Pro-oxidant Phytocompounds and Mitochondrial Vulnerabilities: A Novel Paradigm in Cancer Therapy

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Abstract

Cancer constitutes a major global health concern. Surgery, chemotherapy, and radiation therapy are prevalent treatments; yet, they frequently prove ineffective due to their systemic toxicity, the ineffectiveness of pharmacological agents, and their invasive nature. These challenges necessitate the investigation of innovative therapeutic strategies that specifically target cancer cells while reducing damage to normal tissues.

Natural phytocompounds with pro-oxidant characteristics have gathered interest as potential anticancer agents. Cancer cells, which have high metabolic activity and damaged mitochondria, are always under oxidative stress. This alteration in redox homeostasis makes it more likely that they will have even more reactive oxygen species (ROS) in their systems. Pro-oxidant phytocompounds damage mitochondria, disrupt energy metabolism, and activate apoptotic pathways very selectively by pushing ROS levels past the cellular threshold. This kills the cancer cells while leaving healthy cells unharmed.

New evidence has shown that a vast array of plant-based compounds, including polyphenols, terpenes, and alkaloids, have been identified to act as pro-oxidants by altering the mitochondrial membrane potential, inhibiting antioxidant defense systems, and disrupting redox-sensitive signaling pathways. However, obstacles persist in enhancing their specificity, bioavailability, and delivery systems.

This review discusses the therapeutic potential of natural pro-oxidant phytocompounds in targeting mitochondrial vulnerabilities of cancer cells and bottlenecks that must be addressed for successful clinical translation. Harnessing these agents may pave the way for safer and more effective cancer treatments that exploit the intrinsic weaknesses of tumor bioenergetics.

Keywords: *Prooxidants, Oxidative Stress, Reactive Oxygen Species, Mitochondria*

1. Introduction

One of the major reasons why life expectancy is not going up is that cancer is becoming the most common causes of deaths in the world. In 2022, there were expected to be 20 million new cases of cancer and about 9.7 million deaths from the disease people still die from cancer a lot, even though a lot of research has been done to learn more about the disease and find ways to treat it [1]. A more challenging approach is to treat the more aggressive metastatic tumors which tend to develop resistance to standard therapies over time. Thus, a growing interest to unravel the molecular and cellular mechanisms that drive cancer genesis and progression is been carried out by researchers. [2].

Reactive oxygen species are chemical entities that exist in cells and is produced as derivatives of normal or abnormal cell activity. It has a higher reactivity towards lipids, proteins, and DNA. Oxidative stress promotes tumor initiation, progression, accumulation, resistance to treatment and genomic. At low to moderate levels, these chemical species act as signalling molecules but at much higher level they help cancer cells grow, move, invade, form new blood vessels, and resist treatment. In other words, keeping the right levels of ROS is important for cancer cells to stay healthy, which in turn helps important cellular processes and molecular mechanisms of cell machinery [2].

Cancer cells exhibit a greater tolerance to reactive oxygen species (ROS) than normal cells, mostly owing to their adaptive and versatile antioxidant mechanisms. This introduces the notion of a pro-oxidant–antioxidant threshold, signifying a crucial equilibrium in intracellular redox homeostasis [3]. At low to moderate levels of reactive oxygen species, cancer cells utilize these entities as signaling molecules to enhance proliferation, survival, and metabolic adaptability, hence exerting pro-tumorigenic effects. When ROS levels beyond this threshold, oxidative damage to lipids, proteins, and DNA becomes excessive, eliciting anti-tumorigenic responses such as apoptosis and cellular demise [4]. Thus, the dual role of ROS in cancer progression is governed by this threshold, where controlled ROS levels support tumor growth, while excessive ROS accumulation leads to cytotoxicity and tumor suppression.

Thus, with this, further interest has been gained to develop pro-oxidants as strategies to kill cancer cells, by ROS-modulating agents. In this review, we have highlighted the potential and challenges associated with utilising pro-oxidants for cancer therapy, emphasising the need for targeted delivery and a deeper understanding of the mechanisms involved.

Redox Biology and the Prooxidant–Antioxidant Balance in Cancer

Redox biology is a key part of cellular function that maintains metabolic stability by balancing oxidation and reduction reactions. The accuracy of intracellular signalling is crucial in keeping this balance. Superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) are all types of ROS that are constantly produced naturally by-products of metabolic processes [5]. The ETC (Electron Transfer Chain), cytochrome P450 enzymes are amongst the major contributors of ROS. ROS must be present at extremely balanced levels for cell-to-cell communication, cell development, and a healthy immunological response. Cells protect themselves with an elaborate antioxidant system that includes a multitude of enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), along with peroxiredoxins and thioredoxin reductase (TrxR) [6]. Oncogenic stimuli that drive elevations in the mitochondrial activity and metabolic flux—resulting in chronic oxidative stress—including RAS, MYC, and PI3K/Akt activation, as well as the loss of tumor suppressors such p53. Notably, epithelial–mesenchymal transition (EMT) and genomic instability may be two ways modest oxidative stress promotes tumor formation [7] Redox-sensitive transcription factors including NF-κB, HIF-1α, and AP-1 are activated by this ongoing stress and aid in cell survival, blood vessel growth, and dissemination [8]. However, cancer cells adapt their antioxidant systems to survive [2]. Transcription regulators like NRF2 play a key role by activating important antioxidant genes (such as GCLC, NQO1, HO-1, and SLC7A11) that protect cells from damaging ROS while maintaining a tight oxidative balance that supports growth and prevents cell death [9]. GSH & Trx systems are vital for redox homeostasis. Glutathione (GSH) is the main intracellular antioxidant, and the thioredoxin (Trx) system keeps protein thiols' redox states stable and influences redox-sensitive signaling pathways [10]. These processes work together to figure out how oxidative stress influences the survival of cancer cells. Mitochondria are very essential since they are where ROS are produced and controlled. This part goes into more information about how mitochondria cause oxidative stress and are essential key element in survival, proliferation, and resistance of cancer cells to treatment (Figure 1).

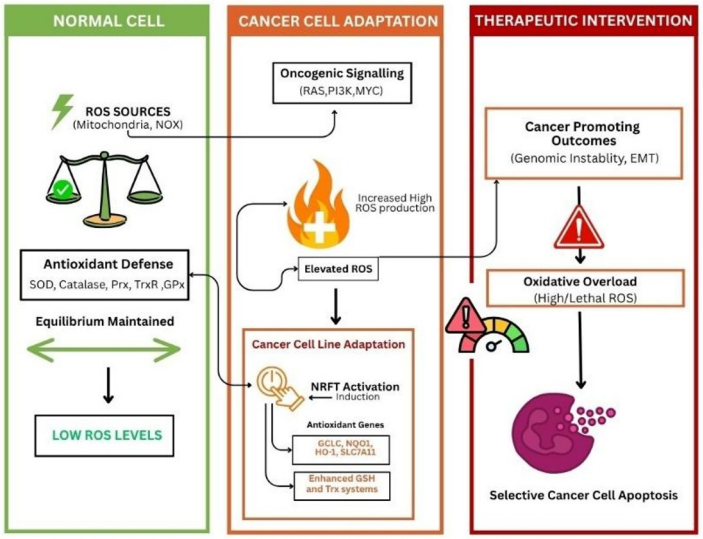

Fig.1- ROS balance in normal cells, cancer adaptation, and therapeutic oxidative overload. Normal cells maintain low ROS through balanced mitochondrial/NOX ROS generation and antioxidant defenses. Cancer cells experience elevated ROS driven by oncogenic signaling and survive by activating NRF2-dependent antioxidant pathways. Therapeutic interventions that push ROS beyond this adaptive capacity cause oxidative overload, leading to selective cancer cell apoptosis.

2. Mitochondria as a Central Hub for Oxidative Stress and Cancer Cell Survival

Mitochondria, recognized as the powerhouse of the cell, are essential for maintaining stability, regulating metabolism, and preserving redox equilibrium inside the cell. Mitochondria, recognized for their pivotal role in ATP synthesis and their varied functions in cellular communication, can regulate metabolic inputs in response to oxidative stress. [11]. Changes in the efficiency of oxidative phosphorylation (OXPHOS) and an increase in glycolytic flux both causes more reactive oxygen species to be produce (ROS) [5]. Reactive oxygen species (ROS) assist with signaling, proliferation, and adaptation at low to moderate levels. However, excess of them can damage macromolecules, showing how vulnerable mitochondria are in cancer cells. Antioxidant enzymes such as glutathione peroxidase (GPx), catalase, and superoxide dismutase (SOD) effectively neutralize these radicals under normal conditions to maintain cellular redox equilibrium [9].

In cancer, however, oncogenic signalling and heightened mitochondrial activity amplify electron leakage, causing chronic ROS accumulation and oxidative stress [5]. Persistent oxidative pressure induces genomic instability, activates oncogenes, and accelerates tumor progression [2]. At the same time, mitochondrial membrane potential (Δψm), calcium balance, and mtDNA integrity problems make OXPHOS even harder and increase ROS generation (Tan et al., 2025). Mitochondrial DNA (mtDNA) is very vulnerable to oxidative damage owing to its strong interaction with the inner membrane, which aggravates genomic instability in numerous cancer types [9]. In cancer, mitochondrial dynamics—fusion and fission—are also changed to keep metabolic flexibility and oxidative stress resistance [2]. Curcumin, resveratrol, sulforaphane, berberine, and quercetin are some phytochemical prooxidants that use these mitochondrial weaknesses to make more ROS or block antioxidant defenses. This induces oxidative stress and selectively eradicates cancer cells [11]. In cancer cells, mitochondria are the metabolic engine and redox regulator. Their capacity to endure mild oxidative stress while being susceptible to elevated reactive oxygen species places them at the forefront of redox-mediated cancer biology and as a promising target for therapeutic intervention.

2.1 Mechanistic Pathways of Prooxidant-Induced Apoptosis in Cancer Cells

Natural phytocompounds that are pro-oxidant in nature tend to selectively exploit the high basal levels of ROS and the disturbed redox buffering in cancer cells [12-13]. Too much of the ROS whether they originate from mitochondria or the cytosol, facilitate the opening of the mPTP by oxidizing regulatory components and disrupting mitochondrial calcium handling [13]. Persistent mPTP opening causes Δψm to be depleted, ATP production to stop, and Cytochrome-c, to be released into the cytosol. Apoptosis-Protase-Activating Factor-1 (APAF-1) and pro-caspase-9 combine with cytosolic cytochrome c to produce the apoptosome, which in turn triggers caspase-9 and executioner caspase activity, which cleaves DNA and destroys the cell. ROS-induced cytotoxicity frequently results in this intrinsic pathway that is focused on the mitochondria [13]. Alongside mitochondrial processes, ROS functions as a secondary messenger that regulates redox-sensitive signaling modules. Reduced thioredoxin (Trx) keeps ASK1 inactive. When ROS oxidizes Trx, it frees ASK1, which then autophosphorylates and activates

downstream MAPKs like JNK and p38 [14]. Bcl-2 family proteins are phosphorylated causing the activation of JNK/p38. This increases the permeability of the mitochondria's outer membrane (MOMP) and increases cytochrome-c release and apoptotic commitment through mPTP-dependent processes. Therefore, under pro-oxidant stress, ASK1/JNK signaling acts both upstream and in feed-forward loops that amplify mitochondrial dysfunction [12]. Pro-oxidant phytocompounds act at several nodes of this network. Some compounds directly increase mitochondrial ROS production (e.g., through interference with electron transport chain complexes I or III), others deplete cellular thiols (glutathione, Trx) or inhibit antioxidant enzymes (glutathione peroxidase, SOD), and several simultaneously trigger ASK1-JNK activation (e.g., berberine, plumbagin). These multimodal actions make phytocompounds particularly effective at breaching the redox threshold that precipitates mPTP opening and apoptotic signalling in malignant cells while sparing normal cells, which typically possess greater reserve antioxidant capacity [11].

In NSCLC mouse models, berberine has shown increased apoptosis. This leads to ROS buildup thus activating the ROS/ASK1/JNK signaling pathway, confirming the ASK1-dependent mechanism in a phytochemical environment. [15]. In the same way, naphthoquinone-class phytochemicals (including plumbagin) and some polyphenols show dose-dependent pro-oxidant action that leads to mitochondrial depolarization, caspase activation and apoptosis [16]. Many polyphenols have a pro-oxidant impact, depending on the circumstances and dosage. This implies that they can function as pro-oxidants at greater, more therapeutic concentrations and as antioxidants at lower concentrations.

This dual vulnerability has immediate therapeutic implications. Pro-oxidant phytocompounds can target cancer cells by (i) exploiting redox differences for selectivity, (ii) employing both kinases signaling (ASK1/MAPK) and mitochondria-mediated apoptosis to induce cell death synergistically, and (iii) enhancing the sensitivity of resistant cells to conventional chemotherapies that elevate oxidative stress. Due to possible disadvantages, such as inadvertent oxidative damage to healthy tissues and the adaptive enhancement of antioxidant responses (e.g., Nrf2/GSH induction) within tumor cells, combinatorial strategies (e.g., phytochemical pro-oxidants coupled with inhibitors of antioxidant pathways) and delivery systems (nanocarriers, targeted conjugates) are required to improve tumor selectivity and bioavailability. In summary, pro-oxidant phytocompounds have anticancer effects by perturbing tumor redox homeostasis and inducing a coordinated dysfunction of mitochondrial activity in conjunction with redox-sensitive MAPK signaling (ASK1/JNK/p38) [17-18].This convergence on mitochondrial permeabilization and caspase activation provides a mechanistically complex and therapeutically promising foundation for redox-targeted, mitochondria-directed cancer therapies, dependent on careful evaluation of delivery, dose, and resistance mechanisms.

3. Pro-oxidant Phytocompounds: Classification and Mechanisms

Prooxidants are substances—either produced within the body (endobiotics) or introduced from outside (xenobiotics)—that produce oxidative stress by producing ROS or weakening the body's natural antioxidant defences [19]. Interestingly, this very oxidative stress can be turned into an advantage when treating cancer. Cancer cells have a high tolerance to oxidative stress which is a result of their abnormal metabolism and rapid division, pushing them beyond their tolerance limit can lead to cell damage and death [20]. Prooxidant comprise of 2 classes-natural and synthetic. These consist of radiation, certain compounds, and even photodynamic treatment (PDT). Chemicals like menadione and arsenic trioxide, for example, are known to increase the generation of ROS and are already being utilized in clinical settings to kill cancer cells. [21]. Radiation, too, kills cancer cells by producing ROS through water radiolysis, while PDT relies on light-activated compounds that create singlet oxygen and other reactive species to cause localised oxidative stress in tumours [22]. Apart from these, several everyday substances and physiological conditions can act as prooxidants. Drugs like paracetamol and methotrexate and even stress or intense physical exertion can disturb the body's redox balance, leading to higher ROS generation [23]. Natural prooxidants of all kinds, particularly those originating from plants, have drawn increasing interest due to their specific toxicity to cancer cells. Depending on the environment, plant substances such as terpenoids (curcumin, resveratrol, sulforaphane), flavonoids (quercetin, kaempferol), and phenolics (found in berries and leafy greens) can function as both prooxidants and antioxidants [24-25]. Synthetic prooxidants, such as paraquat, tert-butyl hydroperoxide, and chemotherapeutic drugs like doxorubicin and cisplatin, also operate through similar pathways—by producing free radicals and disrupting antioxidant systems [26]. Together, both natural and synthetic prooxidants exploit the oxidative weak points of tumour cells, making them promising agents in targeted redox-based therapies. Natural phytocompounds are special because they are both powerful and safe. These bioactive compounds, which come from plants and food, not only raise intracellular ROS levels but also change the redox-sensitive pathways that cancer cells use to stay alive and grow [27] **(Figure 2) (Table 1)**. Natural prooxidant chemicals, or NPCs, are becoming important for cancer treatments that target the mitochondria by using the oxidative weaknesses that are already in tumors. The next section examines some of the most researched NPCs, their plant origins, and how they act as prooxidants causing the cancer cells to undergo apoptosis in response to oxidative stress.

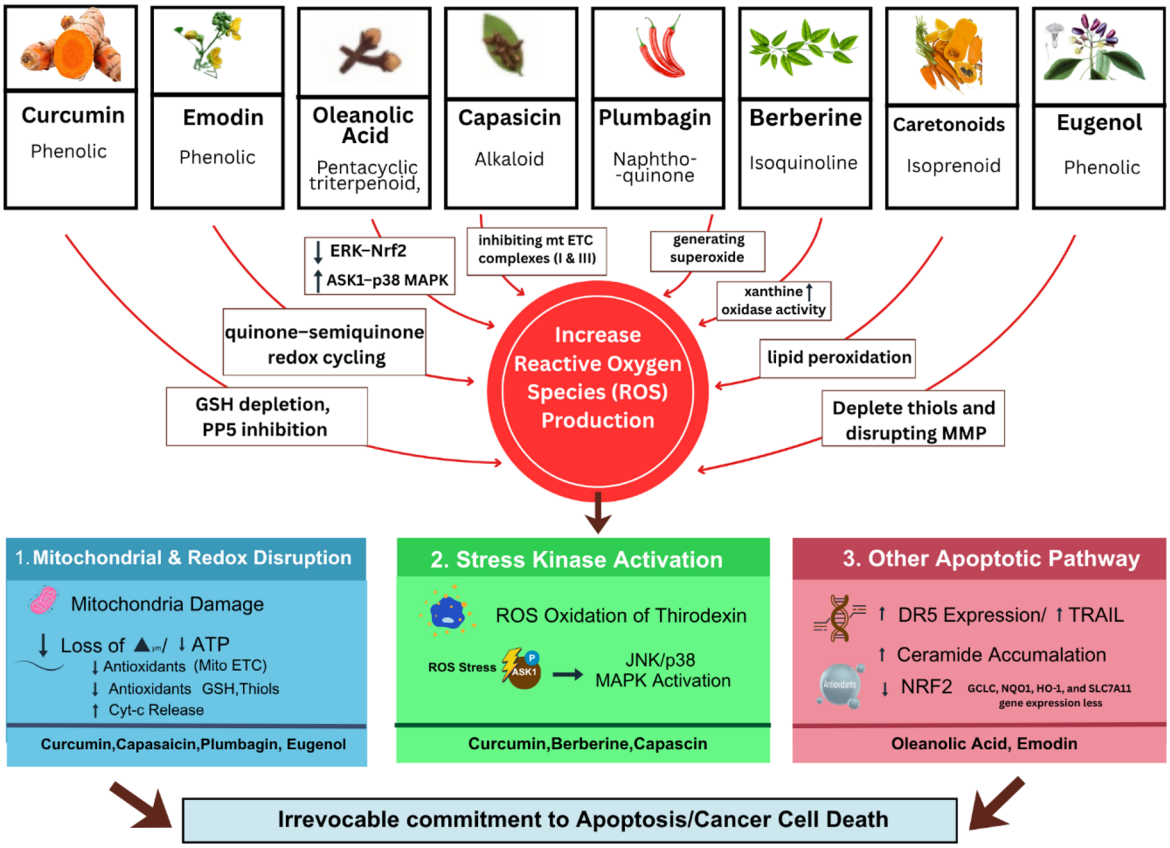

Fig. 2- Natural bioactive compounds induce ROS-mediated cancer cell death through mitochondrial disruption, stress-kinase activation, and apoptotic signalling. Phenolic, alkaloid, terpenoid, and quinone-based compounds (including curcumin, emodin, oleanolic acid, capsaicin, plumbagin, berberine, carotenoids, and eugenol) elevate intracellular ROS via mechanisms such as mitochondrial ETC inhibition, redox cycling, thiol depletion, lipid peroxidation, and ERK–NRF2 suppression with ASK1–p38 activation. The resulting oxidative stress triggers mitochondrial dysfunction, JNK/p38-mediated stress-kinase signalling, and additional apoptotic pathways (e.g., DR5/TRAIL activation, ceramide accumulation), collectively driving irreversible cancer cell apoptosis.

3.1 Curcumin

Curcumin is a phenolic compound possessing prooxidant properties that promote antiproliferation and death in cancer cells [28]. Obtained from the rhizomes of *Curcuma longa L*, curcumin interferes with redox processes in malignant cells, which results in increased formation of ROS. Curcumin induction activates JNK and causes Foxo3 to go to the nucleus in melanoma cells. This causes cells to make too many ROS, which kills them. Curcumin reduces the expression of protein phosphatase 5, which inhibits JNK, leading to increased ROS generation [29]. Curcumin activates sphingomyelinase, which leads to the synthesis of ceramide. This is followed by the depletion of glutathione, which causes an increase in ROS production [30]. The result shows apoptosis in prostate cancerous cells.

Curcumin activates p53, a tumor suppressor, which damages mitochondria and raises oxidative stress. This causes thiols to oxidize, the membrane potential to drop, and ATP synthesis to stop, which starts the process of cellular apoptosis [30]. Curcumin-induced reactive oxygen species (ROS) formation results in the upregulation of death receptor 5 (DR5) in breast cancer cells and human kidney carcinoma cells, leading to the overexpression of TRAIL [31-32]

3.2 Emodin

Emodin which is chemically (1,3,8-trihydroxy-6-methyl-anthraquinone) and is sourced from *Rhamnaceae, Polygonaceae, Rubiaceae, and Fabaceae*. Reports reveal that emodin which is a naturally occurring

anthraquinone derivative demonstrates anticancer effects against human lung adenoma cells and breast cancer cells.
Recent research demonstrates that emodin is an anthraquinone which is structurally similar to DMNQ and mitochondrial ubiquinone, acting as a ROS generator. Quinone is a highly redox-active compound that generates a redox cycle through its semiquinone radicals. Further studies have shown that the quinoid structure of emodin can be changed into a semiquinone radical intermediate. This intermediate reacts with ROS species and thus induce apoptosis in several tumorigenic cells [33-34.].
When there is too much ROS, it alters how Bcl-2 and Bax proteins are spread out and what they perform in cells. When emodin is added to cells, the level of Bcl-2 goes down & the amount of Bax protein goes up. This transfers Bax to the OMM where it makes cytochrome c leave the mitochondria and enter the cytosol, which triggers apoptosis [35-36].

3.3 Oleanolic Acid

Oleanolic acid derived from ginseng (Panax spp.) and olive (Olea europaea) is a pentacyclic triterpenoid [37]. Oleanolic acid has shown its anti-tumorigenic property on breast and pancreatic cancer cells. When cancer cells are exposed with OA, it induces suppression of ERK signalling pathway this causes increase in ROS levels. The phosphorylation of ASK1 in cancer cells also causes further enhancement in ROS [41]. Nrf2-specific siRNA, when it binds to the promoter sequence was found to enhance the transcription of a group of antioxidative genes. The level of Nrf2 was increased in cancerous cells in dose dose-dependent manner when exposed to oleanolic acid [38-40]
Upon OA exposure to cancer cells, ROS generation takes place which subsequently activates cell death via apoptosis signal-regulating kinase 1 and the downstream kinase p38 MAPK [40]

3.4 Capsaicin

Capsaicin is an alkaloid that comes from plants in the Capsicum genus, which has chili peppers in it. Capsaicin has been reported to cause cell death in colorectal, prostate, bladder, and pancreatic cancer by elevating the ROS beyond threshold [42]. Capsaicin regulates elevated ROS levels in pancreatic cells, which is because of the substantial inhibition of the mitochondrial ETC, complex I, complex III, and ATP levels. Capsaicin is known to cause apoptosis by increasing nitric oxide (NO) levels in colon cancer [42]. Further Pramanik et al (2011) reported that Capsaicin subsequently increases the production of caspase cascade, thus activating both mitochondrial and death-receptor pathways [43]. In cancer cells, the build-up of ROS caused by capsaicin causes mitochondrial membranes to lose their charge, which turns on JNK in a way that depends on ROS. This leads to the build-up of ceramide and the death of cells [44],

3.5 Plumbagin

Plumbagin is a naphthoquinone originating from the roots of *Plumbago zeylanica L*. Research indicates that plumbagin exhibits antitumorigenic properties against different types of cancer such as breast, colon and hepatocellular carcinoma [45].
Plumbagin is known to being cytotoxic in nature which is linked to its quinone core, which enables electron conduction and the formation of superoxide. In cancerous cells, plumbagin also forms semiquinone radical under aerobic conditions, which results in the generation of reactive oxygen species (ROS) via the redox cycle [46]. Plumbagin generates excessive reactive oxygen species (ROS), leading to DNA damage and cytotoxic effects on tumor cells. [47]
Excessive ROS results in the inhibition of NF-κB , which lowers the levels of the anti-apoptotic protein Bcl-2 and raises the levels of the pro-apoptotic protein cytochrome-c [48]

3.6 Berberine

Berberine (BBR) is an isoquinoline-like alkaloid extracted from *Phellodendri Cortex*, showing anticancer properties against pancreatic and prostate cancer cells [49]. Park et al. (2014) demonstrates that berberine improves the performance of xanthine oxidase (XO), triggering production of ROS. XO is a significant producer of free radicals and H2O2 in cellular and tissue contexts. Scientists found that berberine increased the activity of XO in pancreatic cancer cells, which led to the death of cancer cells by raising the levels of cytochrome c [11] [50]
Recent research has shown generation of mitochondrial-dependent ROS from the dosage of berberine facilitates the cyt-c release thus causing induction of apoptosis in human colon cancer cells [51]

3.7 Carotenoids

Carotenoids are a type of isoprenoid that comes from Sea buckthorn berries, lutein from Macula lutea, and zeaxanthin from Zea mays. Carotenoids, including β-carotene, lutein, zeaxanthin, α-carotene and β-cryptoxanthin, are present in tissue and blood and exhibit anticancer properties [52]
Research indicates that cancerous cells exhibit reduced levels of antioxidant enzymes, which impede the regeneration of carotenoid radicals (CAR•+). Under high oxidative stress conditions, carotenoids can be subjected to one-electron oxidation, leading to the formation of carotenoid radical cations, denoted as CAR•+. In general, carotenoid radical cations can be reduced back to their native forms through antioxidant systems like vitamin C or other reductants. However, under conditions where this reduction process is impaired, carotenoid radical cations can act as a pro-oxidant species. These carotenoid radicals can react with nearby biomolecules, leading to a series of radical chain reactions, thus promoting lipid peroxidation and oxidative damage to cellular components. In this regard, carotenoids can act as a pro-oxidant under high oxidative stress conditions [53].
An increased level of ROS in human hepatopancreatic carcinoma leads to elevated expression of caspase-3 and caspase-7, resulting in a reduction of Bax-1 protein levels, which induces apoptosis and the cleavage of cancerous cells [54].

3.8 Eugenol

Eugenol is an aromatic pro-oxidant that originates from the clove plant (Syzygium aromaticum (L.)). Eugenol functions as a pro-oxidant by elevating levels of reactive oxygen species (ROS), which are associated with various cancers, including blood cancers, lung cancer, colon cancer, colon cancer, skin cancer, gastric cancer, ovarian cancer, cervical cancer, and bladder cancer [55].
The nature of eugenol induction causes cancer cells to produce excessive ROS leading to apoptosis by lowering the MMP in carcinoma cells and by running out of non-protein thiols [55-56]. Increased ROS production led to DNA fragmentation, a characteristic of apoptosis in eugenol-treated colon cancer cells [56]. Also, higher levels of ROS in colon cancer cells are linked to higher levels of p53 activation, a protein that stops tumors from growing and controls how cells respond to stress [57]. Activated p53 subsequently promotes transcription levels of pro-apoptotic genes like BAX while supressing BCL-2 which is an anti-apoptotic protein. This results in an imbalance in redox homeostasis, inducing mitochondrial permeability transition and the release of cytochrome c into the cytosol by ROS, ultimately leading to DNA fragmentation via intrinsic apoptotic pathway [56].

Table 1: Natural prooxidants effective against various cancers along with the mode of action.

Sno.	Natural Prooxidants	Type Of Cancer	Effect On Cancer Cells	Type Of Cell Death	References
1	CURCUMIN	Colon cancer, breast cancer	Excessive ROS production	Apoptosis	[29-30]
2	EMODIN	Human lung adenoma cells and breast cancer cells	Excessive ROS generation	Apoptosis	[33]

3	OLEANOLIC ACID	Breast cancer, pancreatic cancer	Suppression of ERK signalling pathway leading to excessive ROS production	Apoptosis	[39]
4	CAPSAICIN	Pancreatic Cancer, Breast Cancer	Inhibition of mitochondrial electron transport chain (ETC)	Apoptosis	[43] [44]
5	PLUMBAGIN	Breast cancer, melanoma,	Excessive ROS production	Apoptosis	[47-48]
6	BERBERINE	Prostate cancer, pancreatic cancer	Causes dysfunction of electron transport chain which leads to excessive ROS production	Apoptosis	[49-50]

7	CAROTENOIDS	Colorectal adenocarcinomas, breast, and hepatic adenocarcinoma	Enhances the ROS level by catalysing and propagating the radical chain reactions	Apoptosis	[52]
8	EUGENOL	Colon cancer, leukaemia	Excessive ROS production	Apoptosis	[56-57]

Fig. 2- Natural bioactive compounds induce ROS-mediated cancer cell death through mitochondrial disruption, stress-kinase activation, and apoptotic signaling. Phenolic, alkaloid, terpenoid, and quinone-based compounds (including curcumin, emodin, oleanolic acid, capsaicin, plumbagin, berberine, carotenoids, and eugenol) elevate intracellular ROS via mechanisms such as mitochondrial ETC inhibition, redox cycling, thiol depletion, lipid peroxidation, and ERK–NRF2 suppression with ASK1–p38 activation. The resulting oxidative stress triggers mitochondrial dysfunction, JNK/p38-mediated stress-kinase signaling, and additional apoptotic pathways (e.g., DR5/TRAIL activation, ceramide accumulation), collectively driving irreversible cancer cell apoptosis.

4. **Limitations**

Prior research has indicated diverse therapeutic advantages of natural prooxidants; yet, each exhibits particular constraints. For example, curcumin is limited in the development of therapeutic drugs because it doesn't dissolve well in water, isn't absorbed well, doesn't distribute well in the body, is metabolized quickly, and is excreted quickly [58] Eugenol, while exhibiting significant properties, appears to induce irritation and allergic reactions. Eugenol even has cytotoxic effects by turning off proteins and lysine attachment, which damages cells. This means that humans can only eat it [59].

Interesting research on carotenoids indicates that higher doses of carotenoid supplements lead to elevated keratinized squamous metaplasia, regarded as a precancerous lesion, thereby promoting increased cell proliferation. Capsaicin has positive effects on anti-tumor activity, but it can also cause a burning sensation on the skin in adults and diarrhea, conjunctivitis, and blepharospasm in children [60]. Moreover, emodin could disrupt glutathione (GSH) and fatty acid metabolism in human hepatic cells [61]. When given in high doses, emodin changes the way testicular genes are expressed, lowers the calcium ion concentration in sperm, and stops tyrosine phosphorylation, which is toxic to reproduction [61]. Anthracycline, a synthetic pro-oxidant utilized as an anticancer agent, exhibits specific toxic effects on the cardiovascular system in a dose-dependent manner, leading to doxorubicin-induced congestive heart failure and a subsequent reduction in the production of less cardiotoxic anthracycline drugs [62]. Cisplatin is linked to various systemic toxicities, with nephrotoxicity being the most prevalent, a condition exacerbated by aminoglycoside use. In the kidneys, cisplatin leads to an increased quantity of cytoplasmic vesicles, a localized loss of the microvilli brush border, and the shedding of entirely necrotic cells into the tubular lumen [63].

5. Conclusion

Cancerous cells serve to produce ROS more than normal cells because of increased metabolism, uncontrolled proliferation, and mutation. This heightened level of ROS in cancer cells serves as a means for cell survival and increased redox potential, which is beneficial for cancerous cells. But pushing the cancer cells beyond this threshold by the prooxidants can cause the activation of various molecular death pathways. In this study, we have discussed various natural and synthetic prooxidants that have been discovered, which serve as an effective means for cancer therapeutics by enhancing the level of ROS above the threshold and resulting in cell apoptosis.

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Abbreviations:
ROS- Reactive Oxygen Species
ETC- Electron Transport Chain
mPTP- Mitochondrial Permeability Transition Pore
NPC- Natural Phytocompound
MMP- Mitochondrial Membrane Potential