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Oxidative Stress and Cancer: Harnessing the Therapeutic Potential of Curcumin and Analogues Against Cancer

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Abstract

Reactive oxygen species (ROS) are a class of bioactive molecules that are the by-products of many cellular functions. These molecules are present in normal cells at homeostatic levels but have been studied extensively in cancer due to their dysregulation resulting in pro- and anti-tumorigenic environments. Completely understanding the paradoxical nature of ROS in cancer is imperative to fully realize its modulation as cancer therapy. Studies into ROS have shown far-reaching effects in cancer, including how ROS levels regulate signaling, response to treatment, drug resistance, etc. Many drugs were studied with the hopes of regulating the ROS levels in cancer; however, patient response varied. Plant-derived medications offered new avenues of drug treatment over the last few decades, and the phytochemical Curcumin gained ground as an interesting cancer therapeutic. Curcumin is an active phenolic compound used in traditional medicine around the world. Although it suffers from a poor pharmacokinetic profile, Curcumin exerts anti-tumorigenic, as well as ROS-modulating activities. Analogs and derivatives of Curcumin are under development to improve upon its anti-cancer properties and enhance its bioavailability, currently a major limitation of its usage. This review highlights ROS function in cancer treatment focused on ROS, including Curcumin and its analogs.

Keywords

Oxidative Stress; Curcumin; Curcumin analogs; Cancer therapy; ROS-modulating drugs

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INTRODUCTION

Reactive Oxygen Species

Reactive Oxygen Species (ROS) are chemically reactive species containing diatomic oxygen, including peroxides, superoxide, hydroxyl radicals, and singlet oxygen.[1] ROS is an over-arching term for derivatives of molecular oxygen that were originally thought to be purely by-products of metabolic activities, such as aerobic respiration, in cells. ROS can include radicals, molecules with an unpaired electron, such as superoxide and hydroxyl radicals, or non-radical molecules, like hydrogen peroxide and hypochlorite. ROS are thought to be tumor-suppressing agents since they are produced as a result of the administration of most chemotherapeutic drugs to activate cell death. However, in some cases they exert pro-tumorigenic functions.[2–4] ROS are generated at the plasma membrane level by nicotinamide adenine dinucleotide phosphate (NADPH) or at the mitochondrial level by nicotinamide adenine dinucleotide (NAD) dependent reactions. The evaluation of molecular interactions between certain ROS molecules and particular targets in redox signaling pathways is the focus of research, as their manipulation can result in a wide range of physiological effects. As a result, significant progress has been made in our understanding of how these oxidants affect physiology and disease, including the neurological, cardiovascular, and immunological systems, skeletal muscle, metabolism, aging, and cancer.[5] Using drugs to simply increase or decrease ROS levels has had mediocre results. More targeted approaches were developed, and ROS-modulating drugs are being investigated in many diseases, including cancer.

Generation of ROS

ROS levels are maintained in a healthy cell via various detoxifying processes controlled by antioxidant enzymes. As a result, ROS homeostasis is successfully regulated which helps maintain the redox balance in healthy cells. Numerous endogenous and exogenous biological functions produce ROS, which lead to over- or under-production in response to various stimuli, and result in cellular responses ranging from normal signaling mechanisms to cell death and DNA damage (Figure 1). At the mitochondrial level, specifically the inner mitochondrial membrane, where most ROS are generated during oxidative phosphorylation, there are three major complexes that result in the bulk of ROS production. Complex I (CI) of the electron transport chain (ETC) generates ROS during electron transfer from NADH to Coenzyme Q (CoQ), while CII produces ROS through potential electron leakage. CIII can result in ROS through leaking of a single electron that moves freely through CIII, resulting in non-enzymatic ROS production.[6]

Due to the action of multiple antioxidant systems, which regulate ROS generation by altering metabolic and signaling pathways, normal cells can maintain oxidative equilibrium.[3] Antioxidant defense mechanisms encourage cell death when ROS levels are continually elevated.[7] However, oxidative stress causes harm to numerous molecules and cell structures, resulting in the emergence of pathological conditions like inflammation, aging, cancer, and neurological diseases. Further, ROS are strongly associated with carcinogenesis. To understand the mechanisms of tumor initiation and progression, as well as the development of treatments, it is crucial to summarize the most recent evidence on ROS biology.

Antioxidant Defense and Redox Homeostasis

Oxidative stress is generated when there is an imbalance between the production and elimination of ROS. As mentioned, low levels of ROS promote signal transduction to help the cancer cells proliferate, differentiate, migrate, and invade.[8–10] At high levels, however, ROS induces lipid peroxidation, DNA and RNA damage, protein backbone damage, and alteration of enzyme activity.[11] As such, it is vital for cell survival to prevent accumulation of ROS and maintain redox homeostasis. Various mechanisms, including hypoxia, metabolic defects, ER stress, and oncogenes affect basal levels of ROS.[5] Fortunately, there are several mechanisms by which cells deploy endogenous and exogenous antioxidants or free radical scavengers.[12]

Within many cells, activation of the transcription factor, nuclear factor erythroid 2-related factor 2 (NRF2), plays a pivotal role in regulating antioxidant functions.[3,7,13] Under resting conditions, NRF2 is bound to and constitutively degraded by Kelch-like ECH-associated protein 1 (KEAP1)-Cullin 3 (CUL2) E3 ligase complex. However, when cells experience oxidative stress, NRF2 dissociates from KEAP1 and translocates to the nucleus. In the nucleus, NRF2 binds to and activates the antioxidant response element (ARE) in various antioxidant target genes.[4,14,15] AREs are enhancer sequences found in the promoter region of genes encoding for various antioxidant enzymes. These antioxidants include superoxide dismutases (SODs), catalase (CAT), glutathione reductase, glutathione peroxidases (GPx), UDP-glycosyltransferases (UGTs), NADPH quinone oxidoreductase 1 (NQO1), heme oxygenase (HMOX1), peroxiredoxins (PRx), thioredoxin (TRx), and thioredoxin reductase (TRxR).[16,17] SODs provide the first line of defense against free radicals through the conversion of O_2^- to H_2O_2. The H_2O_2 is neutralized to yield water and O_2 by CAT. Non-enzymatic molecules play a key role in ROS maintenance including glutathione, flavonoids, and vitamins C and E. Overall, the antioxidant defense of tumor cells play a major role in their ability to survive, as there is a delicate balance between the production and neutralization of ROS.

CANCER and ROS

Cancer is a disease in which the body’s cells divide uncontrollably and spread throughout the body. Cancer remains one of the leading causes of death globally, second only to cardiovascular disease. Approximately 1,958,310 new cases and 609,829 deaths are projected to occur in the United States in 2023.[18] Numerous research studies and trials are conducted to better understand and develop new treatment for this deadly disease.

For decades, the activation of oncogenes and inactivation of tumor suppressor genes were thought to be the main cause of cancer development and progression− a phenomenon known as the ‘oncogene addiction’.[19] However, recent studies emphasized the importance of the metabolic changes that cancer cells undergo, as these changes help to evade normal cellular limitations and aid in cancer cell proliferation.[20] Most notable is the increase in aerobic glycolysis, known as the Warburg effect. Cancer cells typically exhibit higher metabolic rates than normal cells, and the amount of ROS production is increased as a result.[7] This increase in ROS is countered by the cells’ ability to upregulate their antioxidant mechanisms.[3] There is a delicate balance between the production and neutralization of ROS,

resulting in a paradoxical effect on cancer cells. Previous research showed that at moderate to low levels, ROS promoted signal transduction to help the cancer cells proliferation, differentiation, migration, and invasion.[8,10,19] At high levels, however, ROS is detrimental to cancer cells survival due to DNA, lipid, and protein damage. Increased levels of ROS induced apoptosis in multiple myeloma and colorectal cancer cells in previous studies.[21,22] Therefore, inducing a high concentration of ROS in cancer cells provides a potential strategy for cancer therapy.

In the early stages of cancer, ROS has pro-oncogenic actions, and antioxidant levels are decreased. Increased ROS production due to elevated metabolic function leads to constitutive activation of various signaling pathways. PI3K/Akt/mTOR mediated survival signaling is commonly seen upon increases of ROS in cancer cells and results in tumor growth and progression.[23,24] ROS also contributes to tumor progression through action against proteins such as PTEN and PTP1B to downregulate apoptosis and inhibit anti-growth signaling.[25,26] However, high levels of ROS present in cancer cells is harmful to tumor progression and tumor cell viability. Abnormal levels of antioxidative enzymes are often found among cancer patients along with elevated levels of ROS and increased oxidative stress.[12,27] Lowering the amounts of ROS within cells through antioxidants is used to prevent the proliferation of cancer cells from occurring.[28] However, raising intracellular levels of ROS leaves cells with lower defenses and increases the chances of death caused by oxidative stress. Increasing levels of ROS may potentially result in cell death for cancer cells while saving normal cells. However, increasing ROS levels could lead to elevated mutational burden in cancer cells, warranting pro-tumorigenic effects.[28]

ROS and CANCER THERAPY

The sliding scale of ROS involvement in cancer makes ROS an interesting target of cancer therapies. New research suggested that instead of solely targeting oncogenes or tumor suppressor genes, the strengthened immune surveillance, aneuploidy, and increased metabolism in cancer cells that ensure survival should also be targeted. Manipulation of ROS pathways is a potential step to provide effective forms of cancer therapy.[29,30]

In the early stages of cancer, it is beneficial to maintain low ROS levels to reduce the survival of tumor-initiating cells (TICs) due to TICs' ability to survive in high levels of ROS through an upregulation of antioxidant levels.[31] If high levels of ROS are present in the early stages of tumor development, then pre-neoplastic cells develop strong antioxidant mechanisms, allowing for the development of drug-resistant tumor cells.[30] Targeting these antioxidant mechanisms allow for cancer cell-specific therapies.

Oncogenes and tumor suppressor genes heavily impact the initiation and progression of tumorigenesis. Studies showed that oncogenes affect NRF2 regulation, and FOXO transcription factors enhanced oncogenic functions due to oncogenic factors like b-catenin.[5] Tumor suppressors were found to activate or suppress antioxidant gene expression.[5] For example, BRCA1 is a required regulator of NRF2 if an efficient antioxidant response is to be produced. But, ataxia telangiectasia mutate (ATM), another tumor suppressor gene that regulates ROS levels, is found to cause bone marrow failure in mice.[5] PKM2 functions as

an oncogene and plays a significant role when ROS levels are high, leading to increased NADPH synthesis, allowing for solid tumors to detach from their matrix.[5,32]

ROS scavengers present a potential anticancer therapeutic strategy. Numerous studies have been conducted in which antioxidants, often Vitamin E, C, and selenium were implemented and found to have positive results, such as reduced mortality rates. Another potential anti-cancer therapy focuses on increasing ROS by using drugs that target two of the three major antioxidant pathways. Currently, chemotherapy induces oxidative stress leading to cell death from potential excessive ROS levels in cancer cells. Platinum conjugated complexes and anthracy-clines are also used to produce excess levels of ROS.[5] Arsenic trioxide and 2-methoxyestradiol showed positive results against different cancers through increased levels of ROS.[33,34] Another effective method for killing cancer cells is using an agent that increases oxidative stress and inhibits HSP90. Inhibiting the enzyme poly (ADP-ribose) polymerase (PARP) is effective in treating breast cancer, and ionizing radiation is found to dramatically increase ROS levels, especially through the activation of NADPH oxidase via radiation exposure.[5] Taking advantage of multiple aspects of ROS manipulation in cancer therapy has led to multiple treatments, including a variety that were successful in a clinical trial setting (Table 1).

ROS Therapy Clinical Trials

Vitamin C or ascorbic acid was involved in various clinical trials; however, the ongoing clinical trial NCT03418038 is observing deeper exploratory effects. Aside from safety and response rates, TET2MT allele, DNA methylation, and plasma cytokine activity are also being studied. Mangafodipir is a traditional MRI contrast agent, however it exhibits antioxidant properties through manganese superoxide dismutase mimetic activity.[35] Clinical trial NCT00727922 aimed to show Mangafodipir's neuroprotective properties in cancer patients who underwent oxaliplatin treatment. Mangafodipir showed significant results with 77% of patients treated with both oxaliplatin and Mangafodipir exhibiting improved or stabilized neuropathy.[36] A study that aimed to show the relationship between resectable colon cancer patients and Niclosamide treatment (NCT02687009) was opened for recruitment in 2016. The phase 1 study was canceled due to low recruitment, however recent evidence suggests Niclosamide, an effective Wnt signaling pathway regulator, as a candidate for colon cancer management as Wnt signaling is heavily upregulated in most patients.[37,38] Besides its' antioxidant properties, Quercetin exhibited the ability to regulate various cancer signaling pathways including PI3K/Akt/mTOR, MAPK/ERK, and Wnt signaling showing anti-metastatic, anti-angiogenic, and anti-proliferative potential.[39] Quercetin is part of clinical trial NCT04733534, an ongoing study aimed at improving the quality of life in adult survivors of childhood cancers. Improvement of frailty and markers observing senescence, inflammation, bone resorption, insulin resistance, and cognitive function are under study. Dimethyl Fumarate was studied in concert with Temozolomide and radiation therapy for patients with glioblastoma multiforme in clinical trial NCT02337426. A maximum tolerated dose was recommended at 240 mg three times daily, and patients saw varying degrees of progression-free survival with a median of 8.7 months and a median survival rate of 13.8 months was noted.[40] Clinical trial NCT04566328 observed Bortezomib in combination with dexamethasone, daratumumab, and lenalidomide for patients with

multiple myeloma. The study is still recruiting, and primary endpoints include overall survival with secondary endpoints aimed at adverse events, including neurotoxicity, recovery rate, and non-hematologic adverse events. Arsenic Trioxide is an interesting anti-cancer candidate that was tested with a variety of cancers for its ability to affect cancer stem-like cells, induce cell cycle arrest and apoptosis, chemo-sensitize, and decrease angiogenic potential.[41] Many clinical trials involving arsenic trioxide were undertaken, one recruiting trial (NCT04897490) evaluates first line arsenic trioxide and all trans retinoic acid treatment for patients with acute promyelocytic leukemia. Primary outcomes include evaluation of overall survival and event free survival with secondary measures observing molecular remission rate, toxicity, and FLT3 as a prognostic marker. Curcumin (Cur) is involved in a plethora of clinical trials (Table 1) touching on a wide range of cancers. Taking advantage of Cur's innate antioxidant and anticancer abilities clinical trials are observing improvements in recurrence-free survival in pancreatic cancer (NCT02064673), safety and tolerability in metastatic treatment-resistant colorectal cancer (NCT01490996), tumor-induced inflammation reduction in endometrial carcinoma (NCT02017353), and efficacy and bioavailability in glioblastoma (NCT01712542).[41] The mechanisms by which Cur affects this array of systems and cancers are discussed in detail below.

CURCUMIN in CANCER THERAPY

Phytochemicals are plant metabolites that possess innate antioxidant properties. Plant by-products offer a unique approach to cancer therapeutics, and multiple drugs like vincristine and paclitaxel are already used in various cancers.[42] There is a high demand for medicines from plant origins; most have relatively low toxicity levels toward normal cells and offer safer alternatives over traditional chemically derived drugs.[43]

Cur is a phytochemical derived from *Curcuma longa*. A commonly used spice originating from Asia, Cur received attention as an anti-cancer therapy. Cur has a history of use in medicines in Asian countries where it was used as an anti-inflammatory and anti-dysenteric, and has recently shown antioxidant properties in the context of various disease instances.[44,45] Cur has become a popular drug for cancer therapy over the last few decades and multiple analogs have arisen based on Cur structure. Mechanistically, Cur has shown the ability to regulate a plethora of molecular targets lending to its anti-cancer properties (Figure 2). The transcription factor NF-kB is one of the longest known targets of Cur and its suppression in a variety of cancers including leukemia and melanoma.[46,47] NF-Kβ suppression from Cur interaction led to the identification of Cur's immunomodulatory effects on various cytokines and immune related proteins such as IL-6, TNF-α, and PD-L1 and is suggested as a potential adjuvant treatment for immunotherapy.[48–50] Regulation of several signaling pathways is evidence of the wide range of effects by Cur. PI3K/Akt, MAPK, and JAK/STAT regulation were noted in a variety of cancers with a long list of downstream target modulation occurring as a result of upstream Cur interference.[51]

The ROS interacting effects of Cur and its analogs were realized as important mechanisms in their ability to combat cancers. At a mechanistic level, multiple explanations are given for Cur and its capacity to perform ROS modulation. Both the keto-enol and phenolic group of Cur are thought to be the site responsible for radical scavenging, and other groups

have suggested that hydrogen cleavage is the preferred ROS interaction mechanism of Cur.[52] In clinical trials, Cur is shown to increase total antioxidant capacity (TAC) and decrease malondialdehyde.[53] It also affects energy metabolism and increases overall ROS accumulation in SiHa cervical cancer cells resulting in increased autophagy and G2/M phase cell cycle arrest.[54] Cur targets multiple enzymes in ROS metabolic pathways. In leukemic cells, Cur showed an inhibition of CBR1/3, NQO1/2, PRDX1, and ADH1A some of which were also upregulated in patient leukemia samples.[55] Through induction of ROS in colorectal cancer cell lines Cur was able to activate KEAP1/NRF2/ARE pathways and serve as an effective therapeutic especially in combination with 5-FU.[56] Cur is an option for resensitization of chemo-resistant cancer cells. Against drug resistant MCF7/TH, A549/ADR, and HCT116R Cur modulated oxidative stress and increased apoptosis through multiple mechanisms including increases in SOD and CAT and an upregulation of SIRT1.[57]

Cur has the ability to overcome carboplatin resistance in triple negative breast cancer cell lines. Recently, Cur demonstrated its ability to overcome carboplatin resistance through increased ROS production leading to downregulation of RAD51 and an upregulation of γH2AX.[58] Wu et al. demonstrated that Cur had a similar result against chemo-resistant lung cancer cells. There was a drastic increase in apoptosis of A549/D16 cells due to ROS guided p38 MAPK phosphorylation.[59] This affect was exaggerated when used in combination with Docetaxel and Vincristine with little toxicity arising upon the Cur addition, suggesting that Cur has a role in enhancing chemotherapeutic effectiveness.[59]

Curcumin Derivatives and Cancer

Several Cur analogs can increase their antioxidant ability. The presence of Cu^{2+}, Pb^{2+}, and Fe^{2+} increased the chelating effect of Cur derivatives and O-methoxy substitution also exhibited increased antioxidant activity in comparison to regular Cur.[60,61] Pyridine and sulfone derivatives in prostate cancer, glucoside and heterocyclic Cur derivatives in breast cancer, and mono-carbonyl and various methoxy and hydroxy derivatives of Cur in colon cancer have increased its effectiveness when compared to Cur.[62] C7-curcuminoids, which have the same framework as Cur, and C5-curcuminoids, Cur derivatives with a removed ethylene group, were found to be more effective than base Cur against K562 leukemic cells and resulted in ROS upregulation.[63] A novel Cur derivative, 1g, was effective against colon cancer cells. The administration of 1g resulted in ROS production, G1 cell cycle phase arrest, and increased ER-stress which was reversed upon addition of NAC, an ROS scavenging agent.[64] Recently, Liu et al. demonstrated the effectiveness of a series of Cur analogs and showed the effectiveness of a mono-carbonyl analog. Non-small cell lung cancer cell lines showed marked increases in apoptosis and ferroptosis driven by the analogs ability to generate ROS through TrxR inhibition.[65] The analog WZ26 increased ROS and cell death in cholangiocarcinoma via STAT3 inhibition and L48H37 was found to have similar results and induced ER-stress in human lung cancer cells.[66,67] An allylated mono-carbonyl Cur analog (CA6) showed effectiveness against gastric cancer cells through TrxR1 inhibition and ROS-dependent apoptotic death.[68] Another Cur analog, WZ37, induced ROS-dependent ER stress and mitochondrial injury, resulting in an increase in cell death and G2/M phase cell cycle arrest along with decreased Akt/mTOR phosphorylation and an upregulation of BAD and PTEN in head and neck squamous cell carcinoma.[69]

Continued development of Cur derivatives will hopefully lead to not only increased targeting of tumorigenic factors such as ROS, but also continued improvement over base Cur formulations.

Multiple limitations surround Cur and its analogs usage including poor bioavailability and cellular uptake which decrease the therapeutic potential of the compound. Studies with doses as high as 12 g/day still resulted in small amounts of traceable plasma Cur, mostly due to low absorption in the small intestine and rapid elimination in the body via the gall bladder.[70–72] Efforts to improve the pharmacokinetic profile of Cur involve nanoparticle formulation and increased analog development. Cur nanoparticles not only increase its ability to attack many of its targets mentioned above, but also show increased antioxidant potential and exhibit improved distribution and absorption by target cells.[73–75]

CONCLUSION

The paradoxical nature of ROS made for a difficult target in the hope for its use in cancer therapy. Relying solely on decreasing or increasing ROS in either direction is still a questionable approach for treatment. However, taking advantage of the antioxidant abilities of drugs shows some promise in terms of its inclusion in treatment regimens. Natural compounds like Cur are especially advantageous in this aspect due to their low toxicity towards healthy cells. Its natural antioxidant ability including its targeting of various protein kinases, transcription factors, and growth factors makes Cur an attractive alternative despite its pharmacokinetic limitations. Further studies into Cur's mechanistic abilities to alter ROS and change antioxidant potential, chemical analogs, and nanoparticle formulation will improve the chances for successful Cur adaptation into cancer treatments.

Utilizing antioxidants in cancer therapy is a delicate balance and the research is still evolving. Since antioxidant activity can protect cancer cells, novel approaches such as modulation of oxidative stress for the implications in therapeutic application is challenging. Rigorous preclinical and clinical studies are essential to ensure safety and efficacy. Clinical testing utilizing antioxidant mechanisms for cancer therapy is ongoing. New discoveries and clinical trials can provide more insights and potential strategies beyond what is currently known.

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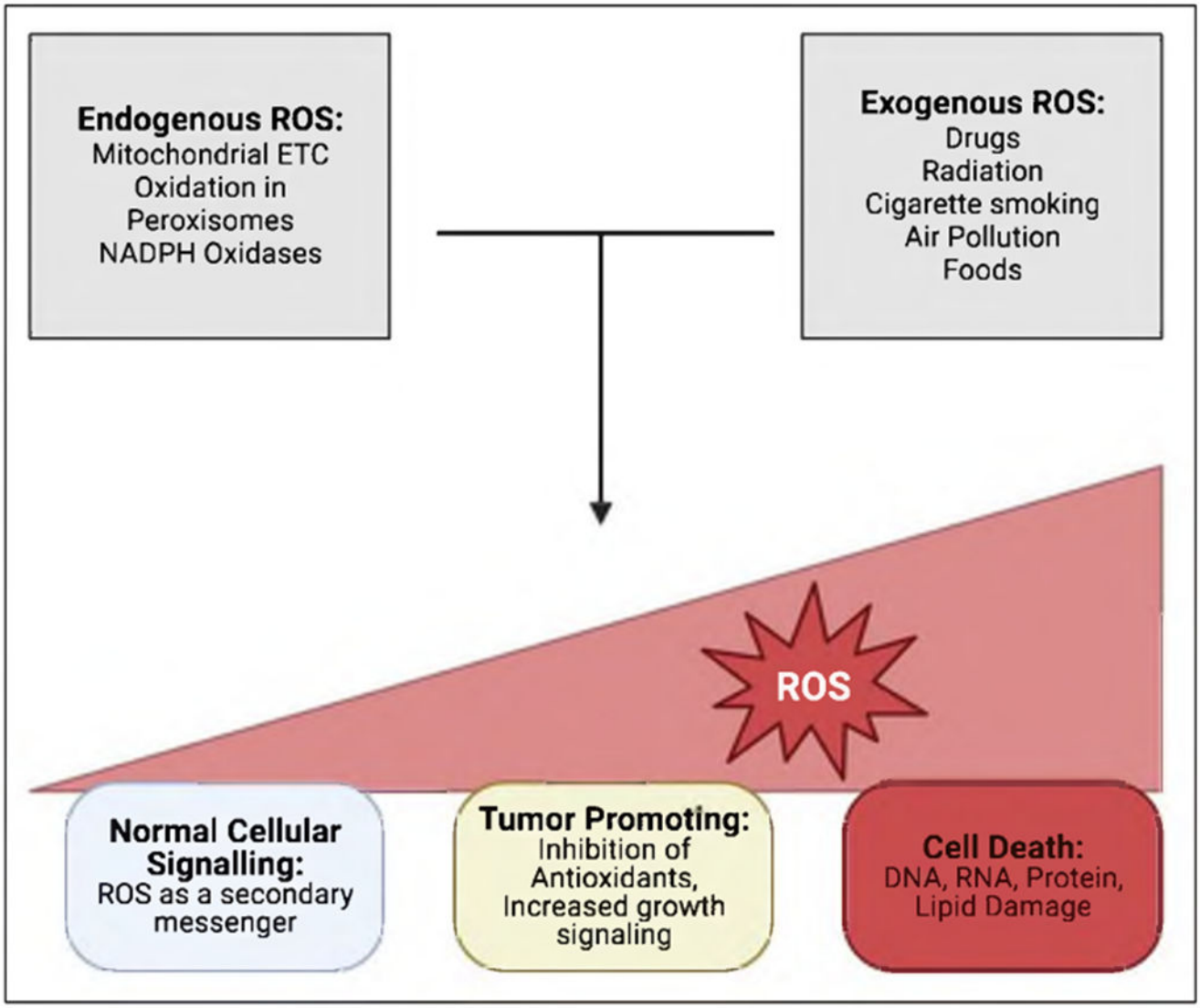

Figure 1.

ROS sources and implication in cancer. There are multiple endogenous and exogenous sources of cancer. All can increase the amount of ROS contributing to the sliding scale of ROS-cancer interaction. This can lead to pro-tumorigenic environment under the right circumstances; however, high levels of ROS are toxic to normal and cancerous cells alike. Created in biorender.com.

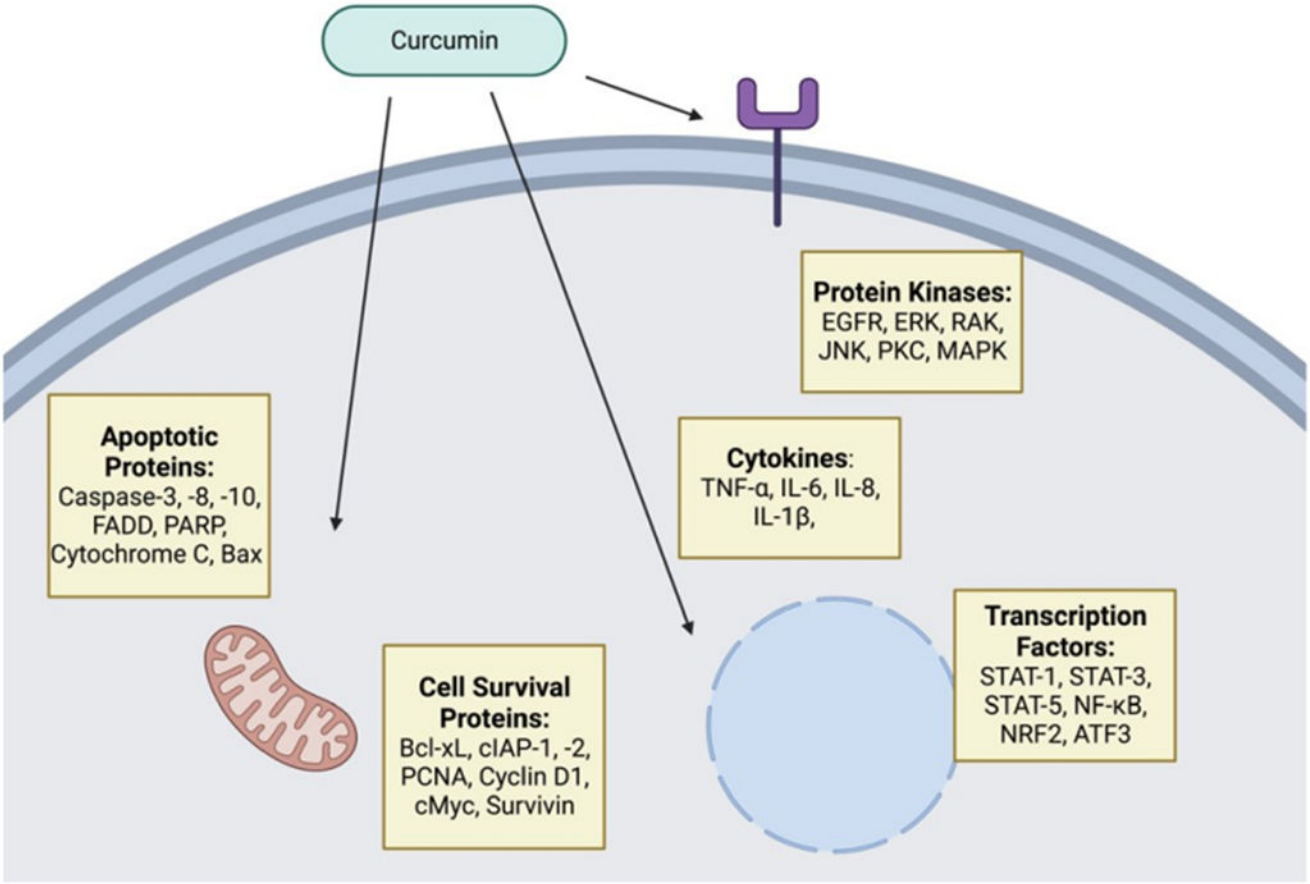

Figure 2.

Curcumin molecular targets. EGFR- epidermal growth factor receptor, ERK- extracellular signal related kinases, JNK- c-Jun N-terminal kinase, PKC- protein kinase C, MAPK- mitogen-activated protein kinase, STAT- signal transducer and activator of transcription, NF-kB- nuclear factor-kappa-light-chain-enhancer of activated B cells, NRF2- nuclear factor erythroid 2-related factor 2, ATF3- activating transcription factor 3, Bcl-xL- B-cell lymphoma-extra-large, cIAP- cellular inhibitor of apoptosis protein, PCNA- proliferating cell nuclear antigen, TNF- tumor necrosis factor, IL- interleukin, FADD- FAS-associated death domain protein, PARP- Poly (ADP-ribose) polymerase. Created in biorender.com.

Table 1.

List of ROS modulating drugs in cancer treatment.

ROS Modulating Drug	Cancer Type	Clinical Trial Phase	NCT Identifier
Vitamin C (Ascorbic Acid)	Relapsed/Refractory Lymphoma	Phase II – Ongoing	**NCT03418038**
Mangafodipir	Multiple, required mild oxaliplatin neuropathy	Phase II – Concluded	**NCT00727922**
Niclosamide	Resectable Colon Cancer	Phase I – Terminated	**NCT02687009**
Quercetin	Childhood Cancers	Phase II – Ongoing	**NCT04733534**
Curcumin	Endometrial Carcinoma, Glioblastoma, Prostate, Colorectal	Multiple Phases	**NCT02064673**, **NCT01490996**, **NCT02017353**, **NCT01712542**
Dimethyl Fumarate	Glioblastoma Multiforme	Phase I – Concluded	**NCT02337426**
Bortezomib	Multiple Myeloma	Phase III – Ongoing	**NCT04566328**
Arsenic Trioxide	Acute Promyelocytic Leukemia	Observational-Recruiting	**NCT04897490**