinephrine (NE). Inflammatory cytokines upregulate the enzyme indoleamine2,3 dioxygenase (IDO), which degrades tryptophan, the precursor for serotonin into kynurenine, reducing serotonin availability. Lower serotonin levels contribute to mood changes, lethargy, and disrupted sleep. Additionally, reduced dopaminergic signalling in the mesolimbic and prefrontal cortex leads to diminished motivation and reward sensitivity, a key feature of central fatigue.Both paclitaxel and doxorubicin have been shown to significantly increases ROS production in mitochondria and elevate systemic cytokines such as IL-6 and TNF-α.

In animal models and patients, these drugs impair mitochondrial respiration, decrease muscle strength, and alter cortisol dynamics- consistent with the multifactorial etiology of chemotherapy induced fatigue. together, fatigue during chemotherapy arises from a synergistic interplay between mitochondrial injury, inflammatory cytokine activation, HPA axis disruption, and neurotransmitter imbalance. These molecular and neuroendocrine alterations create a state of chronic energy insufficiency and emotional dysregulation that cannot be overcome by rest alone.

Targeted interventions aimed at restoring mitochondrial function, controlling inflammation, and regulating neuroendocrine signaling may offer promising avenues to alleviate fatigue and enhance quality of life in cancer patients (Figure 5)[39]

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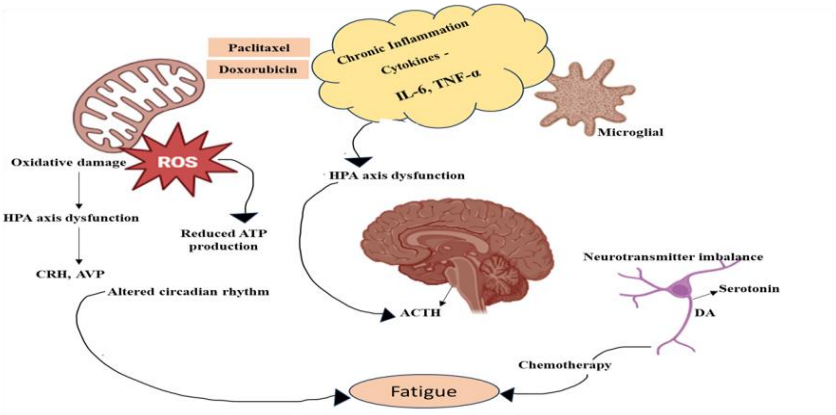

Figure 4. Molecular Mechanism of chemotherapy Induced Diarrhea.

Chemotherapy leads to mitochondrial dysfunction and reduced ATP production due to oxidative damage from reactive oxygen species (ROS). Concurrently, systemic inflammation elevates cytokines, disrupting the hypothalamic pituitary adrenal axis and flattening the diurnal cortisol rhythm. Inflammatory cytokines also alter neurotransmitter signalling by depleting serotonin and impairing dopamine synthesis, resulting in reduced motivation, sleep disturbances, and central fatigue. Together these pathways create a multifunctional disruption of energy regulation and emotional homeostasis.

2.6 Chemotherapy Induced Alopecia: Molecular Mechanisms of Hair Follicle Damage

Alopecia, or hair loss, is one of the most visible and psychologically distressing side effects of chemotherapy. It occurs primarily due to the targeted destruction of rapidly dividing cells- specifically, hair matrix keratinocytes- which share similar proliferative charcteristics with cancer cells. The pathophysiology of chemotherapy induced alopecia (CIA) is particularly associated with disruption of the anagen phase of the hair cycle, which is the active growth phase. This disruption involves complex molecular events, including DNA damage, p53 activation, mitochondrial mediated apoptosis, and dysregulation of cell survival pathways. During the anagen phase, hair follicle matrix keratinocytes at the base of the hair bulb divide rapidly to support the continuous elongation of the hair shaft. Chemotherapeutic agents, particularly alkylating agents like cyclophosphamide and microtubule stabilizing agents like docetaxel, are highly toxic to these cells due to their mechanism of action on DNA replication and mitosis[39,40].

Upon administration, drugs such as cyclophosphamide induce DNA cross linking and strand breaks, which are detected by the cell's DNA damage response (DDR) machinery. This activates the tumor suppressor protein p53, a master regulator of cellular stress responses. Once activated, p53 upregulates pro-apoptotic genes such as Bax and PUMA, a simultaneously downregulates anti-apoptotic proteins like Bcl-2, tipping the balance toward cell death.

This cascade triggers mitochondrial outer membrane permeabilization (MOMP), resulting in the release of cytochrome c into the cytosol. Cytochrome c forms a complex with Apaf-1 and procaspase-9, leading to the formation of the apoptosome, which subsequently activates executioner caspases. These caspases cleave structural and regulatory proteins, leading to controlled cellular demolition of their matrix keratinocytes.

In addition to the intrinsic pathway, extrinsic apoptotic signals also contribute to CIA. Chemotherapy agents have been shown to upregulate Fas receptor (CD95) and its ligand FasL on the surface of hair follicle cells. Binding of Fas to FasL activates caspace-8, which either directly initiates the executioner caspase or amplifies apoptosis by cleaving Bid, a pro-apoptotic Bcl-2 family protein that further engages the mitochondrial pathway.Importantly, these apoptotic events not only destroy the proliferative matrix cells but also didrupt the hair shaft formation and anchoring, leading to rapid shedding of hair- a process referred to as anagen effluvium. This typically begins with 1-2 weeks of chemotherapy intiation and becomes most noticeable by 1 month[41].

Cyclophosphamide is a classic example of an agent that causes alopecia through p53 mediated mitochondrial apoptosis. Docetaxel, a taxane derivative, causes mitotic arrest by stabilizing microtubules, leading to accumulation of DNA damage, activation of P53, and ultimately hair follicle apoptosis. Studies have shown that both drugs result in significant hair follicle regression and uncreased TUNEL-Positive cells in the hair bulb region, indicative of apoptosis.

Overall, chemotherapy induced alopecia results from the rapid induction of apoptotic pathways in hair follicle matrix cells, primarily mediated through p53 activation, mitochondrial cytochrome release, caspase activation, and Fas/FasL interactions. While this response is an unfortunate off target effect of anti-cancer therapy, understanding these molecular mechanisms has opened avenues for potential prevention strategies, such as scalp cooling, p53 pathway modulation, and cytokine-based protectants, aiming to preserve hair follicle integrity during treatment (Figure 6)[42].

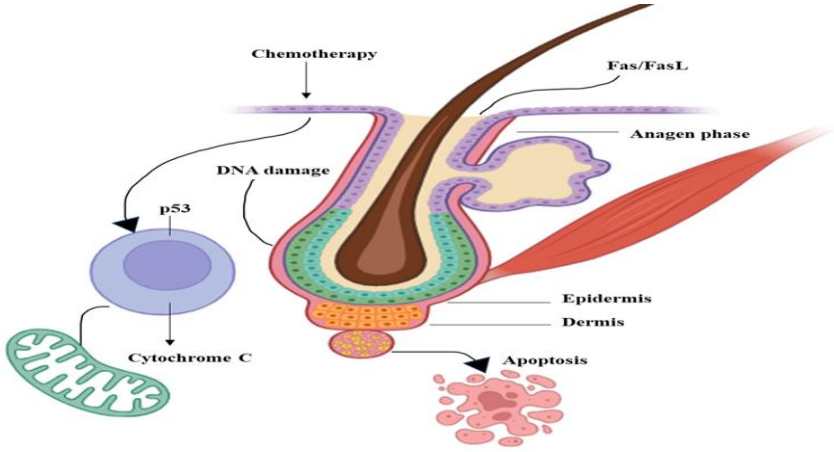

Figure 6. Molecular Mechanism of Chemotherapy Induced Alopecia

Chemotherapeutic agents such as cyclophosphamide and docetaxel damage rapidly dividing hair matrix keratinocytes during the anagen phase of hair growth. DNA damage triggers activation of the p53 pathway, leading to upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins. This activates mitochondrial mediated apoptosis through cytochrome c release and caspase cascade initiation. Additionally, Fas/FasL signalling contributes to extrinsic apoptosis. These pathways result in premature regression of hair follicles and hair shaft detachment, causing rapid hair loss known as anagen effluvium.

2.7 Beyond Cellular Damage: The broader Impact of Chemotherapy Induced side effects

Chemotherapy, while life saving, comes with a considerable burden that extends far beyond its cytotoxic action on tumor cells. The adverse effects of chemotherapy are not confined to physiological domains; they deeply affect the psychological, emotional, social, and financial well being of patients. For many individuals undergoing cancer treatment, the fear of chemotherapy related side effcets such as nausea, fatigue, mucositis, alopecia, and diarrhea- becomes more overwhelming than the fear of cancer itself. This intense apprehension can lead to delays in care seeking behavior, refusal to initiate chemotherapy, or premature termination of treatment cycles, all of which significantly compromise the overall therapeutic outcome[43].

These side effects are particularly distressing because they are often visible, painful, and persistent, eroding he patient's sense of identity and control. For example, alopecia, though not life-threatening, profoundly affects body image and self -esteem. Fatigue and gastrointestinal disturbances reduce the ability tp perform everyday tanks, leading to functional decline and social withdrawal. Over time, these physical symptoms contribute to anxiety, depression, and feelings of isolation, creating a feedback loop that worsens quality of life and psychological resilience during treatment[44].

Moreover, the economic implications of managing chemotherapy induced toxicities are substantial, especially in low- and middle-income countries. Patients often require hospital admissions for severe neutropenia, blood transfusions for anemia, antibiotics to control infections, and nutritional interventions for mucositis and anorexia. The cost of supportive medications, such as antiemetics, antidiarrheals, growth factors, and corticosteroids, adds significantly to the overall financial burden. In regions where health insurance is sparse and out of pocket expenses are high, these costs can be catastrophic, leading to treatment discontinuation and widening health inequities. This further undermines the objectives of national cancer control programs and accentuates global disparities in cancer outcomes.

Despite advances in oncology, current supportive care strategies remain largely reactive. Protocols now routinely include antiemetics, corticosteroids, and analgesics. These agents help mitigate acute symptoms but often fail to prevent the onset of toxicities or address their underlying causes. Additionally, many of these drugs are associated with secondary side effects, such as metabolic disturbances, immunosuppression, and drug-drug interactions, further complicating treatment[45].

One of the critical limitations of current supportive therapies lies in their single target mechanism of action, which is ill suited to manage the multifactorial nature of chemotoxicity. Chemotherapy induced side effects stem from oxidative stress, inflammatory cytokine cascaded, mitochondrial dysfunction, epithelial barrier breakdown, and apoptotic signaling in non-cancerous tissues. Addressing these complex, overlapping pathways with single agents offers only partial relief. Consequently, there is a pressing need for novel adjunct therapies that are multi-functional, biocompatible, and protective of normal tissues without compromising the antitumor efficacy of chemotherapy. Such agents should ideally possess antioxidant, anti-inflammatory, mitoprotective, and regenerative properties. Phytochemicals, nanoparticles, and bioengineered compounds are emerging as promising candidates, with the potential to redefine supportive care and transform the patient experience during chemotherapy[45].

2.8 Emerging Paradigms in Chemotoxicity: Molecular Insights and the promise of Biocompatible Adjuncts

The landscape of cancer therapy is evolving rapidly, not only in the direction of precision oncology and targeted agents but als in our growing understanding of the systemic toxicities associated with conventional chemotherapy. Traditionally, the adverse effects of chemotherapy have been attributed to its non-selective cytotoxicity against rapidly dividing normal cells- such as those in the gastrointestinal tract, bone marrow, and hair follicles. However, emerging molecular insights have unveiled a novel, secondary mechanism of chemotoxicity that challenges this simplistic view and highlights the need for more intelligent supportive interventions.

One of the most intriguing developments in the biology of chemotoxicity is the discovery of cell free chromatin particles (cfChPs) as active mediators of collateral tissue damage. These cfChPs are released from cancer cells undergoing apoptosis or necrosis following exposure to chemotherapeutic agents. Structurally, they consist of fragmented nucleosomes, comprising DNA wrapped around histone proteins, which upon release into the extracellular milieu and systemic circulation, become unintended messengers of toxicity. Healthy cells, including non-dividing or slow dividing somatic cells, can inadvertently internalize these cfChPs through processes such as endocytosis or micropinocytosis[46]. Once inside, cfChPs integrate into host genomic DNA, creating genomic instability, including double strand DNA breaks which activate DNA damage responses and potentially lead to mutagenesis, apoptosis, or senescence.

The downstream consequences of cfChP internalization are not limited to direct DNA injury. These particles also trigger inflammatory pathways, activate Toll like receptors, induce oxidative stress, and upregulate pro-apoptotic signaling cascades. The resulting cellular stress response is a self amplifying loop that recruits immune

cells, further increases the production of reactive oxygen species, and generates a bystander effect, where tissues uninvolved in the original tumor site become collateral targets of toxicity. This paradigm shift implies that chemotherapy induced tissue injury is not merely a result of drug exposure, but a delayed and systemic phenomenon, perpetuated by molecular remnants of dying cancer cells.

This deeper understanding necessitates a shift in the philosophy of supportive oncology. Historically, supportive care has been reactive, focused on symptom management after damage has occurred. While interventions such as antiemetics, corticosteroids, growth factors, and antidiarrheals remain essential, they offer limited protection against the underlying molecular cascade initiated by chemotherapy. Furthermore, these agents come with their own spectrum of side effects and often target single pathways in a multifactorial process[47].

In response to these challenges, there is a growing scientific and clinical interest in natural origin, biocompatible compounds that offer multi modal protection without interfering with the anti-cancer efficacy of chemotherapy. Polyphenols such as curcumin, resveratrol, epigallocatechin gallate (EGCG), and quercetin, as well as plant derived terpenoids, alkaloids, and flavonoids, have demonstrated promising antioxidant, anti-inflammatory, immunomodulatory, and cryoprotective activities in preclinical studies. These compounds can scavenge free radicals, inhibit pro-inflammatory cytokines, upregulate endogenous antioxidant systems like Nrf2, and even modulate apoptosis pathways selectively in normal versus cancerous tissues.

Unlike synthetic pharmacological agents, natural origin compounds are generally well tolerated, non-immunogenic, and biodegradable, traits that are crucial for their safe long term use, particularly in immunocompromised cancer patients. Moreover, these agents do not typically interfere with the DNA damaging mechanisms of chemotherapeutics and may even enhance therapeutic outcomes by improving cellular resilience in healthy tissues[48].

The limitation of natural compounds has historically been their poor bioavailability, rapid metabolism, and low tissue specificity. However, the advent of nanotechnology-based delivery systems has revolutionized this field. Carriers such as liposomes, chitosan nanoparticles, polymeric micelles, alginate beads, and dendrimers can encapsulate bioactive compounds, protect them from degradation, and deliver them in a controlled manner to target tissues. These nanocarriers can be further engineered to respond tp specific environmental cues, such as pH changes in the tumor microenvironment or temperature gradients allowing site specific drug release and minimizing systemic exposure[49].

For example, chitosan-based nanoparticles have been used to deliver curcumin with significantly improved bioavailability and sustained release, resulting in reduced mucosal damage and enhanced antioxidant defences during chemotherapy. Similarly, EGCG loaded polymeric micelles have shown potential in protecting cardiac tissue from doxorubicin induced cardiotoxicity without altering its antineoplastic effects. The integration of natural origin therapeutics with advanced nanocarriers represents a cutting-edge approach in cancer supportive care. It enables prophylactic intervention at the molecular level, reducing oxidative damage, preserving tissue function, and preventing long term complications. More importantly, its envisions a future of integrative oncology where cytotoxic therapy is paired with tissue protective adjuncts, allowing patients to receive full dose chemotherapy with fewer interruptions, improved quality of life, and reduced treatment abandonment. Ultimately, the biology of chemotoxicity is more complex and far reaching than previously understood. The systemic propagation of damage through cfChPs and inflammatory signalling demands a shift from reactive to proactive protection strategies. By leveraging biocompatible, multi-targeted natural compounds and precision nano delivery platforms, the next generation of supportive care can mitigate the collateral damage of chemotherapy, making cancer treatment not only more effective but also more humane[49].

3 CONCLUSION

Chemotherapy has revolutionized cancer treatment, but its adverse effects continue to limit its full potential. The emergence of cfChPs as mediators of systemic toxicity has introduced a new therapeutic target, one that lies not in the tumor, but in the spaces between cells and signals. As we advance toward more personalized and less toxic cancer therapies, the need for innovative, protective, and biocompatible agents becomes urgent. The future of supportive oncology lies in intervention, not reaction. We must seek compounds that pre-emptively shield healthy tissues, interrupt molecular cascades of damage, and preserve organ function without compromising cancer control. In this evolving landscape, there is immense potential for bioactive natural molecules delivered through smart nanocarriers to redefine what it means to survive and thrive through chemotherapy.

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Consent for publication

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Competing interests

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REFERENCES

1.Ricciardi GRR, Russo A, Sanò MV, et al. Efficacy and Safety Analysis of Nab-Paclitaxel Treatment in Elderly Patients with HER-2 Negative Metastatic Breast Cancer: NEREIDE Study. *Cancers*. 2025;17(13):2069.

2.Khudhair AY, Hamad RH. Cancer as a Global Health Threat: A Review of Pathogenesis, Prevention, Access to Care and Application of Nanoparticles in Cancer Treatment. *Journal of Science in Volume*. 2025;3(4)

3.Pandey P, Verma M, Lakhanpal S, et al. An Updated Review on the Nanocarriers Based Co-Delivery System of Chemo Drug Doxorubicin and Phytocompounds. *Polymers for Advanced Technologies*. 2025;36(1):e70050.

4.AlMaazmi FI, Bou Malhab LJ, ElDohaji L, Saber-Ayad M. Deciphering the Controversial Role of TP53 Inducible Glycolysis and Apoptosis Regulator (TIGAR) in Cancer Metabolism as a Potential Therapeutic Strategy. *Cells*. 2025;14(8):598.

5.Yuwanati M, Sarode S, Sarode G, et al. Association of TERT promoter mutation with oral squamous cell carcinoma: a systematic review and meta-analysis. *Scientific Reports*. 2025;15(1):15257.

6.Deli FDP, Juhamran RP, Kusumawardhani SI, Sanna AT, Pratama AA, Poentoro P. Characteristics of Chemotherapy Side Effects in Patients with Nasopharyngeal Cancer. *International Journal of Health and Pharmaceutical (IJHP)*. 2025;5(1):31-38.

7.Middleton C. A double-edged sword: discussing the value and pitfalls of chemotherapy in cancer treatment, a review of current research.

8.Ramadoss R, Padmanabhan R. Calcium Sodium Phosphosilicate in Management of Dentin Hypersensitivity and Strategies for Reconstitution of the Dentin Matrix. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. 2025;113(4):e35576.

9.Bakir M, Dawalibi A, Mufti MA, Behiery A, Mohammad KS. Nano-Drug Delivery Systems for Bone Metastases: Targeting the Tumor–Bone Microenvironment. *Pharmaceutics*. 2025;17(5):603.

10.Ciftci F, Özarslan AC, Kantarci IC, Yelkenci A, Tavukcuoglu O, Ghorbanpour M. Advances in drug targeting, drug delivery, and nanotechnology applications: therapeutic significance in cancer treatment. *Pharmaceutics*. 2025;17(1):121.

11.Rituraj, Pal RS, Wahlang J, Pal Y, Chaitanya M, Saxena S. Precision oncology: transforming cancer care through personalized medicine. *Medical Oncology*. 2025;42(7):246.

12.Gayathri R, Veeraraghavan VP, Selvaraj J, Ramani P. Pro-inflammatory mediator and cancer- associated chemokine CXCL8 as a prognostic indicator of tumor aggressiveness, angiogenesis, and disease progression with focus on therapeutic implications and recurrence monitoring. *Oral Oncology Reports*. 2025;13:100723.

13.Rong Y, Tegtmeier R, Clouser EL, et al. Advancements in Radiotherapy Treatment Workflows for Precision Medicine: A Review and Forward Looking. *International Journal of Radiation Oncology* Biology* Physics*. 2025;

14.Paudel B, Paudel B, Shrestha R, et al. Comparative Outcomes of Doxorubicin and Cyclophosphamide with Sequential versus Concurrent Paclitaxel in the Adjuvant Treatment of Non-Metastatic Breast Cancer: A Cross-Sectional Analytical Study. *Journal of the Nepal Medical Association*. 2025;63(287)

15.Lin C-H, Jiang W-P, Itokazu N, Huang G-J. Chlorogenic acid attenuates 5-fluorouracil-induced intestinal mucositis in mice through SIRT1 signaling-mediated oxidative stress and inflammatory pathways. *Biomedicine & Pharmacotherapy*. 2025;186:117982.

16.Siritientong T, Thet D, Leelakanok N, Areepium N. Oral probiotic supplementation to alleviate diarrhea induced by fluoropyrimidines or irinotecan-based chemotherapy: A systematic review and meta-analysis. *Complementary therapies in medicine*. 2025:103151.

17.Adriaenssens N, Wuyts SC, Steurbaut S, et al. Synergy of Body Composition, Exercise Oncology, and Pharmacokinetics: A Narrative Review of Personalizing Paclitaxel Treatment for Breast Cancer. *Cancers*. 2025;17(8):1271.

18.Gaumond SI, Beraja GE, Kamholtz I, Ferrari LM, Mahmoud RH, Jimenez JJ. Chemotherapy-Induced alopecia in ovarian cancer: incidence, mechanisms, and impact across treatment regimens. *Cancers*. 2025;17(3):411.

19.Jin K, Lin X, Xia X, et al. Incidence and Risk Factors of Platinum-Based Chemotherapy-Induced Nausea and Vomiting: A Systematic Review and Meta-Analysis. *Current Oncology*. 2025;32(6):325.

20.Shan Z, He C, Yang Q, et al. Chenodeoxycholic acid activates the TGR5/TRPA1-5-HT pathway to regulate intestinal motility in breastfed infants and mouse models. *Translational Pediatrics*. 2025;14(6):1213229-1211229.

21.Fernandes GHC, Labat Marcos R, Almeida dos Santos S, et al. Photobiomodulation control the expression of MMP, TNF-α and NK-1 receptors, improving allodynia and cartilage resistance in rheumatoid arthritis model. *Lasers in Medical Science*. 2025;40(1):306.

22.Senthil R, Sundaram KKM, Bupesh G, Usha S, Saravanan KM. Identification of oxazolo [4, 5-g] quinazolin-2 (1H)-one Derivatives as EGFR Inhibitors for Cancer Prevention. *Asian Pacific Journal of Cancer Prevention: APJCP*. 2022;23(5):1687.

23.Zhong W, Shahbaz O, Teskey G, et al. Mechanisms of nausea and vomiting: current knowledge and recent advances in intracellular emetic signaling systems.

International journal of molecular sciences. 2021;22(11):5797.
24.Khalid JP, Martin TM, Prathap L, et al. Exploring tumor-promoting qualities of cancer-associated fibroblasts and innovative drug discovery strategies with emphasis on thymoquinone. *Cureus*. 2024;16(2)
25.Song K-W, Lim M, Monje M. Complex neural-immune interactions shape glioma immunotherapy. *Immunity*. 2025;58(5):1140-1160.
26.Zhang X, Yang J, Li Y, Li Y, Li G. Role of hypothalamus function in metabolic diseases and its potential mechanisms. *PeerJ*. 2025;13:e19532.
27.Abassi W, Ouerghi N, Muscella A, Marsigliante S, Feki M, Bouassida A. Systematic Review: Does Exercise Training Influence Ghrelin Levels? *International Journal of Molecular Sciences*. 2025;26(10):4753.
28.Zhou C, Wu F, He L, et al. An Implant-Free Nanosystem Enabling Synergistic Oxidative Damage Mitigation and Deep Brain Stimulation for Alleviating Parkinsonian Symptoms. *ACS nano*. 2025;
29.Tayyeb JZ, Priya M, Guru A, et al. Multifunctional curcumin mediated zinc oxide nanoparticle enhancing biofilm inhibition and targeting apoptotic specific pathway in oral squamous carcinoma cells. *Molecular biology reports*. 2024;51(1):423.
30.Dahlgren D, Sjöblom M, Hellström PM, Lennernäs H. Chemotherapeutics-induced intestinal mucositis: pathophysiology and potential treatment strategies. *Frontiers in pharmacology*. 2021;12:681417.
31.Brockmueller A, Girisa S, Kunnumakkara AB, Shakibaei M. Resveratrol modulates chemosensitisation to 5-FU via β1-integrin/HIF-1α Axis in CRC tumor microenvironment. *International Journal of Molecular Sciences*. 2023;24(5):4988.
32.Dandapani S, Veeraraghavan VP, Surapaneni KM, Prashar L, Mony U. Targeting protein kinase D in oral squamous cell carcinoma: a promising therapeutic approach. *International Journal of Surgery*. 2025;111(5):3638-3640.
33.Stene C, Xu J, de Andrade SF, et al. Synbiotics protected radiation-induced tissue damage in rectal cancer patients: A controlled trial. *Clinical Nutrition*. 2025;49:33-41.
34.Takei Y, Yamamoto S, Satoh T, Tazumi K, Mizuki M, Arao H. Association between personality traits and self-care behaviors in patients with gastrointestinal cancer undergoing outpatient chemotherapy: A cross-sectional study. *Journal of International Nursing Research*. 2025:2023-0032.
35.Yang X, Chen J, Wang Y, Wu Y, Zhang J. Managing Irinotecan-Induced Diarrhea: A Comprehensive Review of Therapeutic Interventions in Cancer Treatment. *Pharmaceuticals*. 2025;18(3):359.
36.Sebastian S, Martin TM, Kumar MSK. Thymoquinone-Loaded Zinc Nanoparticles Mitigate Inflammation and Inhibit Glioblastoma Progression: A Novel Therapeutic Approach. 2025;
37.García-González D, Medino-Muñoz J, Romero-Elías M, García-Foncillas J, Ruiz-Casado A. Biological mechanisms of cancer-related fatigue in breast cancer survivors after treatment: a scoping review. *Journal of Cancer Survivorship*. 2025;19(1):414-444.
38.Dandagi P, Martin TM, Babu Y. In silico and glioblastoma cell line evaluation of thioflavin-derived zinc nanoparticles targeting beclin protein.*Cureus*. 2024;16(9)
39.Gandhimathi KA, Francis AP, Rengasamy G, Veeraraghavan VP, Sankaran K. Quercetin-coated biogenic titanium oxide nanoparticles: Synthesis, characterization, and in-vitro biological studies. *Particulate Science and Technology*.2025;43(2):198-206.
40.Martin TM. Seaweeds and Their Secondary Metabolites: A Promising Drug Candidate With Novel Mechanisms Against Cancers and Tumor Angiogenesis. *Cureus*. 2024;16(8)
41.Halder K. Chemotherapy Resistance in Cancer: Mechanism and Roadmap to Evade Exploring Apoptosis. *Int J Adv Life Sci Res Volume*. 2024;7(2):17-40.
42.Peera M, Rose L, Kaufman L, Zhang E, Alkhaifi M, Dulmage B. Hair loss: alopecia fears and realities for survivors of breast cancer—a narrative review. *Annals of Palliative Medicine*. 2024;13(5):1235245-1231245.
43.Jiang Y, Chen H, Lin T, et al. Ultrasound-activated prodrug-loaded liposome for efficient cancer targeting therapy without chemotherapy-induced side effects. *Journal of Nanobiotechnology*. 2024;22(1):2.
44.Kholmatov S, Madaminov S, Zokirjonov D, Sobirova D. A comprehensive review of radiotherapy and chemotherapy-induced morphological side effects in breast cancer treatment: Strategies for management and mitigation. *Science and innovation*. 2024;3(D6):11-24.
45.Wang H, Zhu W, Hong Y, et al. Astragalus polysaccharides attenuate chemotherapy-induced immune injury by modulating gut microbiota and polyunsaturated fatty acid metabolism. *Phytomedicine*. 2024;128:155492.
46.Shabrish S, Pal K, Khare NK, et al. Cell-free chromatin particles released from dying cancer cells activate immune checkpoints in human lymphocytes: implications for cancer therapy. *Frontiers in Immunology*. 2024;14:1331491.
47.Raghuram GV, Tripathy BK, Avadhani K, et al. Cell-free chromatin particles released from dying cells inflict mitochondrial damage and ROS production in living cells. *Cell Death Discovery*. 2024;10(1):30.
48.Sofini SP, Balasubramanian D, Girigoswami A, Girigoswami K. Biomedical applications of natural and synthetic polymer based nanocomposites. *Journal of Biomaterials Science--Polymer Edition*. 2024;35(2)
49.Dudhat K. Harnessing metal nanoparticles: revolutionizing cancer therapy through targeted drug delivery and tumor microenvironment modulation. *Nano*. 2024;19(10):2430008.