DOI:10.31557/APJCB.2025.10.4.1061

REVIEW

Chemoprotective Horizons: Bioactive Molecules as Therapeutic Shields Against Cytotoxicity

Taniya Mary Martin, Meenakshi Sundaram Kishore Kumar

Department of Anatomy, Zebrafish Facility, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Tamil Nadu, India.

Abstract

Chemotherapy remains a cornerstone in cancer management, but its lack of selectively between malignant and normal proliferating cells leads to widespread toxicities that significantly reduce patient quality of life and treatment adherence. Recent research has highlighted the promising role of naturally derived bioactive compounds in mitigating chemotherapy induced damage. These compounds, including polyphenols, flavonoids, terpenoids, and alkaloids, exhibit antioxidant, anti-inflammatory, anti-apoptotic, and organoprotective properties through diverse molecular pathways. Agents such as curcumin, resveratrol, quercetin, betanin, theaflavin and thymoquinone have demonstrated significant efficacy in reducing oxidative stress, modulating inflammatory cytokines, stabilizing mitochondrial function, and preserving normal tissue architecture in preclinical and early clinical studies. Importantly, many of these compounds selectively protect normal cells without reducing the cytotoxic effect of chemotherapeutic agents on tumor cells. Advances in formulation technologies, such as nanoencapsulation and combination strategies, further enhance their bioavailability and clinical applicability. This review discusses the mechanistic basis, experimental evidence, and translational potential of bioactive compounds as cytoprotective agents in chemotherapy, underscoring their future role in integrative cancer care.

Keywords: Bioactive compounds- Chemotherapy toxicity- Natural antioxidants- Oxidative stress

Asian Pac J Cancer Biol, **10 (4)**, 1061-1074

Submission Date: 08/11/2025 Acceptance Date: 10/08/2025

Introduction

Cancer remains a leading cause of global mortality, with chemotherapy continuing to serve as a cornerstone of oncologic intervention. Despite its established role in targeting rapidly dividing cells, chemotherapy lacks selectivity between malignant and healthy proliferative cells, leading to a wide range of adverse effects that compromise patient well-being and therapeutic outcomes. These effects range from relatively manageable symptoms such as nausea, vomiting, alopecia, and fatigue to life threatening toxicities including myelosuppression, mucositis, cardiotoxicity, hepatotoxicity, nephrotoxicity, and neurotoxicity. The cumulative impact often reduces treatment adherence, necessities dose reduction, or results in discontinuation of therapy [1].

In recent years, naturally derived bioactive compounds have attracted considerable attention as protective agents against chemotherapy induced toxicity. Bioactive compounds are non-nutritive chemical substances present in plants, marine organisms, fungi, and bacteria that exert beneficial biological effects [2, 3]. They include diverse groups such as polyphenols, flavonoids, terpenoids, alkaloids, glucosinolates, saponins, and betalains. Their cytoprotectie properties are attributed to modulation of oxidative stress, inflammation, apoptosis, and immune responses at the molecular level. Many function as antioxidants, either by directly scavenging reactive oxygen species (ROS) or by enhancing the expression of endogenous antioxidant enzymes through redox sensitive transcription factors like nuclear factor erythroid 2 related factor 2 (Nrf2) [4]. Chemotherapeutic agents, particularly platinum based compounds and anthracyclines, are known to trigger excessive ROS generation, resulting in oxidative damage to DNA, lipids and proteins in normal tissues. By restoring redox

Corresponding Author:
Dr. Meenakshi Sundaram Kishore Kumar
Department of Anatomy, Zebrafish Facility, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Tamil Nadu, India.
Email: meenakshisundaram.sdc@saveetha.com

homeostasis, bioactive molecules reduce oxidative injury and improve tissue resilience during chemotherapy [5].

Among the most studied agents, curcumin, the principal curcuminoid of Curcuma longa, alleviates cisplatin-induced nephrotoxicity via Nrf2 activation while suppressing NF-κB mediated inflammation [6]. It also enhances antioxidant enzyme activity, including superoxide dismutase (SOD), catalase, and glutathione peroxidase, and decreases pro-inflammatory cytokines such as TNF-α, IL-6, and COX-2. Additionally, curcumin provides hepatoprotective and gastrointestinal benefits against drug induced organ injury [7, 8]. Resveratrol, a polyphenol found in grapes, berries, and peanuts, has shown cardioprotective effects against doxorubicin toxicity by modulating the SIRT1/AMPK pathway, improving mitochondrial function, and attenuating apoptosis [9, 10]. Quercetin, abundant in apples, onions, and tea, counteracts bone marrow suppression and gastrointestinal mucositis by free radical scavenging, membrane stabilization, and mucosal protection [11, 12]. Betanin from beetroot upregulates the Nrf2/HO-1 axis and protects liver and kidney tissues from cytotoxic insult, while also reducing inflammation [13, 14]. Thymoquinone, the major bioactive constituent of Nigella sativa, prevents myelosuppression and testicular toxicity in chemotherapy models through modulation of apoptotic pathways and hematopoietic support [15, 16]. Theaflavin, a polyphenol from black tea, exhibits antioxidant and anti-inflammatory effects, safeguarding liver, kidney, and gastrointestinal tissues while preserving hematopoietic integrity [17].

Emerging studies further highlight synergistic protection when bioactive compounds are used in combination, as well as the utility of nanotechnology-based formulations that improve solubility, stability, and bioavailability [18]. Importantly, these protective effects appear to spare or even enhance the anticancer efficacy of chemotherapy, with some compounds sensitizing tumour cells to cytotoxic agents [19]. Mechanistic analyses have demonstrated modulation of oxidative stress markers, cytokines, and apoptosis related proteins, alongside regulation of key pathways such as Nrf2/Keap1, NF-κB, PI3/Akt, and MAPK [20]. Early phase clinical evaluations of compounds like curcumin and resveratrol have reported improvements in treatment tolerance and reductions in therapy related complications [21, 22].

The cytoprotective effects of these agents are largely mediated through their influence on mitochondrial integrity, redox balance, inflammatory regulation, and apoptotic signaling. Nrf2 driven antioxidant defense is particularly central to their activity, as it governs the expression of detoxifying and protective enzymes under oxidative stress [23]. These findings provide a strong biological rationale for investigating bioactive compounds as adjuvants in chemotherapy regimens.

Activation of Antioxidant defense via Nrf2/Keap1/ARE pathway

The Nrf2/Keap1/are signalling axis represents one of the most critical molecular pathways modulated by bioactive compounds to counteract chemotherapy induced oxidative stress. Chemotherapeutic agents such as cisplatin, doxorubicin, and cyclophosphamide are known to generate excessive reactive oxygen species (ROS) as a part of their cytotoxic mechanism. While this contributes to the death of malignant cells, it simultaneously induces collateral oxidative damage in normal tissues including the liver, kidney, heart, and nervous system. The accumulation of ROS disrupts cellular homeostasis, leading to lipid peroxidation, protein denaturation, mitochondrial dysfunction, and DNA strand breaks. In this context, the activation of the endogenous antioxidant defense system becomes paramount to minimize chemotherapy related toxicity (Figure 1) [24].

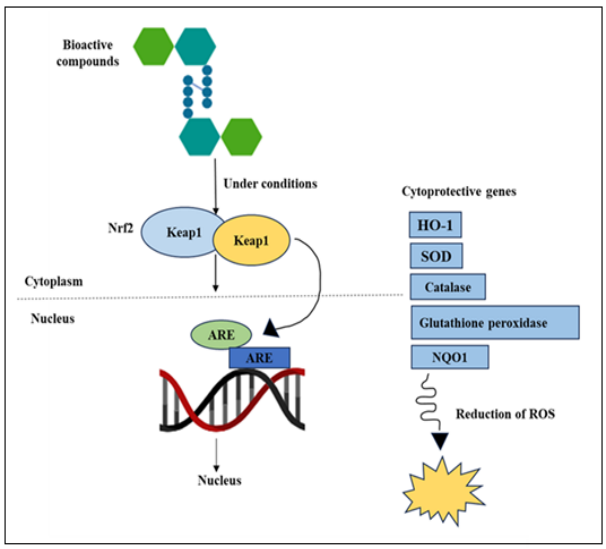

Figure 1. Bioactive compounds disrupt the Keap 1-Nrf2 interaction, enabling Nrf2 to enter the nucleus and active antioxidant genes, reducing oxidative stress and protecting normal cells from chemotherapy induced damage.

Nrf2 is a transcription factor that governs the expression of numerous genes involved in antioxidant defense, detoxification, and cellular protection. Under basal conditions, Nrf2 is bound in the cytoplasm to its negative regulator, Kelch like ECH-associated protein 1 (Keap 1). This association facilitates the ubiquitination and proteasomal degradation of Nrf2, maintaining its levels at a low threshold. However, under oxidative or electrophilic stress, the conformation of Keap 1 is altered, resulting in the release of Nrf2. Freed from Keap 1, Nrf2 translocates into the nucleus, where it binds to Antioxidant Response Elements (AREs) located in the promoter regions of targeted genes. Once in the nucleus, Nrf2 promotes the transcription of a suite of cytoprotective and detoxifying enzymes. These include heme oxygenase-1 (HO-1), which degrades pro-oxidant heme into biliverdin and carbon monoxide; superoxide dismutase (SOD), which converts superoxide radicals into less reactive hydrogen peroxide; catalase and glutathione peroxide, which further detoxify hydrogen peroxide; and NAD(P)H quinone oxidoreductase 1 (NQO1), which reduces quinones to prevent redox cycling. Collectively, these enzymes play a pivotal role in reducing oxidative burden and restoring redox equilibrium in cells challenged by chemotherapeutic

stress [25].

Bioactive compounds such as curcumin, resveratrol, thymoquinone, and betanin have been extensively reported to modulate the Nrf2 pathway. These compounds act as electrophilic stressors or redox modulators that disrupt the Nrf2-Keap1 interaction, thereby stabilizing Nrf2 and facilitating its nuclear translocation. Curcumin, for instance, has been shown to enhance Nrf2-dependent HO-1 expression in models of cisplatin induced nephrotoxicity. Resveratrol increases Nrf2 nuclear translocation in cardiomyocytes and protects against doxorubicin mediated cardiac injury [26]. Thymoquinone and betanin similarly activate Nrf2 and downstream antioxidant responses in hepatic and renal tissue exposed to chemotherapeutic insult. Thus, the Nrf2/Keap 1/ ARE pathway serves as a fundamental line of defense against oxidative stress induced by chemotherapy. Bioactive compounds potentiate this pathway, providing a mechanistic basis for their cytoprotective action. Through enhanced expression of detoxifying enzymes and restoration of redox homeostasis, Nrf2 activation by bioactives represents a promising strategy to reduce off target toxicities and improve the tolerability of cancer treatment [27].

Suppression of Pro-Inflammatory Pathways via NF-κB Inhibition

In addition to oxidative stress, inflammation represents a major mechanism by which chemotherapy contributes to off-target tissue damage and systemic toxicity. Persistent activation of pro-inflammatory signaling cascades not only exacerbates organ injury but also impairs tissue regeneration and immune function. One of the most critical regulators of inflammation is the NF-κB. The NF-κB signalling pathway is a central mediator in the expression of genes involved in immune and inflammatory responses, including those encoding tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and cyclooxygenase-2 (COX-2). These cytokines and enzymes play crucial roles in the pathogenesis of chemotherapy induced mucositis, hepatotoxicity, cardiotoxicity, and other inflammatory complications [28].

Under normal physiological conditions, NF-κB remains inactive in the cytoplasm, bound to its inhibitory protein IκB (Inhibitor of κB). Upon stimulation by various stressors such as chemotherapeutic agents, reactive oxygen species (ROS), and cellular damage signals, the IκB kinase (IKK) complex becomes activated. IKK phosphorylates IκB, leading to its ubiquitination and proteasomal degradation. This event liberates NF-κB, allowing it to translocate into the nucleus, where it binds to specific κB elements in the promoter regions of target genes. The subsequent transcriptional activation of pro-inflammatory genes results in the amplification of the inflammatory response, contributing to tissue injury and organ dysfunction [29].

Bioactive compounds derived from natural sources have demonstrated significant potential in modulating this inflammatory axis. Curcumin, a polyphenolic compound from Curcuma longa, has been shown to inhibit IKK

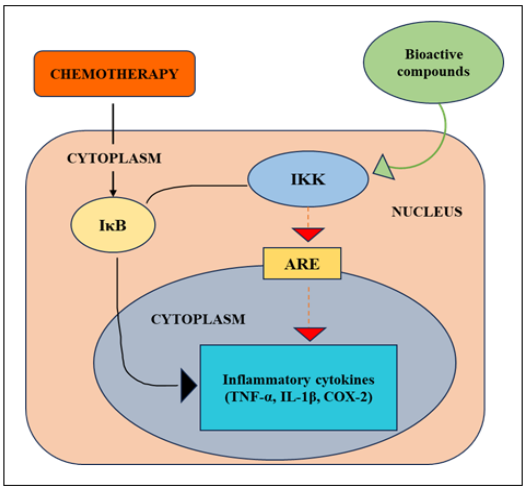

Figure 2. Bioactive Compounds such as curcumin, quercetin, and EGCG inhibit IκB kinase, preventing IκB degradation and thereby blocking NF-κB nuclear translocation. This suppresses the transcription of pro-inflammatory genes, reducing chemotherapy induced inflammation and tissue damage

activation, thereby preventing the degradation of IκB and effectively blocking NF-κB nuclear translocation. As a result, the expression of TNF-α, IL-1β, and COX-2 is markedly reduced in models of chemotherapy induced mucosal and hepatic inflammation. Similarly, quercetin, a flavonoid found in onions and apples, has been reported to attenuate NF-κB activation in cardiomyocytes exposed to doxorubicin, thereby decreasing inflammatory damage and improving cardiac function. Epigallocatechin gallate (EGCG), a major catechin in green tea, also exerts potent anti-inflammatory effects by stabilizing IκB and interfering with upsteam signalling components of the NF-κB pathway [30] (Figure 2).

The inhibition of NF-κB by these compounds results not only in decreased transcription of inflammatory cytokines but also in the modulation of enzymes responsible for prostaglandin synthesis, nitric oxide production, and leukocyte recruitment, all of which are elevated in response to chemotherapy. By dampening these response, bioactive compounds reduce local and systemic inflammation, protect epithelial and endothelial barriers, and promote tissue repair. Importantly, this anti-inflammatory effect is achieved without impairing the anti-tumor activity of chemotherapeutic agents, indicating a favorable therapeutic index.From the above, it can be inferred that suppression of NF-κB signalling represents a critical molecular mechanism by which bioactive compounds confer protection against chemotherapy induced inflammation. Though stabilization of IKK activity, these natural agents downregulate pro-inflammatory gene expression and mitigate tissue injury, Their integration as adjuncts to conventional chemotherapy holds substantial promise for improving patient outcomes and quality of life [31].

Table 1. Protective Effects of Key Bioactive Compounds Against Chemotherapy-Induced Toxicity

Bioactive Compound	Target Pathways	Affected Organs/ Tissues	Mechanism of Action	Protective Outcome
Curcumin	Nrf2/Keap1/ARE, NF-κB, PI3K/Akt, HDAC	Liver, Kidney, Heart	Activates antioxidant genes, inhibits inflammatory cytokines, modulates apoptosis, epigenetic remodeling	Reduces ROS, inflammation, and DNA damage [3]
Resveratrol	Nrf2/ARE, SIRT1, PI3K/Akt/mTOR, miRNA	Heart, Neurons, Bone marrow	Mitochondrial stabilization, a nti-inflammatory, HDAC inhibition, SIRT1 activation	Prevents neuro- and cardiotoxicity [9]
Thymoquinone	Nrf2, p53/Bcl-2, Caspases, NF-κB	Bone marrow, Testes, Liver	Modulates apoptosis regulators, suppresses inflammation, maintains redox balance	Prevents myelosuppression and testicular damage [15]
Betanin	Nrf2/HO-1, Bax/Bcl-2, ROS-scavenging	Liver, Kidney	Upregulates antioxidant enzymes, inhibits caspase cascade	Prevents hepatotoxicity and nephrotoxicity [13]
Quercetin	NF-κB, Mitochondrial membrane, DNA repair	GI Tract, Bone marrow	Enhances mucin production, inhibits inflammation, preserves mitochondrial integrity	Reduces mucositis and bone marrow suppression [11]
EGCG	AMPK/mTOR, NF-κB, Autophagy	Heart, Neurons	Induces autophagy, downregulates pro-inflammatory signals	Protects against oxidative cardiac and neural damage [47]
Theaflavin	NF-κB, Nrf2, MMPs, PI3K/Akt	Lung, Oral mucosa, Bone marrow	Inhibits NF-κB activation, enhances antioxidant enzymes, suppresses MMPs and cytokines	Reduces inflammation, ROS, and tissue remodeling [17]
Genistein	DNMT, Histone acetylation, miRNA	Systemic	DNA demethylation, reactivation of silenced protective genes	Long-term genomic stability and anti-inflammation [27]
Sulforaphane	Nrf2/ARE, DNMT, HDAC	Liver, Intestine	Antioxidant gene induction, epigenetic reprogramming	Reduces genotoxicity and promotes detoxification [28]

Modulation of Apoptotic Pathways (Intrinsic and Extrinsic)

Apoptosis, or programmed cell death, is a tightly regulated physiological process essential for tissue homeostasis and the removal of damaged or dysfunctional cells. In the context of cancer therapy, apoptosis serves as a principal mechanism through which chemotherapeutic agents exert their cytotoxic action on malignant cells. However, these agents lack selectivity and often activate apoptotic pathways in non-malignant, healthy tissues as well, resulting in undesirable toxicities and organ dysfunction. The two primary apoptotic pathways implicated in chemotherapy induced toxicity are the intrinsic (mitochondrial) pathway and the extrinsic (death receptor mediated) pathway, Bioactive compounds derived from natural sources offer cytoprotective effects by modulating these pathways to selectively inhibit apoptosis in normal tissues while sparing or enhancing apoptosis in tumor cells [31].

The intrinsic pathway of apoptosis is governed by mitochondrial integrity and is highly responsive to intracellular stress, including DNA damage, oxidative stress, and metabolic disturbances induced by chemotherapeutic drugs. Mitochondrial outer membrane permeabilization (MOMP) is a pivotal event in this pathway, resulting in the release of cytochrome into the cytoplasm. Cytochrome c binds to apoptotic protease activating factor -1 (Apaf-1), forming the apoptosome complex that subsequently activates initiator caspase-9. This leads to the activation of executioner caspases such as caspase-3, culminating in controlled cellular dismantling. The balance between pro-apoptotic proteins and anti-apoptotic proteins is critical in determining mitochondrial susceptibility to apoptotic stimuli. Bioactive compounds such as thymoquinone, resveratrol, theaflavin, and betanin have been shown to favorably modulate this balance. Thymoquinone enhances the expression of Bcl-2 and supresses Bax, thereby preserving mitochondrial membrane integrity. Resveratrol, in addition to reducing oxidative stress, inhibis caspase-3 activation and prevents cytochrome c release in non-cancerous cardiac and nueral tissues. Betanin similarly stabilizes mitochondrial function and mitigates apoptotic cell death in renal and

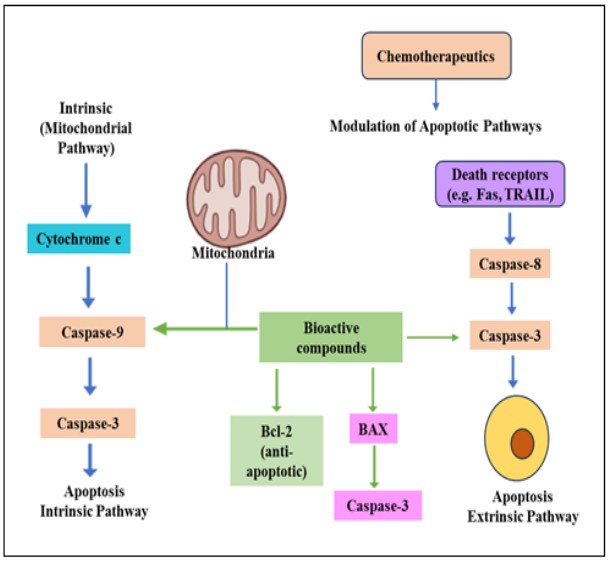

Figure 3. Bioactive compounds such as thymoquinone, resveratrol, and betanin protect healthy cells during chemotherapy by modulating both intrinsic and extrinsic apoptotic pathways. They stabilize mitochondria by upregulating anti-apoptotic Bcl-2 and suppressing pro-apoptotic Bax and caspase -3 in the intrinsic pathway. Concurrently, they inhibit death receptor signaling and caspase-8 activation in the extrinsic pathway, thereby preventing unnecessary cell death in normal tissues.

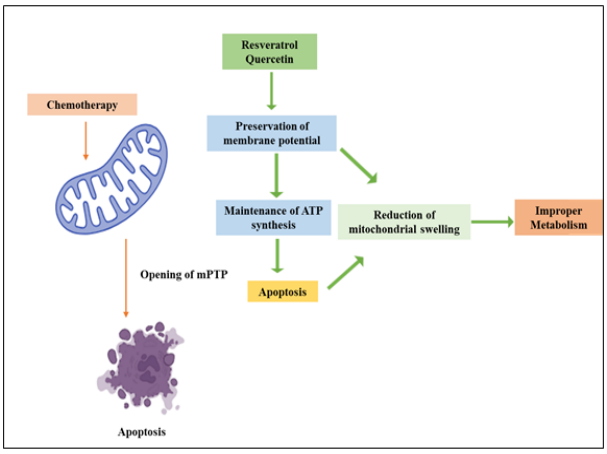

Figure 4. The diagram illustrates how bioactive compounds such as resveratrol and quercetin preserve mitochondrial integrity during chemotherapy. These agents stabilize the mitochondrial membrane potential, prevent the opening of the mitochondrial permeability transition pore (mPTP), and support ATP synthesis. By attenuating ROS production and maintaining mitochondrial homeostasis, they reduce mitochondrial mediated apoptosis in normal cells and enhance cellular survival.

hepatic models exposed to cytotoxic agents [32].

The extrinsic pathway is initiated by the binding of extracellular death ligands sucg as Fas ligand (FasL) or TNF related apoptosis inducing ligand (TRAIL) to their corresponding receptors on the cell surface. This ligand receptor interaction triggers the formation of the death inducing signalling complex (DISC), leading to the activation of caspase-8 and downstream executioner caspases. In normal tissues, this pathway can be excessively stimulated duting chemotherapy, contributing to mucosal damage, bone marrow suppression, and hepatic injury. Bioactive compounds modulate this pathway by inhibiting the expression or activity of death receptors and interfering with caspase-8 activation. For instance, curcumin and EGCG have demonstrated the ability to downregulate Fas and TRAIL receptor expression, therby reducing extrinsic apoptotic signalling in healthy cells (Figure 3). Importantly, the anti-apoptotic effect of these compounds is tissue selective and does not compromise their tumoricidal potential. In fact, several bioactives have demonstrated pro-apoptotic effects in cancer cells by sensitizing them to chemotherapy or directly activating apoptotic signaling (Table 1). This dual action underscores their value as adjuncts that enhance therapeutic efficacy while minimizing collateral damage. Thus, the modulation of intrinsic and extrinsic apoptotic pathways by bioactive compounds represents a promising strategy to reduce chemotherapy induced toxicity and improve treatment tolerability [33].

Prevention of Mitochondrial Function and Membrane Potential (Δψm)

Mitochondria play a pivotal role in cellular energy production, redox homeostasis, and the regulation of programmed cell death. In the context of chemotherapy, mitochondrial dysfunction isa critical factor contributing to off target toxicity in non-cancerous tissues. Many chemotherapeutic agents, including doxorubicin, cisplatin, and etoposide, induce excessive generation of reactive oxygen species (ROS) within the mitochondria, disrupt the electron transport chain, and initiate mitochondrial mediated apoptosis. A hallmark event in this process is the loss of mitochondrial membrane potential (Δψm), which compromises ATP synthesis, enhances ROS leakage, and ultimately triggers the opening of the mitochondrial permeability transition pore (mPTP), leading to the release of pro-apoptotic factors and cellular demise [34].

Preserving mitochondrial function and membrane integrity is thus essential for mitigating chemotherapy induced toxicity. Bioactive compounds such as resveratrol and quercetin have emerged as potent mitochondrial protectants through their multifaced mechanism of action. Resveratrol, a polyphenolic stilbene found in grapes and red wine, is known to interact with mitochondrial membranes and stabilize their potential. It enhances the activity of mitochondrial complex I and improves the efficiency of oxidative phosphorylation, leading to sustained ATP production under stress conditions. Furthermore, resveratrol activates SIRT1 and AMPK, which are involved in mitochondrial biogenesis and the maintenance of mitochondrial dynamics. These actions collectively reduce mitochondria swelling, limit cytochrome c release, and supress caspase activation in non-cancerous tissues subjected to chemotherapeutic medication [35].

Similarly, quercetin, a flavonol present in many fruits and vegetables exerts significant antioxidant and mitochondria preserving effects. Quercetin prevents the collapse of Δψm by scavenging mitochondrial ROS and by modulating the expression of Bcl-2 family proteins that regulate mitochondrial membrane permeability. It has been demonstrated to inhibit mPTP opening, a critical event that leads to mitochondrial swelling, membrane rupture, and the activation of apoptosis. By stabilizing mitochondrial membranes, quercetin not only improves bioenergetics but also protects against oxidative stress induced loss of mitochondrial integrity in cardiomyocytes, hepatocytes, and renal tubular cells. Another key feature of mitochondrial protection by these compounds is the prevention of mitochondrial fragmentation and maintenance of mitochondrial morphology. Under chemotherapeutic stress, mitochondria often undergo excessive fission, a process that is associated with loss of function and enhanced susceptibility to apoptosis. Resveratrol and quercetin counteract this by promoting fusion related proteins and maintain mitochondrial network integrity, which is vital for cellular survival. Overall, the preservation of mitochondrial membrane potential and function by bioactive compounds translates to improve energy metabolism, reduced oxidative stress, and protection against mitochondrial mediated cell death (Figure 4). These effects are particularly significant in tissues with high metabolic demand, such as the heart, kidney, and brain, where mitochondrial impairment contributes heavily to chemotherapy induced organ toxicity. Incorporating such mitochondria stabilizing

agents as adjuncts in chemotherapeutic regiments offers a promising approach to enhance treatment tolerability and safeguard healthy tissues from collateral damage [35].

Inhibition of DNA Damage and Genotoxicity

DNA integrity is essential for cellular homeostasis, and its damage underlies both the therapeutic effects and adverse consequences of many chemotherapeutic agents. Chemotherapy drugs such as cyclophosphamide, doxorubicin, and etoposide are highly effective in targeting rapidly proliferating tumor cells; however, they also induce substantial genotoxic stress in normal tissues. One of the primary cytotoxic mechanisms of these agents is the induction of DNA double strand breaks (DSBs), single strand breaks (SSBs), DNA adducts, and oxidative base modifications. These lesions, if unrepaired, can lead to chromosomal instability, apoptosis or carcinogenic mutations in surviving cells. Therefore, preventing or mitigating DNA damage in non-cancerous cells is a key strategy for reducing chemotherapy induced toxicity and long-term complications [36].

Bioactive compounds particularly flavonoids and phenolic acids have demonstrated significant protective effects against DNA damage through several mechanisms. One of the principal actions involves the enhancement of DNA repair capacity. Compounds such as quercetin, epigallocatechin gallate (EGCG), and caffeic acid have been shown to upregulate key enzymes involved in the base excision repair and homologous recombination pathways, including poly (ADP-ribose) polymerase (PARP), X-ray repair cross complementing protein 1 (XRCC1), and DNA ligase III. These enzymes detect DNA lesions and coordinate repair processes, thus minimizing the accumulation of mutations and strand breaks in normal cells during chemotherapy. In addition to facilitating repair, bioactive compounds effectively reduce the burden of DNA damage by neutralizing the primary culprits reactive oxygen species (ROS). Chemotherapeutic agents often generate ROS as a byproduct of redox cyclin or through mitochondrial disruption, which in turn cause oxidative lesions in nucleic acids. Antioxidant rich bioactives scavenge these free radicals, directly reducing oxidative lesions in nucleic acids. Antioxidant rich bioactives scavenge these free radicals, directly reducing oxidative stress in genomic regions. For example, resveratrol and kaempferol have been shown to lower levels of 8-oxoguanine, a common oxidative DNA lesion, in non-malignant cells exposed to genotoxic stress[37].

Another layer of protection offered by these compounds is their ability to chelate transition metal ions, such as iron and copper, which catalyse the Fenton reaction and generate highly reactive hydroxyl radicals. By binding to these metal ions, flavonoids such as rutin and myricetin prevent the initiation of free radical mediated DNA strand breaks, especially in cells with high mitochondrial or lysosomal metal concentrations. Moreover, bioactive compounds have been observed to modulate checkpoint signaling pathways that regulate cell cycle arrest and DNA repair fidelity. For instance, curcumin and baicalein can influence the activation of ATM/ATR and p53, which

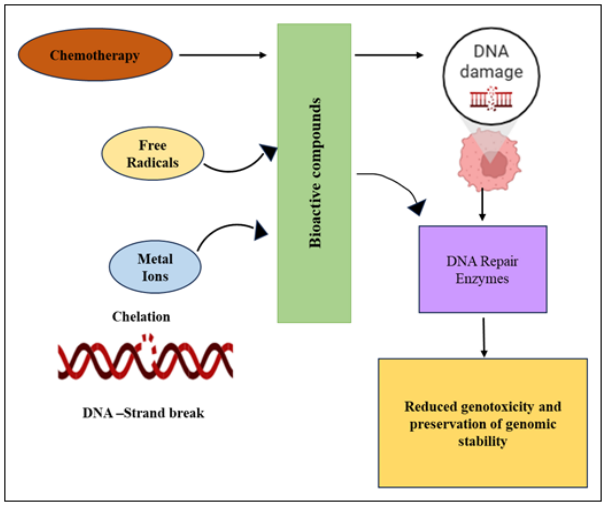

Figure 5. The diagram illustrates how bioactive compounds, including flavonoids and phenolic acids such as quercetin and resveratrol, mitigate chemotherapy induced DNA damage in healthy cells. These compounds enhance the activity of DNA repair enzymes, scavage reactive oxygen species, and chelate transition metal ions to prevent Fenton reaction mediated oxidative damage. The result is a reduction in DNA strand breaks, preservation of genomic stability, and protection of normal tissues from genotoxic stress.

are critical mediators in the DNA damage response. This regulation ensures that healthy cells either repair DNA damage effectively or undergo controlled senescence rather than uncontrolled apoptosis (Figure 5). Thus, the inhibition of DNA damage and genotoxicity by bioactive compounds is achieved through a multi-pronged approach: enhancing endogenous DNA repair mechanisms, reducing ROS induced strand breaks, and minimizing metal catalyzed oxidative stress. These protective actions preserve genomic stability in normal tissues during chemotherapy and reduce the risk of mutagenesis, making bioactives promising adjuncts in cancer therapy [38].

Modulation of P13K/Akt/mTOR Signaling

The phosphoinositide 3-kinase (P13K)/Akt/mTOR signalling axix plays a central role in regulating critical cellular processes including survival, growth, proliferation, and metabolism. In healthy cells, this pathway ensures homeostasis under stress by promoting protein synthesis, mitochondrial function, and resistance to apoptotic cues. However, in the context of cancer aberrant and constitutive activation of the P13K/Akt/mTOR pathway contributes to tumor growth, chemoresistance, and metastasis. Therefore, this signalling pathway represents a paradoxical target one that must be suppressed in tumor cells while being preserved or even enhanced in non-cancerous tissues to reduce off target toxicity during chemotherapy. Bioactive compounds, notably curcumin and resveratrol, have emerged as modulators of the P13K/Akt/Mtor axis with context dependent actions that offer therapeutic selectivity [39].

During chemotherapy, non-cancerous tissues are subjected to oxidative and genotoxic stress that can inappropriately suppress the P13K/Akt pathway, resulting

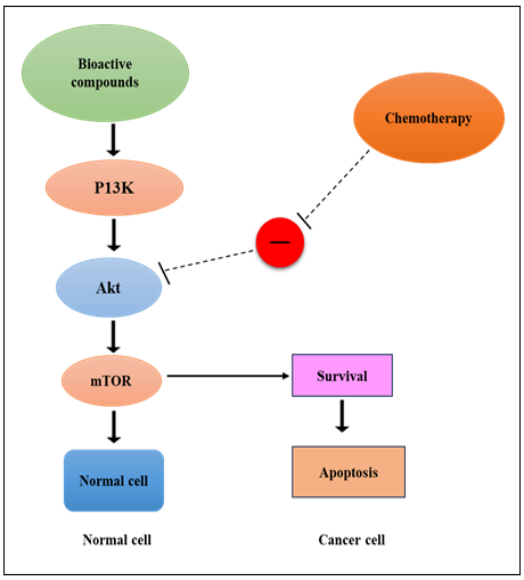

Figure 6. The diagram demonstrates the dual regulatory role of bioactive compounds such as curcumin and resveratrol on the P13K/Akt/mTOR pathway. In non-cancerous cells, these compounds activate P13K and downstream signaling, promoting cell survival, energy metabolism, and anti-apoptotic effects in response to chemotherapeutic stress. Conversely, in tumor cells, the same compounds inhibit hyperactive P13K/Akt/mTOR signaling, reducing proliferation and sensitizing cancer cells to chemotherapy. This context dependent modulation aids in selectively protecting normal tissues while maintaining the anticancer efficacy of chemotherapy.

in impaired survival signalling, increased susceptibility to apoptosis, and compromised tissue integrity. Curcumin and resveratrol restore this balance by activating P13K and downstream effector Akt in normal cells. Akt, once phosphorylated, promotes cell survival by inhibiting pro-apoptotic factors such as Bad and caspase-9, as well as by phosphorylating the transcription factor FOXO, which suppresses genes involved in apoptosis. Simultaneously, Akt activates the mechanistic target of rapamycin (mTOR), a key regulator of protein synthesis and cell growth. Activation of this pathway in healthy tissues under chemotherapeutic assault promotes anabolic recovery, DNA repair, mitochondrial stability, and cellular resistance to apoptosis [40].

Resveratrol has been shown to enhance the phosphorylation of Akt in cardiac and neural tissues exposed to doxorubicin, reducing mitochondrial mediated apoptosis and preserving function. Similarly, curcumin restores P13K/Akt signaling in intestinal epithelial cells undergoing 5-flurouracil induced mucosal damage, thus facilitating mucosal regeneration and barrier restoration. These findings support the cytoprotective role of bioactive compounds in chemotherapy exposed tissues through P13K/Akt/mTOR modulation. Interestingly, in contrast to their protective roles in normal cells, both curcumin and resveratrol demonstrate the ability to inhibit P13K/Akt/mTOR signaling in cancer cells. In tumor models, these compounds downregulate the expression of P13K catalytic subunits and prevent Akt phosphorylation, thereby suppressing mTOR activity. This leads to inhibition of protein synthesis, cell cycle arrest, and activation of intrinsic apoptotic pathways in malignant cells. This dichotomous action protective in healthy cells and suppressive in tumor cells is likely mediated by differences in upstream receptor activation, oxidative microenvironments, and differential expression of pathway components between normal and cancerous cells. Hence, the modulation of the P13K/Akt/mTOR pathway by bioactive compounds offers a unique advantage in chemotherapy: the selective promotion of survival in normal cells while retaining or enhancing cytotoxicity in tumor cells (Figure 6). This context specific regulation underscores the potential of curcumin, resveratrol, and similar phytochemicals as ideal adjuncts in cancer treatment, improving therapeutic outcomes while minimizing systemic toxicity [41].

Suppression of p53 Overactivation in Normal cells

The tumor suppressor protein 53 plays a pivotal role in maintaining genomic stability by regulating cell cycle arrest, DNA repair, and apoptosis in response to genotoxic stress. Under normal conditions. p53 activity is tightly regulated to maintain tissue homeostasis. However, during chemotherapy, which induces widespread DNA damage and oxidative stress, p53 can become excessively activated not only in cancer cells, where it promotes apoptosis, but also in non-cancerous tissues. This overactivation in normal cells can lead to undesired apoptosis, impairing tissue function and contributing to side effects such as mucositis, myelosuppression, cardiotoxicity, and nephrotoxicity. Therefore, a controlled and context specific modulation of p53 activity is essential to minimize off target toxicity while preserving its tumor suppressive effects.In normal cells, p53 is maintained at low levels through its interaction with the E3 ubiquitin ligase MDM2, which targets it for proteasomal degradation. Upon chemotherapy induced stress, DNA damage sensors such as ATM and ATR phosphorylate p53, stabilizing and activating it. Activated p53 induces the transcription of target genes involved in apoptosis, cell cycle inhibition, and DNA repair. While these functions are critical in eliminating damaged or precancerous cells, excessive or prolonged activation of p53 in healthy tissues can be detrimental, leading to apoptosis even in cells that are otherwise capable of recovery [42].

Bioactive compounds such as quercetin and theaflavin have shown the ability to finely modulate p53 signaling in normal cells. Quercetin, a flavonoid abundant in fruits and vegetables, exerts a dual effect on p53 depending on cellular context. In cancer cells, it promotes p53 stabilization and transcriptional activity, thereby enhancing apoptosis. However, in non-malignant cells, quercetin has been observed to attenuate excessive p53 accumulation by modulating upstream kinases and maintaining MDM2 mediated feedback regulation. This modulation prevents unwarranted apoptosis, particularly in tissues such as gastrointestinal mucosa and hematopoietic system. Similarly, theaflavin the major bioactive constituent of black tea, exhibits protective effects by supressing p53 overactivation in healthy tissues

Table 2. Mechanism Based Classification of Bioactive Compounds in Protecting against Chemotherapy Induced Toxicity

Mechanism of Action	Bioactive Compounds	Molecular Targets / Pathways	Physiological Effect	Key Organ Protection
Antioxidant Defense Activation	Curcumin, Resveratrol, Betanin, Theaflavin	Nrf2/Keap1/ARE, HO-1, SOD, GPx	Neutralization of ROS, redox homeostasis	Liver, Kidney, Heart [20]
Anti-Inflammatory Activity	Quercetin, Thymoquinone, EGCG, Theaflavin	NF-κB, COX-2, IL-6, TNF-α	Suppression of cytokine storm, inflammation resolution	GI tract, Oral mucosa, Lung
Mitochondrial Stabilization	Resveratrol, Quercetin, Thymoquinone	Δψm, mPTP, Bcl-2, Bax, Caspase-3	ATP preservation, prevention of mitochondrial-mediated apoptosis	Cardiac, Neural, Renal tissues
Apoptosis Modulation	Betanin, Thymoquinone, Curcumin	Bcl-2/Bax, Caspase-3/9, Fas/TRAIL-R	Inhibition of unnecessary apoptosis in healthy cells	Bone marrow, Liver, Kidney
Autophagy Regulation	Resveratrol, EGCG	AMPK/mTOR, LC3, Beclin-1	Clearance of damaged proteins/ organelles, cellular renewal	Neurons, Cardiomyocytes
DNA Damage Reduction	Quercetin, Curcumin, EGCG, Genistein	PARP, XRCC1, DNMTs, 8-OxoG	Decreased strand breaks, enhanced DNA repair	Intestinal epithelium, Bone marrow
Epigenetic Modulation	Curcumin, Resveratrol, Sulforaphane, Genistein	HDACs, DNMTs, Histone acetylation, miRNAs	Reactivation of protective genes, anti-inflammatory gene reprogramming	Systemic, Long-term gene regulation
PI3K/Akt Survival Signaling	Curcumin, Resveratrol, Theaflavin	PI3K, Akt, mTOR, FOXO	Cell survival, regenerative signaling in normal cells	Mucosa, Cardiomyocytes

exposed to chemotherapeutic agents. Thymoquinone reduces the phosphorylation of p53 and downregulates pro-apoptotic downstream targets such as Bax ans caspase-3 while preserving the expression of DNA repair genes. This fine-tuned modulation ensures that cells with reparable damage survive and restore function, reducing overall tissue injury [43].

Importantly, these bioactive compounds do not interfere with p53 activity in tumor cells, where its overactivation is therapeutically desirable. Instead, they exhibit a context sensitive modulation, enhancing p53 induced apoptosis in cancerous tissues while limiting it in normal cells. This selectively is attributed to differences in redox states, kinase signaling networks, and p53 isoform expression between and cancerous cells. Thus, the suppression of p53 overactivation in normal cells represents a crucial mechanism by which bioactive compounds protect against chemotherapy induced toxicity. Through controlled modulation of p53 signaling, compounds like quercetin and theaflavin reduce collateral tissue damage, promote regenerative capacity, and improve the overall tolerability of cancer treatment (Figure 7).

Regulation of Autophagy for Cytoprotection

Autophagy is an evolutionarily conserved cellular process responsible for degrading and recycling damaged organelles, misfolded proteins, and cytoplasmic debris. It serves as a vital homeostatic mechanism, particularly under stress conditions like nutrient deprivation, oxidative stress, and exposure to cytotoxic agents such as chemotherapeutic drugs. In normal tissues, chemotherapy often induces severe oxidative and genotoxic stress, leading to mitochondrial dysfunction, protein aggregation, and lipid peroxidation. These deleterious effects not only impair celluar metabolism but also trigger apoptosis if not adequately resolved. The regulation of autophagy by bioactive compounds offers a protective mechanism that enhances cellular survival, promotes regeneration, and reduces inflammation in non-cancerous tissues during chemotherapy [44, 45].

Among the key regulators of autophagy is the AMP activated protein kinase (AMPK), an energy sensing kinase that activates autophagic processes when cellular ATP levels drop. AMPK phosphorylates and inhibits the mechanistic target of rapamycin (mTOR), a negative regulator of autophagy. Inhibition of mTOR removes the suppression on the ULK1 complex, thereby initiating the formation of autophagosomes. These vesicles engulf damaged cytoplasmic content and subsequently fuse with lysosomes foe degradation and recycling. This pathway helps maintain cellular energy balance, reduces intracellular ROS, and prevents the accumulation of toxic macromolecules. Bioactive compounds such as resveratrol and epigallocatechin gallate (EGCG) have been shown to effectively modulate this autophagic pathway. Resveratrol. a polyphenol found in red grapes and berries, activates AMPK by increasing the AMP/

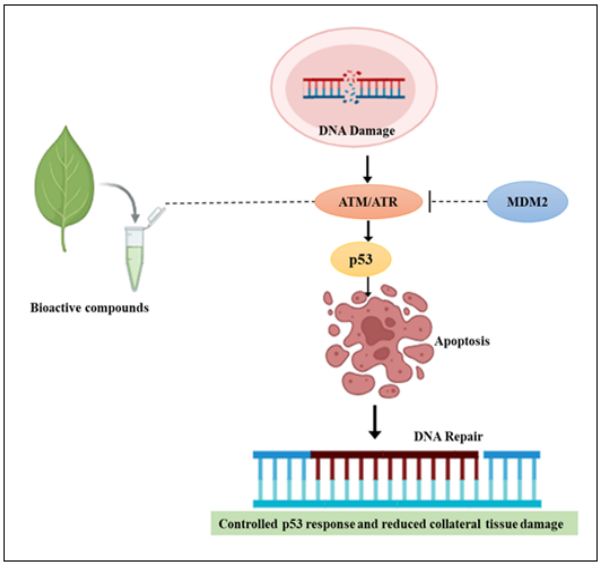

Figure 7. The diagram depicts how bioactive compounds modulate p53 signaling during chemotherapy. By limiting excessive p53 activation in normal cells, they prevent apoptosis and tissue damage, while preserving tumor suppressive effects in cancer cells.

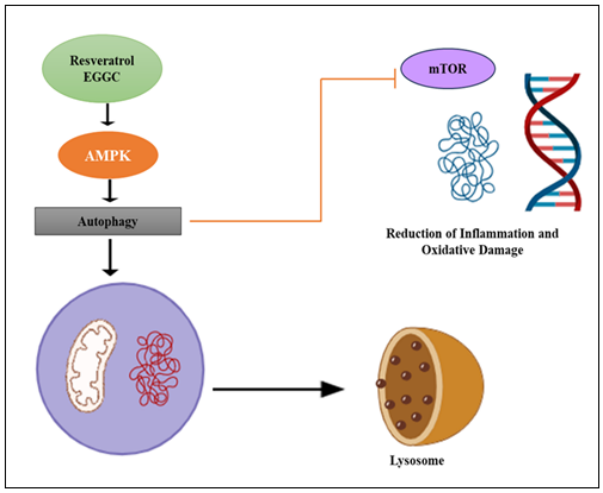

Figure 8. The diagram illustrates how bioactive compounds such as resveratrol and EGCG regulate autophagy through AMPK activation and mTOR inhibition. This signalling casade initiates autophagic clearance of damaged organelles and proteins, thereby reducing oxidative stress and inflammation in non-cancerous cells during chemotherapy, enhancing cellular survival and resilience.

ATP ratio, especially in cells under oxidative stress. By promoting AMPK activity and simultaneously inhibiting mTOR signalling, resveratrol enhances the initiation of autophagy in cardiac and neuronal cells. This mechanism is particularly beneficial in tissues where chemotherapy drugs like doxorubicin or cisplatin are known to induce severe mitochondrial damage and protein aggregation, leading to cell death. Resveratrol mediated autophagy removes these damaged components, preserving tissue integrity and function [46].

EGCG, the primary catechin in green tea, also promotes autophagy via a similar mechanism. In preclinical models, EGCG has been shown to activate AMPK and reduce the activity of Akt/mTOR signaling, enhancing autophagic flux. This results in reduced apoptosis, diminished pro-inflammatory cytokine release, and improved mitochondrial health. Furthermore, EGCG has demonstrated neuroprotective effects by inducing autophagy in neuronal cells exposed to chemotherapeutic agents, thereby alleviating neurotoxicity and cognitive decline. Notably, this autophagic modulation by resveratrol and EGCG is selective for normal cells under stress and does not promote survival in cancer cells. In fact, in many tumor models, these bioactives can induce excessive autophagy or autophagic cell death, which is therapeutically advantageous. This dual context behavior underscores the selective cytoprotective potential of autophagy regulation in chemotherapy (Figure 8). In essence, the regulation of autophagy by bioactive compounds represents a robust defese mechanism that improvs cellular resilience and longevity during cancer treatment. By facilitating the clearance of damaged components and restoring metabolic homeostasis, components like resveratrol and EGCG preserve organ function and reduce systemic toxicity ultimately improving the therapeutic index of chemotherapy [47].

Epigenic Modulation by Bioactive compounds

Epigenetics refers to heritable but reversible modifications in gene expression that occyr without changes to the underlying DNA sequence. These modifications primarily involving DNA methylation, histone acetylation/deacetylation, and non-coding RNA regulation, play critical roles in gene silencing, activation and chromatin remodelling. During chemotherapy, widespread epigenetic disruptions often occur, contributing to cellular stress, inflammation, organ toxicity, and even chemoresistance (Table 2). Interestingly, certain bioactive compounds have demonstrated the capacity to modulate epigenetic landscapes in normal cells, thereby enhancing their resistance to chemotherapy induced damage [48].

One of the key mechanisms of epigenetic regulation involves histone acetylation, controlled by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Acetylation of histone tails by HATs relaxes chromatin structure, promoting gene transcription, while HDACs remove acetyl groups, leading to chromatin compaction and transcriptional repression. Chemotherapy often dysregulates this balance, suppressing genes involved in detoxification, antioxidant defense, and DNA repair. Bioactive compounds such as curcumin and resveratrol have been identified as natural HDAC inhibitors. By inhibiting HDAC activity, these compounds promote the acetylation of histones associated with protective genes such as Nrf2, HO-1, SOD2, and GPx, leading to their transcriptional activation. Curcumin, a polyphenol derived from turmeric, can inhibit HDAC1, HDAC3, and HDAC8, threby restoring the expression of silenced tumor suppressor genes and detoxification pathways. Additionally, it enhances histone acetylation at the promoter regions of anti-inflammatory and antioxidant genes, which mitigates the impact of chemotherapy induced oxidative stress and inflammation. Resveratrol similarly targets class I and II HDACs, and has also been shown to modulate the expression of sirtuins, NAD+ dependent deacetylases involved in stress response and mitochondrial function. Activation of SIRT1 by resveratrol promotes chromatin remodeling that supports genomic stability and cell survival under chemotherapeutic insult [49].

In addition to histone modification, DNA methylation is another epigenetic layer that bioactive compounds can influence. DNA methyltransferases (DNMTs) catalyse the addition of methyl groups to cytosine residues, particularly in CpG islands of gene promoters, resulting in transcriptional repression. Overexpresion of DNMTs during chemotherapy can silence critical genes responsible for cell cycle regulation, antioxidant defense, and apoptosis inhibition. Bioactive compounds such as genistein, sulforaphane, and EGCG have been shown to inhibit DNMT activity, leading to demethylation and re-expression of genes involved in cytoprotection. Furthermore, these compounds influence the levels and activity of non-coding RNAs such as microRNAs (miRNAs), which regulate mRNA stability and translation. For instance, curcumin modulates miR-21, miR-34a, and miR-155 known to regulate inflammatory signalling,

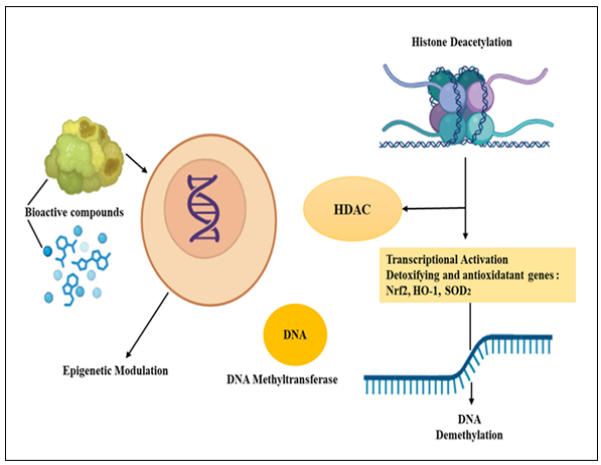

Figure 9. The diagram depicts the epigenetic modulation exerted by bioactive compounds and these compounds act as natural HDAC inhibitors and DNA methylation modulators. By altering histone acetylation and DNA methylation patterns, they promote the transcription of cytoprotective genes involved in antioxidant defense, detoxification, and anti-inflammatory responses, ultimately mitigating chemotherapy induced toxicity and promote tissue resilience.

apoptosis and oxidative stress responses (Figure 9). Through these epigenetic mechanisms, bioactive compounds offer long lasting cellular reprogramming that enhances resilience to chemotherapy while maintaining normal cell viability. Hence the ability of bioactive compounds to modulate the epigenome represents a powerful strategy to counteract the collateral damage of chemotherapeutic agents. By promoting the expression of protective genes and reversing maladaptive silencing events, these natural agents offer durable and tissue specific cytoprotection that complements traditional cancer therapies [50].

Discussion

Chemotherapy, while integral to modern cancer management, is frequently marred by its indiscriminate cytotoxicity toward both malignant and healthy proliferative cells. The resulting collateral tissue damage often leads to debilitating side effects ranging from fatigue, mucositis, and myelosuppression to cardiotoxicity, hepatotoxicity, and neurotoxicity which limit dose intensity and negatively impact patient compliance and quality of life. The urgent clinical need to mitigate these adverse effects without compromising antitumor efficacy has directed attention toward natural bioactive compounds as potential adjuncts to conventional chemotherapeutic regiments. The current study comprehensively examines the protective roles of compounds such as curcumin, resveratrol, thymoquinone, quercetin, betanin, theaflavin, and EGCG, with a focus on their mechanistic engagement in oxidative stress regulation, inflammation suppression, mitochondrial preservation, apoptotic control, autophagy induction, DNA repair and epigenetic remodeling [51, 52].

A primary mechanism of protection observed across multiple compounds is the activation of the Nrf2/Keap1/ARE pathway, a central regulator of antioxidant defense. Chemotherapeutic agents like doxorubicin and cisplatin induce excessive reactive oxygen species (ROS), disrupting redox balance and causing oxidative damage in normal tissues. Compounds such as curcumin, resveratrol, betanin, and theaflavin disrupt the Nrf2-Keap1 interaction, allowing Nrf2 to translocate into the nucleus and upregulate antioxidant genes including HO-1,SOD, GPx, and NQO1. This cascade reduces intracellular ROS accumulation and preserves tissue function, particularly in oxidative stress sensitive organs like the liver, kidney, and heart. The ability of these compounds to engage endogenous cytoprotective pathways underscores their preventive potential during chemotherapy [53].

Another hallmark feature of chemotherapy induced toxicity is inflammation, largely driven by NF-kB activation, which promotes the transcription of pro-inflammatory cytokines such as TNF-α, IL-6, COX-2. Bioactive compounds including quercetin, thymoquinone, EGCG, and theaflavin have demonstrated significant NF-κB inhibitory activity. By blocking IκB degradation or suppressing upstream kinases like IKK, these compounds rretain NF-κB in the cytoplasm, therby preventing its translocation and subsequent gene transcription. This action results in the attenuation of mucositis, hepatotoxicity, and cardiotoxicity observed during chemotherapy. Notably, this anti-inflammatory property works synergistically with their antioxidant effects, as inflammation and ROS production are tightly interconnected in a feed forward loop during cytotoxic stress [54]. Mitochondrial dysfunction is another major consequence of chemotherapeutic exposure, contributing to bioenergetic failure and intrinsic apoptosis. Chemotherapeutic agents induce mitochondrial membrane depolarization, open the mPTP, and trigger cytochrome c release, which activates caspase-9 and caspase-3. Bioactive compounds such as resveratrol and quercetin help maintain mitochondrial membrane potential (Δψm), prevent mPTP opening, and stabilize ATP synthesis. Furthermore, by upregulating Bcl-2 and downregulating Bax and caspase-3, compounds like thymoquinone and betanin protect mitochondrial integrity and suppress apoptosis in non-cancerous tissues. Importantly, these actions are tissue selective; they do not interfere with chemotherapy induced apoptosis in tumor cells, a phenomenon attributed to differing cellular redox states and oncogenic signaling between cancerous and normal cells. The modulation of both intrinsic and extrinsic apoptotic pathways is a shared protective strategy. In addition to stabilizing mitochondrial function, bioactives inhibit death receptor mediated signaling through suppression of Fas, TRAIL-R, and caspase-8. This particularly important in preventing tissue injury in bone marrow, GI epithelium, and other high turnover tissues. Such dual pathway modulation supports tissue specific cytoprotecting without compromising systemic therapeutic intent. A lesser explored but increasingly important mechanism involves regulation of autophagy, a cellular process that removes damaged organelles and aggregated proteins. Autophagic flux is often disrupted during chemotherapy, exacerbating cytoplasmic stress

and promoting apoptosis. Resveratrol and EGCG were shown to activate AMPK and inhibit mTOR, initiating autophagosome formation and lysosomal degradation of damaged components. This only restores cellular homeostasis but also limits secondary inflammation and oxidative stress. In neural and cardiac tissues, this regulation translates into preserved organ function and resilience against long term degenerative effects [55].

Additionally, DNA damage mitigation is critical in preventing long term genomic instability induced by agents like cyclophosphamide and doxorubicin. Flavonoids such as quercetin and phenolic acids like caffeic acid enhance DNA repair enzymes (e.g. PARP, XRCC1), reduce oxidative DNA adducts, and chelate transition metals that catalyse DNA damaging Fenton reactions. These properties reduce strand breaks and chromosomal aberrations, preserving genome fidelity in replicating non-malignant cells such as those in the hematopoietic and gastrointestinal systems. Epigenic remodeling, including histone modification and DNA demethylation, represents a novel and durable mechanism of protection. Curcumin and resveratrol have been shown to inhibit histone deacetylases (HDACs), resulting in relaxed chromatin and transcriptional activation of genes involved in antioxidant defense and inflammation resolution. Furthermore, compounds like genistein and sulforaphane inhibit DNMTs, restoring the expression of silenced tumor suppressor and detoxification genes. This epigenetic reprograming creates a long-term shift in cellular phenotype that enhances resilience during repeated chemotherapeutic exposures and may even reduce the risk of therapy induced secondary malignancies. The P13K/Akt/mTOR pathway, critical for regulating cell survival and proliferation, is also contextually modulated by bioactive compounds. In healthy cells, curcumin and resveratrol activate Akt and mTOR in response to chemotherapy induced stress, promoting survival, tissue regeneration, and protein synthesis. Conversely, in cancer cells, these same compounds suppress P13K signalling, facilitating apoptosis and blocking proliferation. This context specific duality underscores the selectivity and safety of bioactives in therapeutic applications. Another intriguing mechanism is the suppression of p53 overactivation. Although p53 is essential for tumor suppression, excessive activation in healthy cells during chemotherapy can lead to inappropriate apoptosis. Bioactives like quercetin and thymoquinone fine tune p53 responses by modulating upstream kinases or feedback loops involving MDM2. This ensures that p53 promotes repair and survival in normal cells while retaining apoptotic activity in cancerous counterparts [56].

Together, these findings establish that bioactive compounds exert their protective effects through a multi-targeted approach, engaging several intersecting signaling networks to reduce oxidative stress, inflammation, mitochondrial injury, apoptosis, genotoxicity, and epigenetic dysregulation. Their pleiotropic nature offers a distinct advantage over single target synthetic agents, enabling more holistic protection of normal tissues without negating the efficacy of chemotherapeutic agents on tumors. Furthermore, these compounds are often well tolerated, cost effective, and widely available. Their incorporation into cancer care whether as dietary supplements, encapsulated formulations, our nano delivery systems represent a promising adjunctive strategy. However, despite robust preclinical data, clinical translation remains limited. Future directions should prioritize pharmacokinetic optimization, synergistic combinations, and large scale randomized controlled trails to validate the efficacy and safety of bioactive compounds in diverse cancer populations. Thus, the use of bioactive compounds as a protective shield against chemotherapy induced toxicity is grounded in sound molecular rationale and strong experimental evidence. Their ability to target multiple hallmarks of tissue injury with high selectivity and minimal side effects makes them compelling candidates for integrative cancer therapy. Advancing their clinical application holds promise for improving patient tolerance, treatment continuity, and overall outcomes in cancer management [57].

In conclusion, the use of bioactive compounds as adjuncts to chemotherapy represents a promising strategy to alleviate treatment induced toxicity in cancer patients. These naturally occurring molecules, including curcumin, resveratrol, quercetin, theaflavin, thymoquinone, and betanin, exert multifaced protective effects through well characterized molecular mechanisms. By modulating oxidative stress, inflammatory cascades, mitochondrial function, apoptotic pathways, and DNA integrity, they offer selective protection to normal tissues without compromising the cytotoxicity against tumor cells. Importantly, their ability to influence key signalling pathways such as Nrf2/ARE, NF-κB, PI3/Akt, and p53 highlights their potential as intelligent modulators of cellular stress responses. Some bioactives also contribute to long term protection through epigenetic remodeling and autophagy regulation. While preclinical evidence is compelling, translating these findings into clinical oncology requires rigorous validation, including standardization, pharmacokinetic profiling, and dose optimization. Nevertheless, the integration of these compounds into therapeutic regiments could transform chemotherapy from a purely cytotoxic intervention into a more tolerable and supportive cancer care approach, improving patient outcomes and quality of life.

Author Contribution Statement

TM and MS were jointly responsible for the development and completion of this review manuscript. Both authors collaboratively contributed to the conceptualization, literature survey, data interpretation, and structuring of the manuscript. TM was primarily involved in drafting the initial sections, organizing the thematic flow, and referencing. MS contributed significantly to the critical analysis of the literature, manuscript refinement, and language polishing. The entire manuscript underwent multiple rounds of discussion and revision by both authors to ensure clarity, coherence, and scientific accuracy. Both authors read and approved the final version of the manuscript.

Acknowledgements

I would like to extend my sincere appreciation to Saveetha Dental and Medical College, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai, India for their invaluable support and resources that made this research possible. Their commitment to excellence in education and research has significantly contributed to the advancement of knowledge in our field.

Conflict of Interest

The authors of this manuscript declare no conflict of interest.

References

1. Bhargava DS, Abraham DJ, Srinivas DM, Ghosh DS. Unravelling The Complexities of Cervical Cancer: A Comprehensive Exploration: Oncology-Cervical cancer. International Journal of Trends in OncoScience. 2024 04 05;:23-31. https://doi.org/10.22376/ijtos.2024.2.2.23-31
2. None I, Witayateeraporn W, Hardianti B, Pongrakhananon V. Comprehensive review of Bcl-2 family proteins in cancer apoptosis: Therapeutic strategies and promising updates of natural bioactive compounds and small molecules. Phytotherapy research : PTR. 2024 05;38(5). https://doi.org/10.1002/ptr.8157
3. Tayyeb JZ, Priya M, Guru A, Kishore Kumar MS, Giri J, Garg A, Agrawal R, 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 03 15;51(1):423. https://doi.org/10.1007/s11033-024-09407-7
4. Padathpeedika Khalid J, Mary Martin T, Prathap L, Abhimanyu Nisargandha M, Boopathy N, Kishore Kumar MS. Exploring Tumor-Promoting Qualities of Cancer-Associated Fibroblasts and Innovative Drug Discovery Strategies With Emphasis on Thymoquinone. Cureus. 2024 02;16(2):e53949. https://doi.org/10.7759/cureus.53949
5. Wang Y. The interplay of exercise and polyphenols in cancer treatment: A focus on oxidative stress and antioxidant mechanisms. Phytotherapy research: PTR. 2024 07;38(7):3459-3488. https://doi.org/10.1002/ptr.8215
6. 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 02 17;43(2):198-206. https://doi.org/10.1080/02726351.2024.2440462
7. Osman EO, Khalil NA, Magdy A, El-Dash Y. New pyrazole–pyridazine hybrids as selective COX-2 inhibitors: design, synthesis, molecular docking, in silico studies and investigation of their anti-inflammatory potential by evaluation of TNF-α, IL-6, PGE-2 and NO in LPS-induced RAW264.7 macrophages. RSC Medicinal Chemistry.15(8):2692-2708. https://doi.org/10.1039/d4md00135d
8. Mary Martin T, K MS. Seaweeds and Their Secondary Metabolites: A Promising Drug Candidate With Novel Mechanisms Against Cancers and Tumor Angiogenesis. Cureus. 2024 08;16(8):e66662. https://doi.org/10.7759/cureus.66662
9. Utpal BK, Mokhfi FZ, Zehravi M, Sweilam SH, Gupta JK, Kareemulla S, C RD, et al. Resveratrol: A Natural Compound Targeting the PI3K/Akt/mTOR Pathway in Neurological Diseases. Molecular Neurobiology. 2025 05;62(5):5579-5608. https://doi.org/10.1007/s12035-024-04608-4
10. Jayaraman S, Veeraraghavan VP. Deoxyelephantopin induces cell death in oral cancer cells via the downregulation of AKT1-mTOR-mediated mechanisms. Journal of oral and maxillofacial pathology: JOMFP. 2025;29(2):193-205. https://doi.org/10.4103/jomfp.jomfp_41_25
11. Medoro A, Davinelli S, Scuderi L, Scuderi G, Scapagnini G, Fragiotta S. Targeting Senescence, Oxidative Stress, and Inflammation: Quercetin-Based Strategies for Ocular Diseases in Older Adults. Clinical Interventions in Aging. 2025;20:791-813. https://doi.org/10.2147/CIA.S516946
12. Villa A, Lodolo M, Sonis S. Oral mucosal toxicities in oncology. Expert Opinion on Pharmacotherapy. 2025 03;26(4):481-489. https://doi.org/10.1080/14656566.2025.2464106
13. Annals MSR. Beetroot and Its Therapeutic Effects on Hypertension: A Natural Remedy for Blood Pressure Management. 2025 07 12. https://doi.org/10.5281/zenodo.15868249
14. Dandagi P, Yuvaraj Babu K, Mary Martin T, Meenakshi Sundaram K. In Silico and Glioblastoma Cell Line Evaluation of Thioflavin-Derived Zinc Nanoparticles Targeting Beclin Protein. Cureus. 2024 09;16(9):e69319. https://doi.org/10.7759/cureus.69319
15. Sebastian S, Martin TM, Kumar MSK: Thymoquinone-Loaded Zinc Nanoparticles Mitigate Inflammation and Inhibit Glioblastoma Progression: A Novel Therapeutic Approach. 2025.
16. Piyarathne N, Hettiarachchi K, Yuwanati M, Sivaramakrishnan G, Ramanathan A, Jayasinghe R, Chala S, Chaurasia A. Osteopontin as a prognostic biomarker in head and neck cancer- a systematic review and meta-analysis. Evidence-Based Dentistry. 2025 09;26(3):146-147. https://doi.org/10.1038/s41432-025-01133-8
17. Sarkar D, Das U, Chatterjee S. Theaflavin-enriched black tea: Uses and applications. Tea in Health and Disease Prevention (Second Edition). 2025 01 01:649-660.
18. Centonze M, Aloisio Caruso E, De Nunzio V, Cofano M, Saponara I, Pinto G, Notarnicola M. The Antiaging Potential of Dietary Plant-Based Polyphenols: A Review on Their Role in Cellular Senescence Modulation. Nutrients. 2025 05 19;17(10):1716. https://doi.org/10.3390/nu17101716
19. Divaskara CS, Sinduja P, Sekaran S, Priyadharshini R. miRNAs Regulating RUNX2 and their Expression Pattern Copper-Zinc Alloy Nanoparticles. Advances in Sports Science and Technology. CRC Press; 2025. 949-954.
20. Abuzinadah MF, Shaik RA, Ahmad A, Islam MN, Eid BG. Alantolactone protects against doxorubicin-induced nephrotoxicity by modulating Nrf2/HO-1, NF-κB, and Bax/Bcl-2 activity: molecular and in silico insights. Molecular Biology Reports. 2025 06 04;52(1):544. https://doi.org/10.1007/s11033-025-10620-1
21. Kouri MA, Tsaroucha A, Axakali T, Varelas P, Kouloulias V, Platoni K, Efstathopoulos EP. Targeting Cancer Cell Fate: Apoptosis, Autophagy, and Gold Nanoparticles in Treatment Strategies. Current Issues in Molecular Biology. 2025 06 14;47(6):460. https://doi.org/10.3390/cimb47060460
22. Maheshwarla Saravanan S, Prathap L, Padathpeedika Khalid J, Mary Martin T, Kishore Kumar MS. Serotonin's Role in Inflammatory Signaling Pathway Modulation for Colon Cancer Suppression. Cureus. 2024 08;16(8):e66040. https://doi.org/10.7759/cureus.66040
23. Liskova A, Samec M, Koklesova L, Brockmueller A, Zhai K, Abdellatif B, Siddiqui M, et al. Flavonoids as an effective sensitizer for anti-cancer therapy: insights into multi-faceted mechanisms and applicability towards individualized patient

profiles. The EPMA journal. 2021 06;12(2):155-176. https://doi.org/10.1007/s13167-021-00242-5
24. Zhang M, Sun W, Yang J, Shi D, Dai X, Li X. The Effect of Preventing Oxidative Stress and Its Mechanisms in the Extract from Sonchus brachyotus DC. Based on the Nrf2-Keap1-ARE Signaling Pathway. Antioxidants (Basel, Switzerland). 2023 08 27;12(9):1677. https://doi.org/10.3390/antiox12091677
25. Ucar BI, Ucar G, Saha S, Buttari B, Profumo E, Saso L. Pharmacological Protection against Ischemia-Reperfusion Injury by Regulating the Nrf2-Keap1-ARE Signaling Pathway. Antioxidants (Basel, Switzerland). 2021 05 21;10(6):823. https://doi.org/10.3390/antiox10060823
26. Ahmed M. Targeting aging pathways with natural compounds: a review of curcumin, epigallocatechin gallate, thymoquinone, and resveratrol. Immunity & Ageing: I & A. 2025 07 03;22(1):28. https://doi.org/10.1186/s12979-025-00522-y
27. Konstantinou EK, Gioxari A, Dimitriou M, Panoutsopoulos GI, Panagiotopoulos AA. Molecular Pathways of Genistein Activity in Breast Cancer Cells. International Journal of Molecular Sciences. 2024 05 20;25(10):5556. https://doi.org/10.3390/ijms25105556
28. Habtemariam S. Anti-Inflammatory Therapeutic Mechanisms of Isothiocyanates: Insights from Sulforaphane. Biomedicines. 2024 05 24;12(6):1169. https://doi.org/10.3390/biomedicines12061169
29. Prabhuvenkatesh D, Ramani P, Yuwanati MB, Sukumaran G. Association of Insulin Receptor Substrate 1 Expression in the Prognosis of Head and Neck Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis. Oncology. 2025;103(3):253-264. https://doi.org/10.1159/000541004
30. Lee J, Uddin S, Jeong C, Han SB, Cho S. Methanol extract of Euphorbia cotinifolia L. leaf attenuates inflammation and oxidative stress in RAW 264.7 macrophages via TAK1-mediated suppression of NF-κB/MAPK and activation of Nrf2 pathways. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2025 09;190:118372. https://doi.org/10.1016/j.biopha.2025.118372
31. Sadati S, Khalaji A, Bonyad A, Khoshdooz S, Hosseini Kolbadi KS, Bahrami A, Moeinfar MS, et al. NF-κB and apoptosis: colorectal cancer progression and novel strategies for treatment. European Journal of Medical Research. 2025 07 14;30(1):616. https://doi.org/10.1186/s40001-025-02734-w
32. Pierro F, Fazio M, Murdaca G, Stagno F, Gangemi S, Allegra A. Oxidative Stress and Mitochondrial Dysfunction in Myelodysplastic Syndrome: Roles in Development, Diagnosis, Prognosis, and Treatment. International Journal of Molecular Sciences. 2025 07 03;26(13):6415. https://doi.org/10.3390/ijms26136415
33. Ghogare SS, Pathan EK. Intratumor fungi specific mechanisms to influence cell death pathways and trigger tumor cell apoptosis. Cell Death Discovery. 2025 04 21;11(1):188. https://doi.org/10.1038/s41420-025-02483-z
34. Wang D, Zhou Y, Hua L, Hu M, Zhu N, Liu Y, Zhou Y. The role of the natural compound naringenin in AMPK-mitochondria modulation and colorectal cancer inhibition. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2024 08;131:155786. https://doi.org/10.1016/j.phymed.2024.155786
35. Sundaram KKM, Bupesh G, Saravanan KM, Sundaram KKM, Bupesh G, Saravanan KM. Instrumentals behind embryo and cancer: a platform for prospective future in cancer research. AIMS Molecular Science. 2022;9(1):25-45. https://doi.org/10.3934/molsci.2022002
36. Wang W, Yang F, Zhang L, Wang M, Yin L, Dong X, Xiao H, Xing N. Targeting DNA Damage and Repair Machinery via Delivering WEE1 Inhibitor and Platinum (IV) Prodrugs to Stimulate STING Pathway for Maximizing Chemo-Immunotherapy in Bladder Cancer. Advanced Materials (Deerfield Beach, Fla.). 2024 01;36(1):e2308762. https://doi.org/10.1002/adma.202308762
37. Patil MN, Bhandurge PJ, Kadam SS, Datkhile KD. Sequence Variation in X-ray Cross Complimenting (XRCC4, XRCC5, XRCC6 and XRCC7) Genes and the Risk of Gastrointestinal Cancer in South-Western Maharashtra: A Hospital Based Case-Control Study. Asian Pacific journal of cancer prevention: APJCP. 2025 05 01;26(5):1571-1579. https://doi.org/10.31557/APJCP.2025.26.5.1571
38. Li C, Chen H, Chen X, Wang P, Shi Y, Xie X, Chen Y, Cai X. Identification of inflammatory response-related molecular mechanisms based on the ATM/ATR/p53 pathway in tumor cells. Computers in Biology and Medicine. 2024 09;180:108776. https://doi.org/10.1016/j.compbiomed.2024.108776
39. Yang D, Namila N, Hashentuya N, Tana N, Wuyunsiqin N, Zhao W, Menggenduxi N, Wang M. Mongolian medicine Qiqirigan-8 inhibition of PI3K/AKT/mTOR signaling pathway activation to ameliorate non-alcoholic Steatohepatitis. Journal of Pharmaceutical and Biomedical Analysis. 2025 Nov 15;265:116975. https://doi.org/10.1016/j.jpba.2025.116975
40. Marunganathan V, Kumar MSK, Kari ZA, Giri J, Shaik MR, Shaik B, Guru A. Marine-derived κ-carrageenan-coated zinc oxide nanoparticles for targeted drug delivery and apoptosis induction in oral cancer. Molecular Biology Reports. 2024 01 07;51(1):89. https://doi.org/10.1007/s11033-023-09146-1
41. Grabarczyk M, Justyńska W, Czpakowska J, Smolińska E, Bielenin A, Glabinski A, Szpakowski P. Role of Plant Phytochemicals: Resveratrol, Curcumin, Luteolin and Quercetin in Demyelination, Neurodegeneration, and Epilepsy. Antioxidants (Basel, Switzerland). 2024 Nov 07;13(11):1364. https://doi.org/10.3390/antiox13111364
42. Wu K, Ge X, Duan X, Li J, Wang K, Chen Q, Huang Z, Zhang W, Wu Y, Li Q. Wip1 phosphatase activator QGC-8-52 specifically sensitizes p53-negative cancer cells to chemotherapy while protecting normal cells. Drug Resistance Updates: Reviews and Commentaries in Antimicrobial and Anticancer Chemotherapy. 2025 03;79:101196. https://doi.org/10.1016/j.drup.2024.101196
43. Pourbarkhordar V, Rahmani S, Roohbakhsh A, Hayes AW, Karimi G. Melatonin effect on breast and ovarian cancers by targeting the PI3K/Akt/mTOR pathway. IUBMB life. 2024 Dec;76(12):1035-1049. https://doi.org/10.1002/iub.2900
44. Moreau K, Luo S, Rubinsztein DC. Cytoprotective roles for autophagy. Current Opinion in Cell Biology. 2010 04;22(2):206-211. https://doi.org/10.1016/j.ceb.2009.12.002
45. Senthil R, Meenakshi Sundaram KK, 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 05 01;23(5):1687-1697. https://doi.org/10.31557/APJCP.2022.23.5.1687
46. Qu Y, Zhang N, Zhao Y. Resveratrol Inhibits Abdominal Aortic Aneurysm Progression by Reducing Extracellular Matrix Degradation, Apoptosis, Autophagy, and Inflammation of Vascular Smooth Muscle Cells via Upregulation of HMOX1. Journal of Endovascular Therapy: An Official Journal of the International Society of Endovascular Specialists. 2025 08;32(4):1224-1236. https://doi.org/10.1177/15266028231202727
47. Ferrari E, Bettuzzi S, Naponelli V. The Potential of Epigallocatechin Gallate (EGCG) in Targeting Autophagy

for Cancer Treatment: A Narrative Review. International Journal of Molecular Sciences. 2022 05 28;23(11):6075. https://doi.org/10.3390/ijms23116075
48. Martínez-Iglesias O, Naidoo V, Carrera I, Corzo L, Cacabelos R. Natural Bioactive Products as Epigenetic Modulators for Treating Neurodegenerative Disorders. Pharmaceuticals (Basel, Switzerland). 2023 01 31;16(2):216. https://doi.org/10.3390/ph16020216
49. Shahcheraghi SH, Salemi F, Peirovi N, Ayatollahi J, Alam W, Khan H, Saso L. Nrf2 Regulation by Curcumin: Molecular Aspects for Therapeutic Prospects. Molecules (Basel, Switzerland). 2021 Dec 28;27(1):167. https://doi.org/10.3390/molecules27010167
50. Vilchis-Landeros MM, Vázquez-Meza H, Vázquez-Carrada M, Uribe-Ramírez D, Matuz-Mares D. Antioxidant Enzymes and Their Potential Use in Breast Cancer Treatment. International Journal of Molecular Sciences. 2024 05 23;25(11):5675. https://doi.org/10.3390/ijms25115675
51. Umadevi K, Sundeep D, Vighnesh AR, Misra A, Krishna AG. Current Trends and Advances in Nanoplatforms-Based Imaging for Cancer Diagnosis. Indian Journal of Microbiology. 2025 03;65(1):137-176. https://doi.org/10.1007/s12088-024-01373-9
52. Anbarasu M, Martin TM, Priya P, Sivamurugan V, Kumar MSK, Shaik MR, Kari ZA, Guru A. Assessing the impact of Ag-ZnO nanoparticle on the induction of oxidative stress, hematological, and molecular changes in zebrafish (Danio rerio) and McCoy fibroblast cell lines. Aquaculture International. 2024 08 01;32(4):5373-5392. https://doi.org/10.1007/s10499-024-01611-3
53. Payra M, Mohanraj KG, Mary Martin T, K MS. Modulation of Inflammation in McCoy Cells by Zinc Nanoparticles Conjugated With β-Chitosan. Cureus. 2024 09;16(9):e68653. https://doi.org/10.7759/cureus.68653
54. Umakanth K, Mary Martin T, K MS. An In Vitro and In Silico Study of Luteolin-Loaded Zinc Oxide Nanoparticles: Enhancing Bioactivity and Efficacy for Advanced Therapeutic Applications Against Cariogenic Microorganisms. Cureus. 2024 08;16(8):e68058. https://doi.org/10.7759/cureus.68058
55. Mazurakova A, Koklesova L, Vybohova D, Samec M, Kudela E, Biringer K, Šudomová M, et al. Therapy-resistant breast cancer in focus: Clinically relevant mitigation by flavonoids targeting cancer stem cells. Frontiers in Pharmacology. 2023;14:1160068. https://doi.org/10.3389/fphar.2023.1160068
56. Nnamani PO, Onokala OB, Odeku OA. Bioactive-Based Nanocarriers for Cancer Treatment and Targeting. Bioactive-Based Nanotherapeutics. 2025:265-297.
57. Salmani H, Nasiri S, Ahmadi M. The advantages, disadvantages, threats, and opportunities of electronic patient-reported outcome systems in cancer: A systematic review. Digital Health. 2024;10:20552076241257146. https://doi.org/10.1177/20552076241257146