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Review

An Update on Phytochemicals in Redox Homeostasis: "Virtuous or Evil" in Cancer Chemoprevention?

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Abstract: Redox homeostasis, a dynamic process ensuring a balance between cellular oxidizing and reducing reactions, is crucial for maintaining healthy cellular physiology and regulating many biological processes, requiring continuous monitoring and fine-tuning. Reactive species play a critical role in intra/intercellular signaling, and each cell has a specific system guarding cellular redox homeostasis. ROS signaling and oxidative stress are involved in cancer initiation and progression. However, the generation of reactive species beyond the threshold level inside the tumor microenvironment is considered one of the therapeutic approaches. Various studies have shown that some phytochemicals can target the redox homeostasis of the tumor microenvironment. Recent advances have focused on developing and introducing phytochemical interventions as favorable therapeutic options against cancer. However, studies have also suggested the "virtuous" and "evil" impacts of phytochemicals. Some phytochemicals enhance therapeutic efficacy by promoting intracellular oxidant accumulation. However, under certain conditions, some phytochemicals may harm the cellular microenvironment to promote cancer and tend to target different pathways for cancer initiation and development instead of targeting redox homeostasis. In this context, this review is focused on providing an overall understanding of redox homeostasis and intends to highlight the potential positive and negative impacts of phytochemicals in redox homeostasis and disease development. We also discuss the recent nanotechnology-based advancements in combating cancer development.

Keywords: redox homeostasis; antioxidant; reactive species; phytochemicals; nano-phytochemicals

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1. Introduction

Inside the cellular system, several molecules interact with each other to form a network that facilitates the continuous flow of information into a functioning module. Biochemical signals are relayed by an enzyme-orchestrated signaling mode or inherent reactive electrophilic signals. Reactive species act akin to classical enzyme systems and modify their targets [1]. During normal cellular metabolism, many reactive species are formed, which include reactive oxygen species (ROS) and reactive nitrogen species (RNS). Other reactive species are also present inside the cell, such as reactive sulfur species (RSS) and reactive electrophilic species (RES) derived from the reaction of ROS/RNS with other substrates. These reactive groups interact with the cellular components and bring about changes in redox homeostasis and environments [1]. Reactive species are the oxidizing free radicals and non-radicals that are neutralized by the cellular endogenous antioxidant system, which is another important unit of redox homeostasis. Redox homeostasis is maintained by the optimum reactive species and endogenous antioxidant systems level [2].

Cancer is a global disease with a high incidence and mortality rate. The cause of cancer is mainly associated with genetic and epigenetic changes and exposure to an environmental malignant carcinogen. However, cancer is not a single cause-and-effect disease but rather a multistep process that involves several mutational and aberrant changes inside the cellular environment leading to uncontrolled cellular proliferation. Various research has pointed to

the contribution of oxidative stress in cancer development and treatment [3]. The formation of reactive species (oxygen, nitrogen, and sulfur) inside the cells independently attacks various cellular macromolecules and causes impairment of various cellular functions. The imbalance in the level of reactive species and cellular antioxidant defence system leads to oxidative stress, which further leads to genomic instability and cancer. Moreover, oxidative stress damages macromolecules present inside the cells, including proteins and lipids of the cell membrane [4]. Additionally, a study on the gain or loss of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and the glutathione system has revealed its involvement in cancer progression. An imbalance in the level of antioxidant enzymes creates a favorable environment for DNA damage and tumor promotion [5]. It has been observed that the antioxidant enzyme SOD1 binds to lipophilic electrophiles and forms a dimer, leading to excess hydrogen peroxide (H_2O_2) and consequent aberrant cell signaling. The accumulation of H_2O_2 and aberrant cell signaling are associated with the development of cancer [6]. In another study, it was found that glutathione peroxidase (GPx) is regulated epigenetically and acts as a tumor suppressor in various cancers [7].

Based on various studies, it is firmly established that reactive species favor the activation of oncogenic signaling pathways to a certain optimum value, which might act as a tumor suppressor if generated beyond the threshold value. The ongoing theory is that reactive species at low levels are important for biological processes and facilitate survival and adaptation to the stressful environment through cellular signaling, while these reactive species cause oxidative stress at high concentrations. Various therapeutic interventions are designed to achieve the threshold ROS level and cease cancer progression. One of the effective anticancer therapeutic interventions is using phytochemicals either with the combination of current therapy or alone [8]. Phytochemicals are plant metabolites showing various biological efficacy, including anticancer properties. Phytochemicals show anti-proliferative, anti-metastatic, proapoptotic, and chemosensitizing properties against chemoresistant cells. Moreover, phytochemicals show little or no toxicity or adverse effects on normal cells [9]. However, not all phytochemicals are safe to consume or have the desired biological efficacy against cancer. In fact, some phytochemicals tend to have carcinogenic properties. Capsaicin is a primary ingredient of chili pepper that provides intensity or hotness when ingested. Reports have shown that Capsaicin has carcinogenic properties and promotes skin carcinogenesis when applied topically, along with 12-O-tetradecanoylphorbol-13-acetate (TPA) [10]. In this review, we discuss the dual role of secondary metabolites in regulating redox homeostasis in cancer pathogenesis and prevention.

2. Cellular Redox Dynamics in Cancer Pathogenesis

2.1. Source and Chemistry of Cellular Redox Dynamics

Electron transfer is an important step in different enzymatic reactions characterized by the simultaneous incident of two independent half reactions, oxidation or reduction of substrate. The transfer of electrons from reduced to oxidized compounds is known as a redox reaction. Redox reactions are important for cell homeostasis and energy metabolism. Moreover, redox reactions are also involved in gene expression, cell cycle regulation, immune response, and apoptosis [11]. In the biological system, cellular redox processes are intertwined with each other and are regulated by a variety of biochemical parameters. Cellular redox processes are paradoxical and tend to defy the simple cause–effect logic and linearity. Moreover, the redox process within the cell is rarely in the state of thermodynamic equilibrium and is generally ultrasensitive [12]. The presence of reactive species greatly influences cellular redox dynamics. These species react readily with other molecules present in the vicinity and start a chain reaction. Moreover, reactive species react with the structural components of the cells, such as membranous lipids and proteins, and introduce irreversible modification, which leads to the loss of functions. The high reactivity of oxidants produced during cellular metabolism can cause severe cellular damage by creating an oxidizing environment within the cells. To optimize cellular functioning and

reduce free radical damage, antioxidant systems present within the cells contrive the reducing environment [13].

In the biological system, sources of reactive species can be endogenous and exogenous. In eukaryotic cells, the principal endogenous source of reactive species is mitochondria. Under normal conditions, when electron transport chain (ETC) complexes are over-reduced, few of the electrons flow back to complexes via a phenomenon known as reverse electron transport and cause the leak of electrons. The leaked electrons react with oxygen to form reactive species. The FMN (IF) and CoQ binding (IQ) sites are the main sources of ROS. During acute hypoxia, the sudden increase in the superoxide ions in arterial endothelial cells is mainly due to the involvement of complex I (CI) of ETC [14]. Aside from mitochondria, peroxisomes are other organelles that are implicated in the generation of cellular ROS. It has been found that xanthine oxidase in the peroxisomal matrix and membranes can generate superoxide and peroxides [15]. Another source of ROS is the transmembrane enzyme family NADPH oxidase (NOX), a transmembrane protein found on the cell and mitochondrial membranes. The NOX family produces superoxide, which is then transported inside the cytoplasm as peroxide, which acts as a secondary messenger for cell survival and proliferation [16]. Superoxide can also react with NO to form a peroxynitrite ($ONOO^-$) ion, which is generated during the decomposition of arginine to citrulline catalyzed by NADPH-dependent nitric oxide synthase (NOS). NO is more stable than any other radicals but react with reactive species present in the surrounding to produce more RNS [17].

ROS is an umbrella term that includes radical and non-radical oxidizing agents formed during normal cellular metabolism. Free radicals are uncharged molecular fragments with one or more unpaired electron in their outer atomic or molecular orbit [13]. These molecules are short-lived and react very readily with their surrounding components. Non-radical oxidizing reagents, on the other hand, are transformed into free radicals by reacting with other oxidants [18]. Free radical oxidizing agents include superoxide, hydroxyl, peroxyl, and hydroperoxyl ions, while non-radical agents include H_2O_2, hydrochloric acid, and ozone [13]. Reactive electrophilic species (RES) are the secondary electrophiles produced during the interaction of ROS with biomolecules. Lipid-derived electrophiles are formed via the peroxidation of polyunsaturated fatty acids (PUFA). The resulting electrophiles, such as α,β-unsaturated carbonyls, modulate various physiological processes, including development, aging, apoptosis, immune response, and heat shock response. Other commonly known lipid-derived electrophiles are cytotoxins malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE), and 4-oxo-2-nonenal (4-ONE), which further react with other cellular macromolecules such as nucleic acid and protein [19]. Moreover, cholesterol and its precursors are highly vulnerable to free radical oxidation leading to the production of reactive electrophiles [19]. In addition, the reactive electrophile aldehyde produced due to lipid peroxidation can attack the nucleophilic residue of protein to form an adduct and cause an apparent loss of protein function or aggregation. Reactive aldehydes can form adducts with protein nucleophilic residues either by Michael addition to Lys, His, or Cys residue or by Schiff base formation of the carbonyl group to Lys residues [20].

Another family of reactive species includes nitric oxide (NO)-derived compounds, including higher oxides of nitrogen, nitrosyl anion (HNO^-), nitrosonium cation (NO^+), S-nitrosothiols (RSNOs), $ONOO^-$, and dinitrosyl iron complexes. RNS possess pleiotropic properties and play an important role in the physiological regulation of smooth and cardiac muscle, neural, and juxtaglomerular cells. Inside the cell, NO is produced by converting arginine into citrulline with the help of NOS. Although NO and its derived compounds are non-toxic and physiologically important at low concentrations, these molecules and radicals tend to cause cell damage at high concentrations [21]. In the kidney, NO helps in reducing the contractile activity of vascular smooth muscle cells. The NO-derivative, $ONOO^-$, readily decomposes into nitrogen dioxide (NO_2) and hydroxyl radical ($^{\bullet}OH$). $^{\bullet}OH$ is a highly reactive radical that further reacts with the surrounding biological molecules.

Moreover, NO_2 reacts with carbon dioxide to produce nitrosoperoxycarbonate ($ONOOCO_2^-$), which further breaks into a carbonate radical (CO_3^-) and NO_2. CO_3^-

has similar reactivity to $^{\bullet}OH$, and both exert cellular damage, which is exploited by the phagocytes of the cells during respiratory bursts [22]. RNS induces post-translational modification in various proteins, consequently altering protein structure and function. Three common post-translational modifications invoked by RNA are (i) S-nitrosylation of regulatory protein where NO moiety attaches to the thiol moiety to form an S-nitrosothiol derivative, (ii) glutathionylation where S-nitrosylation of glutathione (GSH) or other thiols further mediate post-translational modification, and (iii) tyrosine nitration where reactive species oxidize tyrosine to generate tyrosyl radical which further reacts with nitrogen dioxide to form nitrotyrosine. Nitrotyrosine is a highly reactive oxidant that can react with iron-sulfurs and zinc-thiolate groups [23].

Sulfur is an important constituent of many proteins and enzymes. In general, sulfur is central to the thiol group involved in redox reactions. Thiol groups are easily oxidized and reduced; however, the sulfur group can also form reactive species [24]. RSS and ROS have chemical similarities. RSS and ROS are produced from the sequential one e^{-} reduction of sulfur and oxygen, respectively [25]. RSS is formed when the sulfur of thiols and disulfides are oxidized to their higher oxidation state. The RSS family includes thiol radicals, disulfides, sulfenic acids, and disulfide oxides, which upon oxidation, inhibit thiol proteins and enzymes [26]. Moreover, RSS is also involved in normal physiological cell signaling and metabolic regulation as the diverse redox landscapes of RSS allow it to be easily modulated by other redox-active systems. Hydrogen sulfide is an important gasotransmitter that exerts cytoprotection, anti-inflammatory, and vasodilatory properties on cardiac muscles at low concentrations. H_2S interacts with NO, forms per/polysulfide, and reacts with metalloenzymes to perform various cell signaling important for biological processes [27].

Low levels of reactive species are important for a plethora of biological processes, but at high concentrations or due to inadequate removal of reactive species can lead to oxidative stress. A wide range of antioxidant defence systems exist to optimize the level of reactive species inside the cellular system. The antioxidant defence system includes a range of enzymatic and non-enzymatic antioxidants such as SOD, CAT, GPx, glutathione reductase (GR), thioredoxin reductase (TR), β-carotene (vitamin A), ascorbic acid (vitamin c), α-tocopherol (vitamin E), etc. [28]. SOD is a group of metalloenzymes comprising three isoforms based on metal cofactor (Cu, Zn-SOD, Fe-SOD, Mn-SOD), located at a different location in the cells, and is a front-line defence against reactive species. SOD interacts with superoxide anions to form molecular oxygen and H_2O_2 [29]. CAT and GPx then convert H_2O_2 into harmless products that the body can easily utilize. In addition to GPx, the glutathione detoxifying family consists of GST and GR, which helps maintain the level of GSH inside the cell. Glutathione is an important antioxidant that maintains the cellular system's redox homeostasis [30]. The reactive species and antioxidant system levels are maintained at an optimum level, creating a redox balance, as shown in Figure 1.

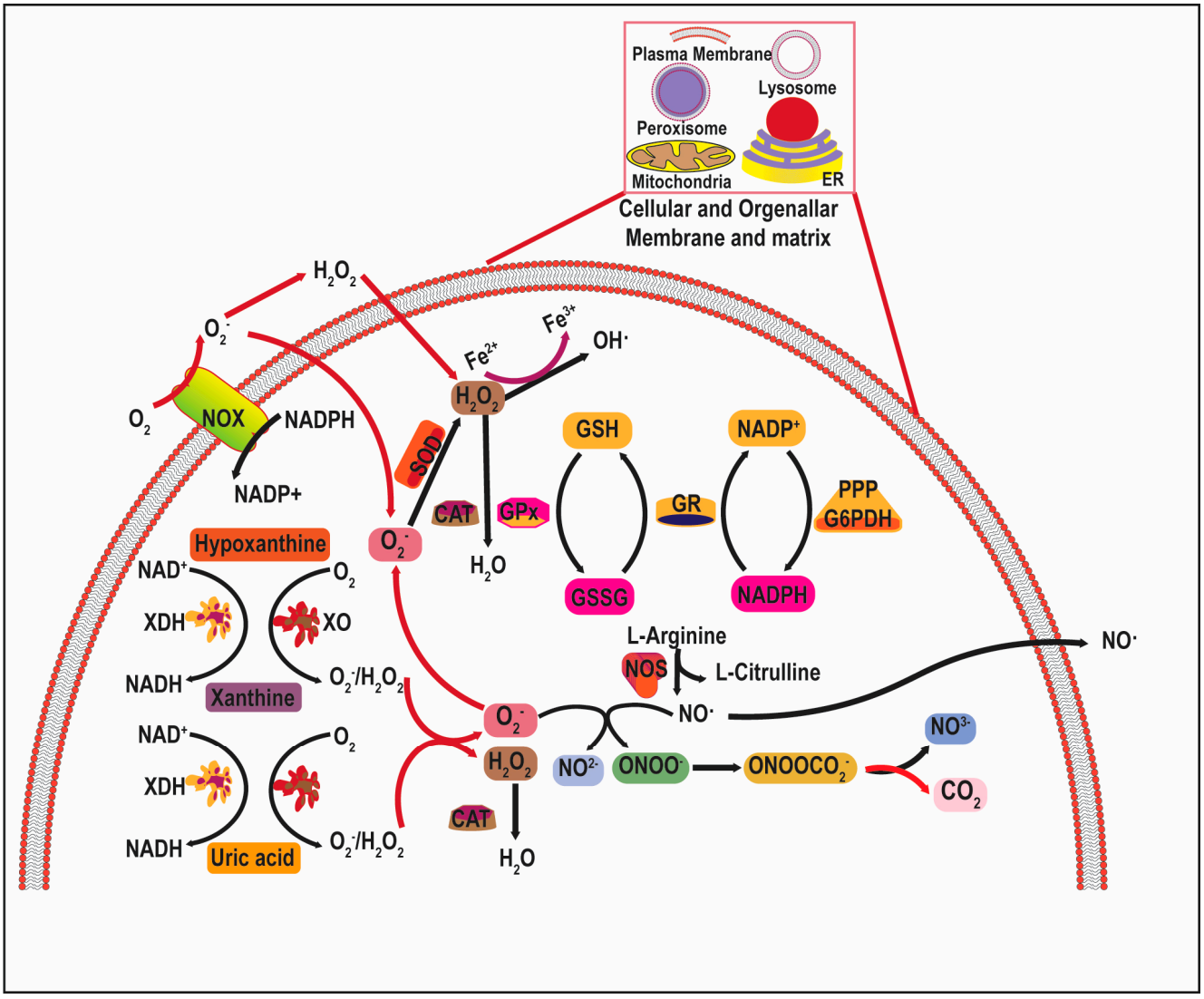

Figure 1. The reactive species and antioxidant system inside the cell maintain redox homeostasis. Free radicals and non-radical species generated during normal cellular functions are neutralized by the various antioxidants present inside the cell. The optimum balance between reactive species and antioxidants is important for the proper functioning of the cells. CAT: Catalase; CO_2: Carbon Dioxide; G6PDH: Glucose 6-Phosphate Dehydrogenase; GPx: Glutathione Peroxidase; GR: Glutathione Reductase; GSH: Glutathione (reduced); GSSG: Glutathione (oxidized); H_2O_2: Hydrogen Peroxide; NADPH: Nicotinamide Adenine Dinucleotide Phosphate (reduced); NAD^+: Nicotinamide Adenine Dinucleotide Phosphate (oxidized); NO_2^-: Nitrite ion, NOS: Nitric Oxide Synthase; NOX: NADPH Oxidase; O_2^-: Superoxide ion; •OH: Hydroxyl radical; ONOO-: Peroxynitrite; $ONOOCO_2^-$: SOD: Superoxide Dismutase; XDH: Xanthine Dehydrogenase; XO: Xanthine Oxygenase.

2.2. Free Radicals in Cancer Biology

Depending upon the concentration, reactive species influence cancer progression in conflicting ways, either by stimulating carcinogenesis and promoting cancer cell proliferation or causing cell death [31]. Aberrant production of free radicals and consequent oxidative stress is common during the evolution and progression of cancer cells (Figure 2). Hyperactivation of anabolic pathways is considered one of the likely mechanisms of oxidative stress inside cancer cells. Moreover, hyperfunctioning of mitochondria, mitochondrial DNA mutations, dysfunction of the ETC, and oncogenic pathway activation are the reason for increased oxidative stress within the tumor microenvironment [32]. Although anomalistic production of reactive species and redox homeostasis is pro-tumorigenic, a high

level of ROS is found to be detrimental to cancer cells. During the proliferation of cancer cells, the aberrant production of reactive species is accompanied by the overproduction of antioxidants to neutralize the oxidative burden and bring the redox balance back to the reduced state [31]. Excessive ROS generation by endogenous and exogenous factors leads to DNA damage, including depurination, depyrimidination, DNA breakage, base modifications, and crosslinks of DNA and proteins.

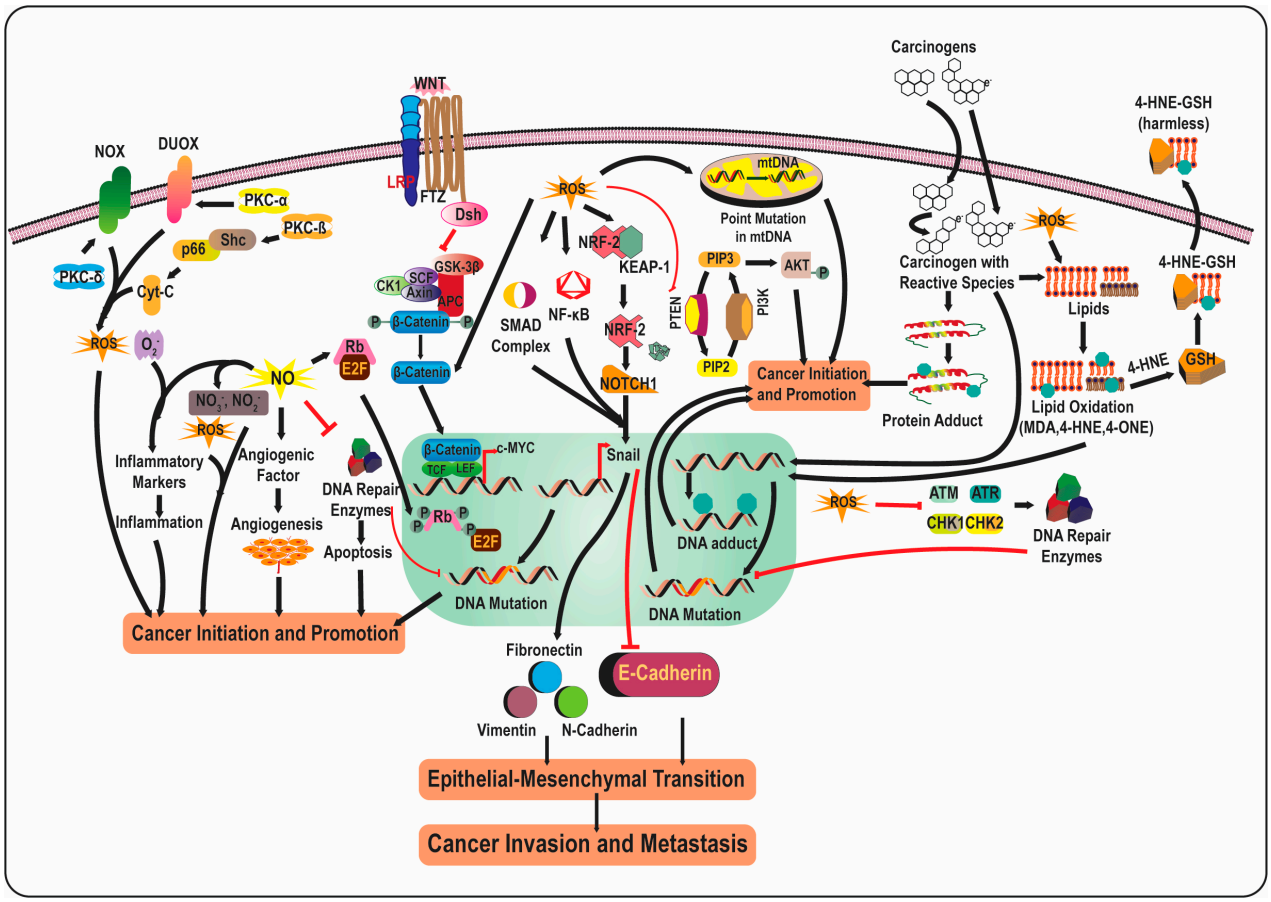

Figure 2. Diagrammatic representation of involvement of reactive species in cancer. Reactive species such as ROS and RNS activate various pathways implicated in cancer initiation, progression, development, invasion, and metastasis. Reactive species can inhibit DNA repair enzymes, stimulate inflammatory markers, damage macromolecules, and activate oncogenic pathways. 4HNE: 4-Hydroxy-2-Nonenal; 4-ONE: 4-Oxo-2-Nonenal; AKT: Protein Kinase B; CK-1: Casein Kinase 1; Cyt C: Cytochrome C; Dsh: Dishevelled; Rb: Retinoblastoma; FTZ: Frizzled; GSK-3β: Glycogen Synthase Kinase-3 Beta; GSSG: Glutathione (oxidized); GSH: Glutathione (reduced); LRP: Low-Density Lipoprotein Receptor-related Protein 1; mtDNA: Mitochondrial DNA; MDA: Malondialdehyde; NF-κB: Nuclear Factor kappa-B; NO: Nitrogen Oxide; NO_2^-: Nitrite ion; NO_3^-: Nitrate ion; NOX: NADPH Oxidase; NRF-2: Nuclear Factor Erythroid 2–Related Factor 2; O_2^-: Superoxide ion; p66/SHC: Src Homologous and Collagen; PI3K: Phosphoinositide 3-Kinase; PIP3: Phosphatidylinositol (3,4,5)-Trisphosphate; PIP2: Phosphatidylinositol (4,5)-Bisphosphate; PKC: Protein Kinase C; PTEN: Phosphatase and TENsin homolog; SCF: Skp, Cullin, F-box containing Complex; ROS: Reactive Oxygen Species; SMAD: Mothers Against Decapentaplegic Homolog 2; TCF/LEF: T-Cell Factor/Lymphoid Enhancer Factor.

ROS affects sensor kinases, ATM and ATR, and transducer kinase; CHK1 and CHK2, oxidize cysteine residue of DNA repair enzyme; OGG1, thus not only delaying the identification but also preventing the repair of the damaged region [16]. The accumulation of DNA damage induces permanent alteration of the genetic material, thus driving a vital

step of carcinogenic mutagenesis [16]. Elevated ROS drives many signaling pathways in different cancers that facilitate cancer cell survival, growth, proliferation, differentiation, glucose metabolism, protein synthesis, and inflammation [15]. Recent studies have implicated ROS, c-MYC, and WNT/β-CATENIN pathways to promote cancer cell proliferation. Moreover, the ROS-mediated WNT/β-CATENIN pathway and activation of c-MYC lead to increased metastasis, cancer stem cell (CSC) properties, and chemoresistance [33]. PKC isoenzymes facilitate the production of ROS during cancer development by activating NOX and altering redox balance inside the tumor cells. PKC-α activates DUOX (member of NOX family), PKC-β stimulates and phosphorylates p66/Shc, which in turn interacts with Cytochrome C to promote ROS generation, PKC-δ alters redox homeostasis to activate NOX, which consequently affects the differentiation status of tumor cells and promote cancer [34]. It has been observed that HBV/HCV infection, lipid deposition, and alcohol abuse result in excessive ROS production. The elevated ROS inside the liver tissues further leads to oxidative stress, mitochondrial damage, and DNA mutation, which culminates in hepatocarcinogenesis [35].

In many cancers, growth factor phosphoinositide 3-kinase (PI3K) pathways are hyperactivated, leading to increased proliferation, survival, and cellular mobility. It has been observed that ROS inactivates the negative regulator of the PI3K pathway, phosphatase, and tensin homolog deleted on chromosome 10 (PTEN). PTEN is a phosphatase that converts PIP3 into PIP2. Inactivation of PTEN causes the perpetual activation of the PI3K pathway leading to increased AKT signaling and ultimately to enhanced growth proliferation and tumorigenesis [36]. Cellular oxidative stress-mediated point mutation and mtDNA instability are reported with higher frequency in prostate cancer (CaP). An interesting report suggests that in older CaP patients, mtDNA deletions are higher than in younger patients. In older patients, the accumulation of oxidative stress with age might be the reason for mtDNA's higher buildup of mutation [37]. In another study, it was reported that the overproduction of ROS induces the accumulation of phosphorylated AKT, leading to oral cancer cell proliferation and apoptosis evasion [38]. The upstream molecules of factor-kappa B (NF-κB), one of the redox-sensitive transcription factors, generate a high amount of ROS, which further helps activate NF-κB. Moreover, high ROS production can activate the c-Jun NK2-terminal kinase (JNK) pathway by separating JNK from its suppressor [39]. Moreover, ROS can facilitate epithelial–mesenchymal transition (EMT) to promote cancer cell invasion and metastasis. ROS was observed to promote the expression of the transcription factor, Snail, by either activating NF-κB) or via SMAD complexes which then promote the expression of Vimentin, Fibronectin, and N-Cadherin and downregulate the expression of E-Cadherin, promoting EMT. In addition, ROS production can degrade Kelch-like ECH-associated protein 1 (KEAP1) and stabilize nuclear factor-erythroid 2-related factor (NRF-2) to enhance the nuclear translocation of NOTCH1, which ultimately promotes Snail expression, thereby promoting EMT and metastasis [40].

It is suggested that if the adduct formed due to the attack of RES on the nucleophilic DNA fails to be fixed by the DNA repair mechanism, it might lead to carcinogenesis. Most exogenous carcinogens are linked with RES production and classified as direct-acting and indirect-acting carcinogens. Direct-acting carcinogens are activation-independent carcinogens that consist of electrophilic groups and interact directly with macromolecules, whereas indirect-acting carcinogens are activation-dependent carcinogens that transform to their electrophilic forms inside the cellular system and drive their carcinogenic properties [41]. The RES can form an adduct with nucleophilic molecules present in the surrounding. The lipid-derived cytotoxins MDA, 4HNE, and 5-ONE were found to form adduct nucleic acid. The electrophile adduction to nucleic acid is linked to cancer caused due to lifestyle [19]. Lipids undergo various metabolic transformations due to radical and non-radical attacks, including lipid oxidation involving enzymatic and non-enzymatic mechanisms. It has been observed that lipid oxidation leads to electrophiles forming an adduct with protein, commonly known as protein lipoxidation [42]. Protein lipoxidation leads to the altered structure and function of protein which might drive pathological conditions such as cancer

by influencing cancer cell behavior or immune response to cancerous cells. Lipid oxidation product 4-HNE has been found to have a carcinogenic effect due to its effect on DNA repair enzymes. However, several disputed studies have arisen that put the role of 4-HNE in a controversial spotlight. It was observed that 4-HNE was converted to harmless 4-HNE-GSH conjugate and easily removed from the cellular barrier. However, studies have also reported the role of 4-HNE-protein adducts in increasing grades of malignancy in astrocytic and ependymal glial tumor cells [43].

NO, a component of RNS, can modify DNA and inactivate DNA repair enzymes. It was observed that NO could hyperphosphorylate and consequently inactivate retinoblastoma protein, resulting in increased proliferation of human colon cancer cells. Moreover, $ONOO^-$ produced from the reaction of NO with $O_2{}^-$ is considered an important biomarker in inflammation-linked cancers [17]. Moreover, it was observed that increased reactive nitrosamines (nitrates and nitrites) along with ROS are implicated in the reduced antioxidant level inside the saliva of oral squamous cell carcinoma (OSCC) patients [44]. Fascinatingly, increased $NO^\bullet$ production by the macrophages of tumor cells helps in tumor cell survival by preventing apoptosis and promoting chemoresistance. Moreover, $NO^\bullet$ production also induces angiogenesis in oral cancer cells. Furthermore, the apparent reduction in tetrahydrobiopterin levels leads to the uncoupling of NOS and overproduction of NOO^- which ultimately promotes tumorigenesis in various cancers [45]. Chronic inflammation in liver cancer causes altered blood flow and hypoxia, leading to RNS generation. The hypoxic parenchyma, laden with RNS, leads to the upregulation of various angiogenic factors, which facilitates angiogenesis and the growth of tumors [46].

3. Limitations to the Conventional Cancer Therapy and Role of Alternative Medicine

Gradually, a great regimen of cancer treatment has been developed depending on the type and stage of cancer. The main choices of treatment are chemotherapy, radiotherapy, and surgical resection. Radiotherapy and surgical resection are used to treat particular areas of the body, and chemotherapies are often systemic in nature [47,48]. One of the greatest limitations in cancer therapeutics is chemoresistance due to increased efflux pumps in the cell membrane, which expel drugs out of the cells [49]. Other limitations include toxicity and collateral damage to normal cells along with cancer cells and cancer recurrence, which occurs due to inadequate therapies to kill CSCs. CSCs are capable of self-renewal and generate new tumoral microenvironments [50,51]. Chemotherapies based on cytotoxicity often exert their killing properties via oxidative stress, decreasing inflammatory response, genotoxicity, and immune attack. However, these mechanisms also harm normal cells and decrease a patient's life quality. Because therapies are systemic in action, they can also harm other organs. Enzalutamide, a known hormone therapy, and Doxorubicin used against CaP can induce hepato-renal and cardiac toxicity by increasing oxidative stress inside the cells [4,52]. Moreover, the FDA-approved drug Sorafenib was observed to cause various organ toxicity, including liver and kidney [53].

Radiotherapy of a malignant tumor is accompanied by secondary damage to the surrounding normal tissues. Moreover, in the tissue within the radiation field, radiation-induced stress triggers the release of damage-associated molecular patterns (DAMPS), cytokines, and chemokines and stimulates innate and adaptive immune cell recruitment, which culminates in tissue inflammation to repair tissue and balance redox homeostasis. However, excessive tissue inflammation and ROS production in the damaged area can cause acute tissue inflammation, a common side effect of radiotherapy [54]. In fact, a series of side effects have been observed in the radiotherapy–chemotherapy combination. For instance, combining radiotherapy with Cisplatin against head and neck cancer leads to oral mucous inflammation, oral cavity ulceration, difficulty swallowing, taste distortions, systemic infection, and depreciated quality of life [55]. In tissues with slow turnover, late complications are observed following radiotherapy, including fibrosis, atrophy, necrosis, telangiectasia, and cancer recurrence [56].

The side effects and poor patient survival leads to the search for better alternatives that can exert anticancer potential and reduce their toxic effects. Several scientific studies have shown that phytochemicals have antitumor potential. The transition from chemically synthesized drugs to natural product-based compounds has been colossal in the last few decades [9]. Phytochemicals can easily scavenge free radicals from the cells and induce the stress-related signals that involve activation of NRF-2-kelch-like EC-associated protein1 (Keap1-complex). This complex activates the cellular defense mechanism and antioxidant enzymes, which protects the cell from ROS/RNS or reactive metabolites of carcinogenic species [9]. Phytochemicals are reported to exert chemopreventive activity by targeting various cancer stages, including the cell cycle, proliferation, and apoptosis [57]. Phytochemicals such as Lupeol, Apigenin, Curcumin, Resveratrol, Quercetin, etc., show exemplary anticancer behavior in vitro, preclinical, and clinical setup [58].

4. Phytochemicals in Redox Homeostasis: Friend or Foe in Cancer Pathogenesis?

4.1. Phytochemicals as a Chemopreventive Agent

Reactive species are known to have a double edge role in carcinogenesis. The level of reactive species is said to play an important role in cancer progression or tumor suppression. It has been observed that at a certain level, reactive species facilitate cancer growth and proliferation, while above that level, reactive species are implicated in the suppression of tumor cells (Table 1). Several studies have pointed toward the cytotoxic role of reactive species in tumor cells. Dietary phytochemicals have drawn much attention because of their extensive therapeutic effects in preventing the onset and progression of a disease. Phytochemicals and their derivatives have been thought to be involved in chemoprevention and chemosensitization, and their therapeutic efficacy has been extensively studied [9]. Many plants have shown anticancer properties owing to the phytochemicals present in them. More than 15 *Allium* spp. have shown anticancer properties due to their secondary metabolites. *Allium* spp. contain S-allyl mercaptocysteine, Quercetin, Flavanoids, and Ajoene, which facilitate cytotoxicity, immunomodulation, anti-inflammation, and apoptosis in various cancers. Moreover, these compounds also balance cellular redox homeostasis by scavenging ROS, reducing macromolecular damage, and increasing GST activity [59]. Phytochemicals are found to exert an antioxidant effect in the normal cell, while in cancer cells, phytochemicals tend to increase reactive species beyond the threshold level at which the survival adaptation of the cell is rendered futile. Dietary phytochemicals exert anticancer, chemopreventive, and chemosensitizing properties by generating excessive reactive species levels at which the oxidative stress inside the cell is so high that the cell becomes destined to die (Figure 3).

Curcumin is a naturally occurring polyphenol found in the rhizome of turmeric (*Curcuma longa*). Curcumin can target multiple signaling molecules to exert its biological efficacy, such as antioxidant, antimicrobial, anti-inflammatory, anti-mutagenic, antimicrobial, and anticancerous properties [60]. Curcumin (diferuloylmethane) neutralizes ROS generated from chemical carcinogens by inducing GST (a phase II metabolizing enzyme) and Quinine reductase. Not only does Curcumin scavenge ROS by inducing ROS-scavenging enzymes such as GST, Hemeoxygenase-1, and redox-sensitive inducible enzyme, but Curcumin can also exploit ROS generation to kill cancer cells [61]. Curcumin is found to generate ROS beyond the threshold level to induce apoptosis by downregulating anti-apoptotic protein, NF-κB, and COX-2 and upregulating the activity of tumor suppressor p53 [62]. In colon cancer, Curcumin induces apoptosis by increasing the production of ROS, Ca^{2+}, upregulating the expression of proapoptotic proteins (BAX, Cytochrome C, p53, and p21), Caspase 3, and reducing the mitochondrial membrane potential [9,63]. Moreover, Curcumin exerts its anticancerous activity by inhibiting proinflammatory enzymes such as inducible NOS (iNOS) and tumor necrosis factor-α (TNF-α). In addition, Curcumin can inhibit hypoxia-induced ROS in hepatic carcinoma cells (HCC) by downregulating the expression of hypoxia-inducible factor-1 (HIF-1) [64].

Figure 3. Role of oxidant–antioxidant levels in cancer cells and cancer cell death. Phytochemicals exert their anticancer property by targeting the redox status of cancer cells. They exert cytotoxic action by scavenging reactive species or generating reactive species burst inside the cells. Caspase-med-Apoptosis: Caspase-mediate Apoptosis; COX: Cyclooxygenase; Cyt-C: Cytochrome C; GGT: γ-Glutamyl Transpeptidase; GST: Glutathione S-Transferase; HDAC2: Histone Deacetylase; HIF: Hypoxia-Induced Factor; HO: Hemeoxygenase-1; LPO: Lipid Peroxidation; MDA: Malondialdehyde; MMP: Mitochondrial Metalloproteinase; NAF: Nutrient-deprivation Autophagy Factor-1; NRF-2: Nuclear Factor Erythroid 2–Related Factor 2; NF-κB: Nuclear Factor kappa-B; NQO1: NADPH Quinone Oxidoreductase; PI3K: Phosphoinositide 3-Kinase; QR: Quinone Reductase; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species.

Another polyphenol, Resveratrol (3,5,4′-trihydroxy-trans-stilbene), belongs to the stilbenoids groups and comprises two phenol rings linked by an ethylene bridge. Resveratrol is commonly found in the skin and seeds of grapes and many other plant species. Resveratrol has several biological efficacies, including antioxidant and anticancer properties. It has been found that Resveratrol induces its anticancer efficacy by numerous mechanisms, including but not limited to the overproduction of reactive species. It has been found that Resveratrol suppresses the expression of NAF-1 by facilitating NRF-2 signaling and overproducing ROS in pancreatic cancer cells [65]. Moreover, in colon cancer cells, Resveratrol inhibits iNOS expression along with post-translational modification and translocation of NF-κB, resulting in the inhibition of inflammation associated with cancer cells [65].

Apigenin (4′,5′,7-trihydroxyflavone) is a flavone extracted from plants that are abundantly found in vegetables, fruits, medicinal plants, etc., that has shown its biological efficacy as an antioxidant, organ protector, and anticancer agent [66]. Apigenin was found to exert its anticancer properties through apoptosis, cell cycle arrest, immune response, and ROS. Administration of Apigenin (12.5–50 μM) in the papillary thyroid carcinoma cells

leads to cell cycle arrest via inhibiting the expression of CDC25c and overproduction of ROS, which ultimately causes DNA damage [67]. Apigenin is also used as a ROS amplifier to enhance the cytotoxic effect of Metformin in vitro and in vivo. The combination of Metformin (5 μM) and Apigenin (20 μM) is found to induce ROS-dependent severe DNA damage and apoptosis in human pancreatic cells. Moreover, in vivo combination of Metformin (75 mg/kg b.w.) and Apigenin (5 mg/kg b.w.) is found to have a profound effect on tumor weight [68]. Quercetin (3′,3′,4′,5′,7 pentahydroxyflavone) belongs to the flavonol group and is abundant in nature and common to the human diet. Quercetin exhibits chemopreventive properties owing to its antioxidant properties. It has been observed that the presence of an OH group and double bonds in Quercetin has provided antioxidant capability to the Quercetin molecules. Quercetin can scavenge both ROS and RNS [69]. Zhang et al. [70] observed that the antioxidant properties of Quercetin (15) μM helps in enhancing the therapeutic efficacy of Paclitaxel (12.5 μM) against CaP by inducing endoplasmic reticulum stress and intracellular ROS leading to CaP cell cycle arrest and death. Moreover, Quercetin can form Quercetin radicals to scavenge peroxyl radicals. The formation of Quercetin radicals can overall increase the intracellular ROS level. Quercetin is also observed to induce free radical-mediated apoptosis by p38/ASK1/AMPKα1/COX-2 [71].

Rutin (3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside) is a flavonol commonly found in passionflower, buckwheat tea, apple, and many other plants. Rutin prohibits liver cancer cell proliferation at the IC_{50} value of 52.7 μM/L and enhances cell death. Moreover, Rutin treatment significantly alters the expression of drug-metabolizing CYP3A4 and CYP1A1 and phase II reaction catalyzing enzyme NADPH Quinone oxidoreductase I (NQO1) and GST variant P1 [72]. In another study, the administration of Rutin is followed by a reduction in cell viability due to enhanced ROS generation and dose-dependent nuclear condensation in cervical cancer cells [73].

Caffeic acid (3,4-Dihydroxycinnamic acid) belongs to a subgroup of hydroxycinnamic acids of polyphenol groups and is believed to possess antioxidant properties that help in many biological activities [74]. Caffeic acid (0–500 μM) induces cell death in the colon and cervical cancer by inhibiting Histone Deacetylases (HDAC) 2. Furthermore, inhibition of HDAC2 leads to the overproduction of ROS, cell cycle arrest, and caspase-3-mediated apoptosis in the cancer cells [75]. Caffeic and Ferulic acid are found to chelate RNS and form stable intermediates with these reactive species [76]. The scavenging capacity of Ferulic acid (0–100 μM) facilitates cytoprotection by inhibiting DNA damage, inflammation, lipid peroxidation, and stimulating apoptosis [77]. Sinapic acid (3-(4-hydroxy-3,5-dimethoxyphenyl) prop-2-enoic acid) exhibits a chemopreventive effect on colon carcinogenesis. The authors observed that Sinapic acid (40 mg/kg b.w.) could decrease tumor prevalence, modulate LPO markers, and increase antioxidant defense by regulating phase I and II detoxifying enzymes [78]. In another study, Sinapic acid showed anticancer properties both in free and nano-capsulated form. It was observed that Sinapic acid (125.23 μM) showed an apparent increase in the ROS level in HeP-2 cells, leading to oxidative stress and a mitochondria-dependent pathway of apoptosis [79].

Gallic acid (3,4,5-trihydroxybenzoic acid) is grouped with phenolic acid and found in hazel, tea leaves, oak barks, etc. Gallic acid (0–50 μM & 100–200 μM) induces lung cancer apoptosis by increasing ROS levels and decreasing GSH levels, leading to the loss of mitochondrial membrane potential. Moreover, Gallic acid-induced ROS at 50 g/mL facilitates c-Jun-NH_2 kinase (JNK) mediate apoptosis in lung fibroblast cells. Formation and accumulation of H_2O_2 lead to the activation of the p53 pathway and JNK pathway, culminating in apoptosis [80]. Furthermore, Gallic acid exerts anticancer properties against CaP, leukemia, esophageal cancer, and cervical cancer through the ROS burst and antioxidant defense system [80].

Table 1. Occurrence and anticancer mechanism of the phytochemicals.

Phytochemicals	Found in	Function	Role in Redox Balance	Ref.
Curcumin	Turmeric	Anticancer	Induce Glutathione S-transferase, Quinine reductase, and Hemeoxygenase, induce apoptosis by upregulating the expression of ROS beyond a threshold level, Ca^{2+}, BAX, Cyt C, p53, p2, Caspase 3 and reducing MMP, inhibit iNOS and TNF-α, HIF-1, hypoxia-induced ROS	[61–64]
Resveratrol	Grapes	Anticancer	Facilitate Nrf-2 expression, overproduction of ROS, suppresses NAF-1 and iNOS expression, and post-translation modification and translocation of NF-κB	[65]
Apigenin	Parsley, Chamomile, Celery, Vine-Spinach, Artichokes, and Oregano	Organ protective and Anticancer	Inhibiting the expression of Cdc25c, overproduction of ROS, DNA damage	[66–68]
Quercetin	Citrus fruits, Apples, Onions, Parsley, Sage, Tea, Red wine, Olive oil, Grapes, Cherries, Blueberries, Blackberries, and Bilberries	Chemopreventive	Scavenge ROS and RNS, enhance Paclitaxel efficacy, ER-stress and increase ROS beyond a threshold level, induce free radical-mediated apoptosis by p38/ASK1/AMPKα1/COX2.	[69–71]
Rutin	Passionflower, Buckwheat, Tea, and Apples	Anticancer	Alter the expression of CYP3A4 and CYP1A1, NQO1, and GST variant P1. Enhances ROS beyond threshold level and nuclear condensation	[72,73]
Caffeic acid	Coffee, Red wine, Berries, and Apples	Anticancer	Inhibit HDAC2, overproduction of ROS, cell cycle arrest, Caspase-3-mediated apoptosis	[75]
Ferulic acid	Rice, Wheat, Oats, Pineapple, Grasses, Grains, Beans, Coffee Beans, Artichokes, and Peanuts	Cytoprotective	Scavenge ROS, inhibit DNA damage, inflammation, LPO, stimulate apoptosis	[77]
Sinapic acid	Spices, Citrus, Berries, Fruits, Vegetables, Cereals, and Oilseed crops	Chemopreventive	Decrease tumor prevalence, modulate LPO markers, increase phase I and phase II detoxifying enzymes. Increase ROS, oxidative stress, mitochondrial-dependent apoptosis	[78,79]
Gallic acid	Hazel, Tea Leaves, and Oak Barks	Anticancer	Increases ROS, decreases GSH, MMP loss, activates p53, facilitates JNK-mediated apoptosis	[80]
Betulinic acid	Birch, Eucalyptus, and Plane trees	Anticancer	Neutralizes ROS, upregulates GST, γ-glutamyl transpeptidase, and DT-diaphorase, reduces MDA levels	[81]
Lupeol	White cabbage, Green pepper, Strawberry, Olive, Mangoes, and Grapes	Anticancer	Excessive ROS generation, apoptosis, downregulation of m-TOR/PI3K/AKT axis, loss of MMP	[82]
Capsaicin	Chilli pepper, Oregano, Cinnamon, and Cilantro	Carcinogenic	Increase tumoral load and prevalence, histone modification by HDAC and TLR4 dysregulation	[83,84]
Cycasin	Cycad nuts	Carcinogenic	Promotes neoplasia	[85]
β-myrcene	Verbane, Lemongrass, Bay, Rosemary, Basil, Cardamom	Carcinogenic	Promote adenomas and carcinoma	
Alkylbenzenes	*Artemisia dranunculus*, Nutmeg	Carcinogenic	Form DNA adducts, micronuclei, malignant tumors	[86]

Table 1. *Cont.*

Phytochemicals	Found in	Function	Role in Redox Balance	Ref.
Coumarin	Cinnamon, Tonka Beans, and Sweet Clover.	Carcinogenic	Adenomas and carcinomas	
Safrole and Methyleugenol	*Artemisia dranunculus*, Nutmeg	Carcinogenic	Genotoxicity, mutagenicity, chromosomal aberrations	[87,88]
Aristocholic acid	Birthworts or pipevines and Asarum	Carcinogenic	DNA damage, DNA adduct, premalignant alterations	[88]
Isothiocyanates	Cruciferous, Watercress, and Radish	Carcinogenic	Papillary of nodular hyperplasia and carcinoma	[89]

Terpenoids or isoprenoids are diverse phytochemicals showing various biological efficacy, including chemopreventive and chemosensitizing effects in in vitro, preclinical, and clinical settings. Betulinic acid (3β-hydroxy-lup-20 (29)-en-28-oic acid) shows a chemopreventive effect by modulating xenobiotic and antioxidative enzyme activities. Betulinic acid (10 mg/kg b.w.) has been observed to easily neutralize the reactive species by upregulating the activity of phase II enzymes such as GST, γ-Glutamyl transpeptidase, and DT-diaphorase and reducing MDA levels [81]. Moreover, Betulinic acid interacts with xenobiotic metabolizing enzymes to prevent the development of skin papilloma and carcinomas in DMBA (10 mg/kg b.w.)-treated groups [81]. Another triterpene, Lupeol, exhibits anticancer potential against human lung carcinoma cells by excessive ROS generation, apoptosis, and downregulation of the mTOR/PI3K/AKT axis. Moreover, it has been observed that the cytotoxic potential of Lupeol was governed by the loss of MMP, which further leads to higher ROS levels and apoptosis [82]. The phytochemicals and their role in anticancer therapy by perturbing redox homeostasis of the cancer cells can be exploited extensively as one of the important benefits of using natural compounds is few to no side effects in normal cells.

4.2. Toxic Effect of Phytochemicals

More than 10,000 plant metabolites have been identified to date; however, the toxicological characterization of many of these secondary metabolites is not yet preclinically and clinically defined. Another challenge in phytochemical research is the contradictory effects reported in different setups. The contradictory effects of phytochemicals might be dose/concentration related. The different doses might elicit different effects. Few phytochemicals have anticancer properties and show chemopreventive activity when applied in different setups. For instance, Capsaicin acts as a co-carcinogen with DMBA/TPA to induce skin cancer. Applying phytochemicals such as Capsaicin on the dorsal skin of a DMBA-initiated TPA-promoted skin cancer model increases the number, size, and amount of cancer [83]. A recent study showed that continuous exposure of low dose Capsaicin facilitates colorectal cancer progression by further promoting abnormal expression of HDAC and histone modification leading to dysregulation of Toll-like receptor 4 (TLR4) [84].

Another phytochemical, Cycasin (methylazoxymethanol-D-glucoside), commonly found in cycad nuts, was reported to have carcinogenic properties. It was observed that Cycasin and its metabolite, Methylazoxymethanol, promotes neoplasia in the liver, kidneys, and intestines, which prompted the international agency of research on cancer to identify Cycasin and its metabolite as a carcinogen to humans [85]. Furthermore, oral administration of Acyclic monoterpene, β-myrcene (1000 mg/kg b.w.), which is commonly found in verbena, lemongrass, bay, rosemary, basil, cardamom, etc., proliferates liver and kidney (adenomas and carcinomas) cancer [85].

Alkylbenzenes such as Asarones, Elmicin, Estragole, and Safrole, found in essential oils or parts of the Aristolochiaceae plants, *Artemisia dracunculus*, nutmegs, are reported to have carcinogenic properties by forming DNA adducts, micronuclei, and malignant tumors. Moreover, benzopyrene, such as Coumarin, increases the incidence of renal

tubule adenomas, alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinoma, HCC, etc. [86]. Moreover, rodent studies have demonstrated that Safrole and methyleugenol act as hepatocarcinogens. In silico data also report that Myristicin might play a role in carcinogenesis, but studies specify that 2 mM/kg/day of Myristicin for 2 years would lead to a significant but weak increase in hepatic tumor burden. However, conclusive evaluation or data regarding the carcinogenic properties of Myristicin does not exist [87]. Safrole, methyleugenol, and betel quid are further implicated in increased HCC risk, genotoxicity, mutagenicity, and chromosomal aberrations [88].

Aristocholic acid or herbs containing Aristocholic acid are reported to promote HCC both in vitro and in vivo. Aristocholic acid increases HCC incidence of DNA damage, DNA adduct, and premalignant alterations in mice and canines. Moreover, *Gingko biloba* extracts increase the incidence of HCC, hepatocellular necrosis, and hepatoblastoma [88]. Hirose et al. [89] reported the cancer-promoting properties of isothiocyanates. Their study observed that Benzyl isothiocyanates and Phenylethyl isothiocyanates (0.1% of diet) could increase the incidences of papillary nodular hyperplasia and carcinoma in the urinary bladder of the DEN and N-butyl-N-(4hydroxybutyl) nitrosamine-treated rat model. However, several reports have also shown the anticancer activity of the isothiocyanates, suggesting that the dose [90], duration of treatment, or any other circumstance might play the defining role of a phytochemical as a carcinogen, co-carcinogen, or anti-carcinogen (Table 2).

Table 2. Anticancer and carcinogenic effect of phytochemicals doses and toxicity models used.

Phytochemical	Doses	Effect	Models	Ref.
Curcumin	2% *w*/*v* for 30 days	Scavenges ROS and induce scavenging enzymes	Male mice	[61]
	1 kg/day for 2 days	Inhibited NF-kB	HCT116 xenograft in nude mice	[62]
	5–75 µM, for 6–72 h	Inhibited COX-2	HT-29 cells	[62]
	60 µM	Inhibit p53 phosphorylation	Colon Cancer cells	[62]
	0, 5, 10, 20 and 50 µM for various time periods.	Increase ROS, Ca^{2+}, BAX, Cytochrome C, p53, and p21, Caspase 3, and reduce MMP	Colo-205 colon cancer cells	
Resveratrol	50 µM for 24 h	Suppress NAF-1 and upregulate Nrf-2, ROS	Human pancreatic cancer cell lines Panc-1, Mia paca-2, CF pac-1, and BxPC-3	[65]
Apigenin	12.5–50 µM	Overproduction of ROS, genotoxicity, and cell cycle arrest	Papillary thyroid carcinoma cells	[67]
	(20 µM with 10 µM Metformin) or (5 mg/kg b.w with 75 mg/kg b.w. Metformin)	ROS-dependent DNA damage and antioxidant	Human pancreatic cells and mice	[68]
Quercetin	15 µM with 12.5 µM Paclitaxel	ER stress and ROS-induced DNA damage	Prostate cancer cell line	[70]
	0–400 µM	Increased ROS	Breast cancer, MCF-7	[71]
Rutin	0–100 µM	Increase antioxidant status	Liver cancer, HEPG2	[72,73]
	60–100 µM	ROS-generation	Cervical cancer, HPV-C33A	
Caffeic acid	0–500 µM	HDAC inhibtion and ROS generation	Cervical cancer (HeLa and SiHa) and colon cancer (HCT-116 and HCT-15)	[75]

Table 2. *Cont.*

Phytochemical	Doses	Effect	Models	Ref.
Ferulic acid	0–100 μM	Inhibit DNA and lipid damage	Cytoprotective	[77]
Sinapic acid	40 mg/kg b.w.	Modulate LPO markers and increase antioxidant enzyme	Mice	[78]
	125.23 μM	Increase in ROS level	HeP-2 cells	[79]
Gallic acid	0–200 μM; 50 g/ml	Increase in ROS level	Lung cancer, Calu-6 and A549	[80]
Betulinic acid	10 mg/kg b.w.	Upregulate phase II antioxidant enzyme	Mice	[81]
Lupeol	12.5–50 μM	Increased ROS generation	Lung cancer, A427	[82]
Capsaicin	10 mg/kg b.w.	Promoted cancer	Female mice	[83]
	10 mg/kg b.w.	Promoted cancer	Male Wistar rate	
Cycasin	50–75 mg/kg b.w. for 5 days	Promoted cancer	Monkey	[85]
β-myrcene	1000 mg/kg b.w. for 5 days/week	Promoted cancer	Mice	
Coumarin	200 mg/kg b.w.	Promoted cancer	Mice	[86]
Safrole and Methyleugenol	5000 mg/kg b.w.; 0.05 μM/b.w.	Promoted cancer	Mice	[87,88]
Aristocholic acid	5 mg/kg b.w. for 3 weeks	Promoted cancer	Mice	[88]
Gingko biloba extract	0–1000 mg/kg b.w., 5 days per week for 14 weeks.	Promoted Cancer	Mice	[88]
Isothiocyanates	0.1% of diet	Promoted cancer	Mice	[89]
Annexin A2-conjugated curcumin loaded PLGA nanoparticles.	0–80 μM	Inhibit angiogenesis and cancer cell survival	Breast cancer cell lines	[91]
Resveratrol-loaded nanoparticles	100–300 μM	Inhibit metastasis and regulate redox homeostasis	Mice	[92]
DMSA conjugated Apigenin nanoparticles	0–16 μg/mL; 5 mg/kg b.w.	Increased bioavailability and anticancer effect	Lung cancer, B16F10 and A549; Mice	[93]
Quercetin loaded chitosan nanoparticles	12.5–200 μM; 25 mg/kg b.w.	Reduce tumor volume and increase the antioxidant level	Lung cancer, A549; breast cancer, MDA MB 468; Mice	[94]
Nanoemulsion of Rutin	30–300 μM; 20–300 μM; 50–300 μM	Increased bioavailability and anticancer effect	Lung cancer, A549; Colon cancer, Caco-2 human fibroblast cells, respectively	[95]
Rutin loaded-PCL-PEG and PLGA nanoparticles	5–50 mg/kg b.w.	Suppress oxidative stress	Rat	[96]
Rutin loaded PCL-PEG nanoparticles	0–60 μM	Suppress oxidative stress	Human ovarian cancer, Skov3	[97]
Betulinic acid loaded PLGA nanoparticles	10–80 μg/mL; 100 mg/kg b.w.	Balance redox homeostasis	Hep-G2 cells; Wistar rats	

5. Nano-Phytomedicine Is a Hope for Improved Cancer Therapeutics: Evidence from Preclinical Studies

Nanotherapeutics, or nanomedicine, is an emerging field of medical research that focuses on developing and applying nanoparticles for preventive, diagnostic, and therapeutic purposes. The FDA has already approved nanotherapeutics for treating autoimmune diseases, microbial infections, macular degeneration, cancer, and many other conditions [98].

Current anticancer diagnoses and treatment regimes are invasive, non-targeted, and lacking specificity; ergo, they can cause significant undesirable side effects. Nanoparticle-based diagnostics provide more sensitive imaging strategies, and nanotherapeutics provide the option of effective, targeted, and non-invasive treatment [98]. Despite the extensive studies regarding the therapeutic effect of phytomedicine, one of the most debatable aspects of phytotherapy is the poor bioavailability and increased systemic clearance of the phytomedicines. Various alternatives and modifications are being considered to increase phytochemicals' absorption and bioavailability while retaining their biological efficacy [9]. Nanophytomedicine is the annex of nanomedicine that combines the benignancy of nanotherapy and phytomedicine to treat not only infectious diseases but also diseases such as cancer and diabetes, and can be the answer to resolve the poor bioavailability of phytochemicals. Different nanoformulations with different dosages are being developed, including nanocapsules, nanogels, herbal nanoparticles, nanotabelets, nanopaste, nanopowder, and nanoemulsions with the scope of higher solubility and better bioavailability [99].

Low bioavailability and unfavorable pharmacokinetics are one of the major complications of Curcumin based phytotherapy. An interesting study demonstrated that poly-lactic-co-glycolic acid (PLGA)-based Curcumin nanoparticles had improved biological efficacy by bypassing p-glycoprotein efflux actions. Annexin A2 (AnxA2) antibody-conjugated Curcumin-loaded PLGA nanoparticles have shown effective uptake in metastatic breast cancer cells and can successfully target cancerous tissues in vivo. Moreover, AnxA2-CPNPs can effectively inhibit angiogenesis, cancer cell survival, invasion, and metastasis due to the systemic accumulation and sustained release of nanoformulations in the tumor [91]. Cancer therapy has used a variety of Resveratrol-based nanomaterials, including lipids, synthetic polymers, proteins, and glycans. Resveratrol-loaded nanoparticles were found to regulate redox homeostasis in cancer cells. In the melanoma-bearing mouse model, the administration of Resveratrol nanoformulations inhibits metastasis and pulmonary hemorrhage by significantly increasing necrosis and decreasing tumor volume [92].

Apigenin-loaded PLGA nanoparticles and surfaces functionalized with meso-2,3-dimercaptosuccinic acid (DMSA) exhibit therapeutic efficacy against lung cancer and metastasis. Moreover, it was observed that intravenous administration of DMSA-conjugated Apigenin-loaded nanoparticles showed increased retention of Apigenin in mice lungs at 6 and 8 h. Moreover, DMSA-conjugated Apigenin-loaded nanoparticles have shown improved bioavailability along with antitumor and anti-metastasis efficacy following oral administration [93]. Baksi et al. [94] investigated the anticancer efficacy of Quercetin nanoparticles in vitro and in vivo. The intravenous administration of Quercetin-loaded Chitosan nanoparticles in xenograft mice significantly reduced the tumor volume and increased the serum antioxidant level. The bioavailability and solubility of Rutin are improved by premixing with Tween-80 and PEG-600, which form nanoemulsions under biological conditions. The pre-nanoemulsion of Rutin (spherical, 15 nm) has shown anticancer properties in lung and colon cancer cells [95]. Rutin-loaded Poly(ε-caprolactone)-poly(ethylene glycol) and PLGA nanoparticles have shown anticancer properties against ovarian cancer and HCC cells, respectively. The nanoparticle showed higher activities in suppressing oxidative stress, downregulating inflammatory markers, upregulating antioxidant enzymes, and increasing the expression of proapoptotic genes [96,97].

The novel Betulinic acid-loaded 50:50 PLGA nanoparticle showed better therapeutic potential against HCC than its parent compound. The administration of Betulinic acid nanoparticles (100 mg/kg b.w.) balanced redox homeostasis under HCC conditions by restoring various physiological, biochemical, and oxidative parameters. Moreover, Betulinic acid exerts its anti-proliferative properties by overexpressing Caspases [100]. Cho et al. [101] reported a tumor-homing ROS nanoparticle platform that can selectively target malignant tumors. The authors reported that diethyldithiocarbamate (SOD1 inhibitor)-loaded tumor homing ROS NP was administered in combination with sodium nitroprusside. The nanoparticles combined with sodium nitroprusside generate $ONOO^-$ to kill (>95%) cancer cells and ablate them via magnetic hypothermia. Many nano-based phytochemicals are

being prepared in the lab, and their cytotoxic and biological efficacy is being tested. The nano-based phytochemicals have many advantages over natural compounds, including precision in delivering the compounds to organs or tissue only and increased bioavailability.

6. Ascendency of Phytochemicals Mediated Combination Therapy in Chemoprevention

Researchers and scientists are experimenting with various approaches, including the combination of two or more therapeutic drugs, to hunt for a more effective strategy to treat cancer. In recent decades, combination therapy has become becoming the mainspring of cancer research and therapy [102]. Monotherapies are often cytotoxic to both cancer and normal cells, which can cause adverse effects on the overall well-being of the patient. However, the calculated and careful use of combination therapy might help in reducing adverse effects while increasing the efficacy of conventional drugs [102]. Several studies have shown that combination therapies have a better effect on patients' survival rates than monotherapies. Combination therapies include combining (i) traditional chemotherapy along with targeted agents that can inhibit two or more targets in a single, parallel, or compensatory pathway, (ii) gene therapies, and (iii) immunotherapies [103].

Various biological effects of phytochemicals enable them to induce cytotoxicity in cancer cells but also help in enhancing the overall efficacy of already existing therapies, including chemotherapies, radiotherapies, miRNA therapies, and nano-delivery-based therapies [104]. Many chemotherapeutic drugs are observed to function by generating high ROS, inflammatory, and immune responses. Several studies have shown that using plant-based products/compounds/metabolites helps in the chemosensitization of cancer cells. Cisplatin (SP-4-2)-diamminedichloridoplatinum (II) shows therapeutic effects against ovarian, head, cervical, melanoma, ovarian, and lymphoma cancer [105]. Quercetin and Caffeic acid phenyl ester are observed to scavenge Cisplatin-induced free radicals, restore homeostatic balance inside the cells, and protect against apoptosis of bone marrow cells [106]. Lupeol (500 μM/0.2 mL acetone/animal), combined with another phytochemical, Pterostilbene, significantly reduced the volume, number, and multiplicity of skin tumors. The combination groups exert their antioxidative effects by lowering the generation of ROS inside the tumor microenvironment to decelerate tumor proliferation and development [107]. Another study reported that Lupeol, combined with Doxorubicin, acted synergistically on the breast cancer cell line. Lupeol acted as an anticancer agent and adjuvant to reduce proliferation, inhibit migration, and promote apoptosis. Furthermore, the combination compounds downregulated MMP-9 expression to reduce metastasis [108]. Guo et al. [109] reported that breast cancer metastasis was mediated by upregulating the ROS-ERK-MMP9 signaling axis, where an increased concentration of ROS-induced ERK-signaling pathway further stimulated MMP-9 expression.

Chemosensitization and phytochemicals help in combating the toxicity induced by chemotherapeutic drugs to enhance the protective effect of therapy. It has been observed that a combination of Apigenin (3 mg/kg b.w.) and Myricetin (3 mg/kg b.w.) has nephroprotective properties. Apigenin's and Myricetin's protective effects were observed against Cisplatin-induced nephron toxicity. The combination of Apigenin and Myricetin inhibits inflammation, targets the Caspase-3–TNF-α pathway, and reduces serum creatinine levels. Moreover, the phytochemical combination increased GSH and CAT levels while decreasing lipid peroxidation and histopathological damage [110]. In another study, Apigenin (50 mg/kg b.w.) was found to reduce the adverse effects of Sorafenib by decreasing genotoxicity, balancing redox homeostasis, and reducing tissue damage in the liver and kidneys [53].

7. Conclusions and Future Perspective

Redox state and homeostasis play an important role in the survival of cancer cells. It has been observed that until the threshold level is increased, reactive species can help in cancer cell survival and proliferation, while beyond that level, reactive species can cause apoptosis of the cancer cells. Many FDA-approved drugs target the redox balance of cancer

cells to exert cytotoxic effects. Phytochemicals are excellent antioxidants that can modulate redox signaling to kill cancer cells while sparing normal cells. The properties of phytochemicals to target cancer cells while sparing normal cells make them an excellent candidate for cancer therapy. Some phytochemicals are implicated in cancer promotion, progression, and survival. However, it has been observed that they do not cause cancer by disbalancing redox homeostasis but by different pathways. Cancer-promoting effects are generally revealed at higher doses and long exposure. Moreover, many phytochemicals have shown promising effects in combinational therapy. Phytochemicals can act synergistically, as adjuvants, or help in ameliorating the toxic effects of already-approved drugs. However, most of the studies were in vitro, so further preclinical and clinical trials are required to confirm these effects. Additionally, the low bioavailability of phytochemicals can limit their potential benefits. Using newly synthesized derivatives and nano-structured compounds can help increase the phytochemicals' solubility, biological efficacy, and bioavailability.

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Abbreviations

4-HNE	4-Hydroxy-2-Nonenal
4-ONE	4-Oxo-2-Nonenal
ATM	Ataxia-Telengiectasia-Mutated
ATR	ATM and Rad-3 Related
CHK1/2	Checkpoint Kinase
DMBA	7,12-Dimethylbenz[a]anthracene
GPx	Glutathione Peroxidase
MMP	Matrix Metalloproteinase
NOS	Nitric Oxide Synthase
NOX	NADPH Oxidase
NRF-2	Nuclear Factor Related-Erythroid 2
PI3K	Phosphoinositide 3-Kinase
PIP2/3	Phosphatidylinositol di/trisphosphate
PTEN	Phosphatase and Tensin Homolog
PUFA	Polyunsaturated Fatty Acid
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SOD	Superoxide Dismutase
TPA	12-O-Tetradecanoylphorbol-13-Acetate
TR	Thioredoxin Reductase

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