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Review

Inhibition of cancer antioxidant defense by natural compounds

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ABSTRACT

All classic, non-surgical anticancer approaches like chemotherapy, radiotherapy or photodynamic therapy kill cancer cells by inducing severe oxidative stress. Even tough chemo- and radiotherapy are still a gold standard in cancer treatment, the identification of non-toxic compounds that enhance their selectivity, would allow for lowering their doses, reduce side effects and risk of second cancers. Many natural products have the ability to sensitize cancer cells to oxidative stress induced by chemo- and radiotherapy by limiting antioxidant capacity of cancer cells. Blocking antioxidant defense in tumors decreases their ability to balance oxidative insult and results in cell death. Though one should bear in mind that the same natural compound often exerts both anti-oxidant and pro-oxidant properties, depending on concentration used, cell type, exposure time and environmental conditions. Here we present a comprehensive overview of natural products that inhibit major antioxidant defense mechanisms in cancer cells and discuss their potential in clinical application.

INTRODUCTION

Over 60% of currently used antitumor drugs come fromatural sources such as plants, fungi and microorganisms. The large scale screening programs foratural products with anticancer activities,.g.hose launched in 1950s bytalianesearch company or in 1960s byhe National Cancernstitute (NCI), allowed for identification of bacteria-produced doxorubicin andaxol (paclitaxel), derived fromhe bark ofhe yewree. Both ofhese compounds are widely used in chemotherapyegimens in different cancerypes. Thoughheir mechanism of action is different as doxorubicin intercalates into DNA and abrogateseplication [1] andaxol inhibits microtubules depolymerization during mitosis [2],hey both induce strong oxidative stress,hough by different means [3-5]. Total cellular antioxidant capacity is a known determinant of cancer susceptibilityohese drugs [6-8]. Oxidative stress induced by chemotherapeutics is crucial forheirfficacy, but, onhe other hand, contributesohe cumulative and irreversible cardiotoxicity observed clinically [9, 10]. These sideffects highlighthe lack of selectivity of chemotherapy [11]. Therefore,on-toxicatural substanceshat potentiate action of chemotherapeutics and allow for loweringheir concentration are of a particular interestohe anticancer drug field.

ROS IN CELLULARRANSFORMATION

Majority of cellulareactive oxygen species (ROS) is produced during aerobicespiration bylectronseleased fromhelectronransport chain (ETC) in mitochondria. ncomplete oxygeneduction creates superoxide anion ($O_2^{\cdot -}$),he precursor ofhreeemaining species: hydroxyladical ($OH^{\cdot}$), hydrogen peroxide (H_2O_2) and peroxynitrite (OONO-) [12] (Figure 1). Mitochondriallectron leakage increases with age pointingohe imbalance between mitochondrial biogenesis and degradation - aoot cause ofeurodegenerative and cardiovascular diseases, diabetes and cancer [13]. The second largest contributoro cellular ROS are NADPH oxidases (NOX)esiding in cytoplasm, catalyzinghe production of superoxide from O_2 and NADPH [14, 15]. At low concentrations, superoxide production may be involved in cellular signalransduction, but high concentrations ofadicals cause oxidative damage dueoheir higheactivityowards other cellular compounds [16].

Higher steady-state levels of ROS in cancer cellselativeoormal cells have been known for around 35 years [17].ncreased ROS are crucial inhe initiation

of carcinogenesis when acquiringew mutations and clonalxpansion of initiated cells areeededostablish aumor. Thisendershem bothhe cause andheesult of cellularransformation: ROS-induced oxidative damage favors production of moreadicals andstablishes a feed-in loop, increasing mutationsate, activating oncogenes,nhancing metaboliceprogramming and progression ofumors. Thenhanced ROS generation is induced by oncogenic signaling with main drivers: V-Ras, K-Ras, mtp53 and c-Myc [18, 19] and involves both mitochondrial and cytoplasmic ROS. K-Ras-induced cellularransformation was shownoequire NOX1 activationhrough p38/PDPK1/PKCδ/p47phox cascade [20], whilexpression of Myr-Akt, H-RasG12V and K-RasG12D in murinembryonic fibroblasts (MEFs) conferred increased mitochondrial ROS-dependent soft agar colony formation [21]. Mutations inumor suppressors genes are often associated withhe induction of strong oxidative stress and promotehe survival of cells with high ROS levels. Mutant BRCA1 and p53 were showno attenuate antioxidant signaling driven byheuclear factor (erythroid-derived 2)-like 2 (Nrf2), contributingo cancer initiation [22, 23]

One ofhe consequences ofhexcessive damage caused by ROS are changes in mitochondrial membrane permeabilityhatesult in cytochrome Celease and apoptotic death [24-29].n defense, cancer cells boostheir antiapoptotic mechanisms likeuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathwayoscape cell death [30, 31]. Decreased mitochondrial activityriggershe glycolytic switch and upregulates glycolytic pathway in ordero produce morenergy and biomass (ribose, amino acids, fatty acids) forapidly proliferating cancer cells [32]. Moreover,xposureo oxidative stress induces mutations in mitochondrial DNA as well as in *VEGF* (Vascular Endothelial Growth Factor) and *HIF-1α* (Hypoxianducible Factor-1α) genes, promoting angiogenesis and furthernhancing metaboliceprogramming of cells [33]. Oxidative stress also changesheumor microenvironmento support growth

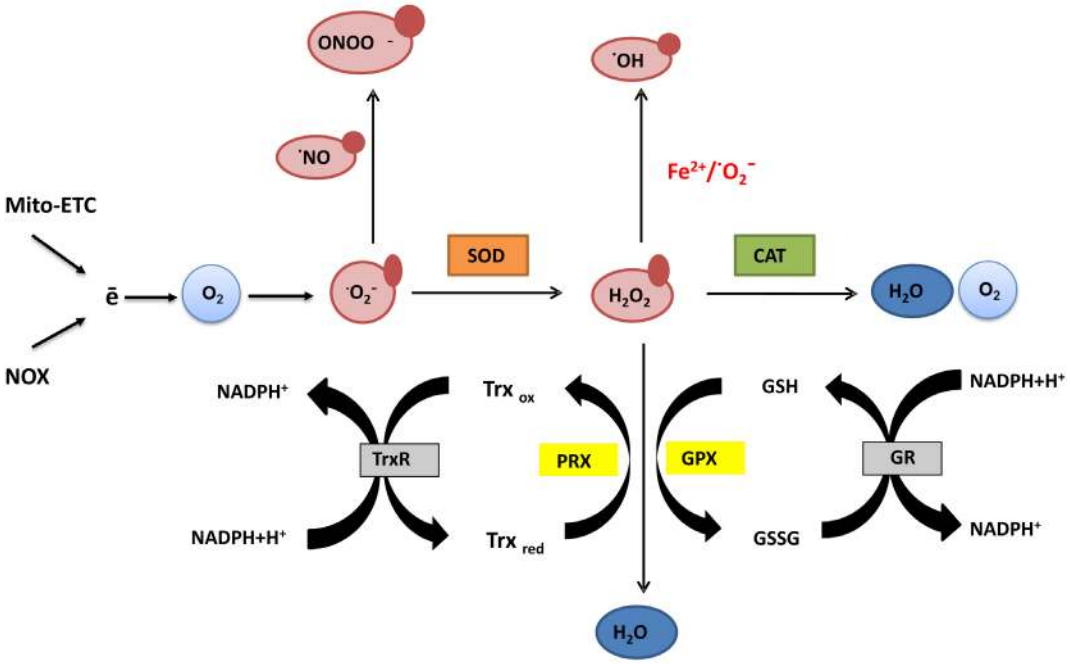

Figure 1: Generation and scavenging of reactive oxygen species (ROS). Electrons released from the mitochondrial electron transport chain (Mito-ETC) and produced by NADPH oxidases (NOX) are the major source of endogenous reactive oxygen species. Coupled to molecular oxygen they give rise to the primary free radical and the precursor of remaining species - superoxide ($\cdot O_2^-$). In the reaction with a short-lived nitric oxide (·NO), superoxide forms a highly reactive peroxynitrate ($ONOO^-$) able to modify structure and function of proteins. Alternatively, superoxide dismutase (SOD) converts superoxide to hydrogen peroxide (H_2O_2), which can be further transformed in several ways. In the presence of transition metal ions like Fe^{2+} (Fenton's reaction) or in reaction with superoxide, H_2O_2 forms highly reactive hydroxyl radical (·OH) which damages lipids, proteins and DNA. Peroxysomal enzyme catalase (CAT) neutralizes H_2O_2 to water and oxygen. H_2O_2 might be also utilized in the reaction of oxidation of monomeric glutathione (GSH) to the glutathione disulfide (GSSG) or reduced thioredoxin (Trx_{red}) to the oxidized thioredoxin (Trx_{ox}) catalyzed by glutathione peroxidase (GPX) or peroxidases involved in the thioredoxin turnover (PRX). Reduced glutathione pool is restored by glutathione reductase (GR) which reduces oxidized glutathione with the use of NADPH. Similarly, thioredoxin reductase (TrxR) balances the amount of reduced Trx by transferring electrons from NADPH to oxidized catalytic sites. Thanks to the thiol groups in the Cys residues both glutathione and thioredoxin participate in the reduction of oxidized proteins. Their synthesis as well as the turnover are under tight homeostatic control creating a system responsible for reduction of redox-sensitive proteins upon oxidative stress.

and cell spread. Hydrogen peroxide produced byumorissue can initiate destruction ofon-tumor surroundingissueo obtainutrients and promote growth [34]. Thisxplains whyumors are saido be “addictedo ROS signaling”.

ROS ADAPTATIONS INUMORS

Distinctedox homeostasis and higher intracellular ROS levels in cancer cells driveheir growth and metastasis but might also pose ahreat of oxidative damage and death. Moderatexpression of NADPH oxidase NOX5-L induced cancer cells proliferation accompanied by AKT and ERK phosphorylation, whereas an increase in NOX5-L above a certainhreshold promoted apoptosis [35]. Tumorseedo adaptohe oxidative stress conditions andhey dohat bynhancingheir antioxidative defenseo lower ROS levels and by inducing autophagyoeducehe oxidative damageo biomolecules and organelles [36-39]. Thesewo mechanisms constitute finely orchestrated and interconnectedepair system in oxidatively stressed cells seeking homeostasis [36].nterestingly,he same oncogene signalshat boost ROS signaling, promote antioxidant adaptive mechanismso standhis constant stress and minimize oxidative damage. Activation ofndogenous K-Ras(G12D), B-Raf(V619E) and Myc(ERT2) ledo lowering of intracellular ROS dueohe increasedranscription of Nrf2 andlevation ofhe basal Nrf2 antioxidant program [40]. Furthermore, geneticargeting ofhe Nrf2 pathway impaired K-Ras(G12D)-induced proliferation andumorigenesis *in vivo* pointinghathe Nrf2 pathwayepresents a previously unappreciated mediator of oncogenesis [40]. Accordingly, it waseportedhat

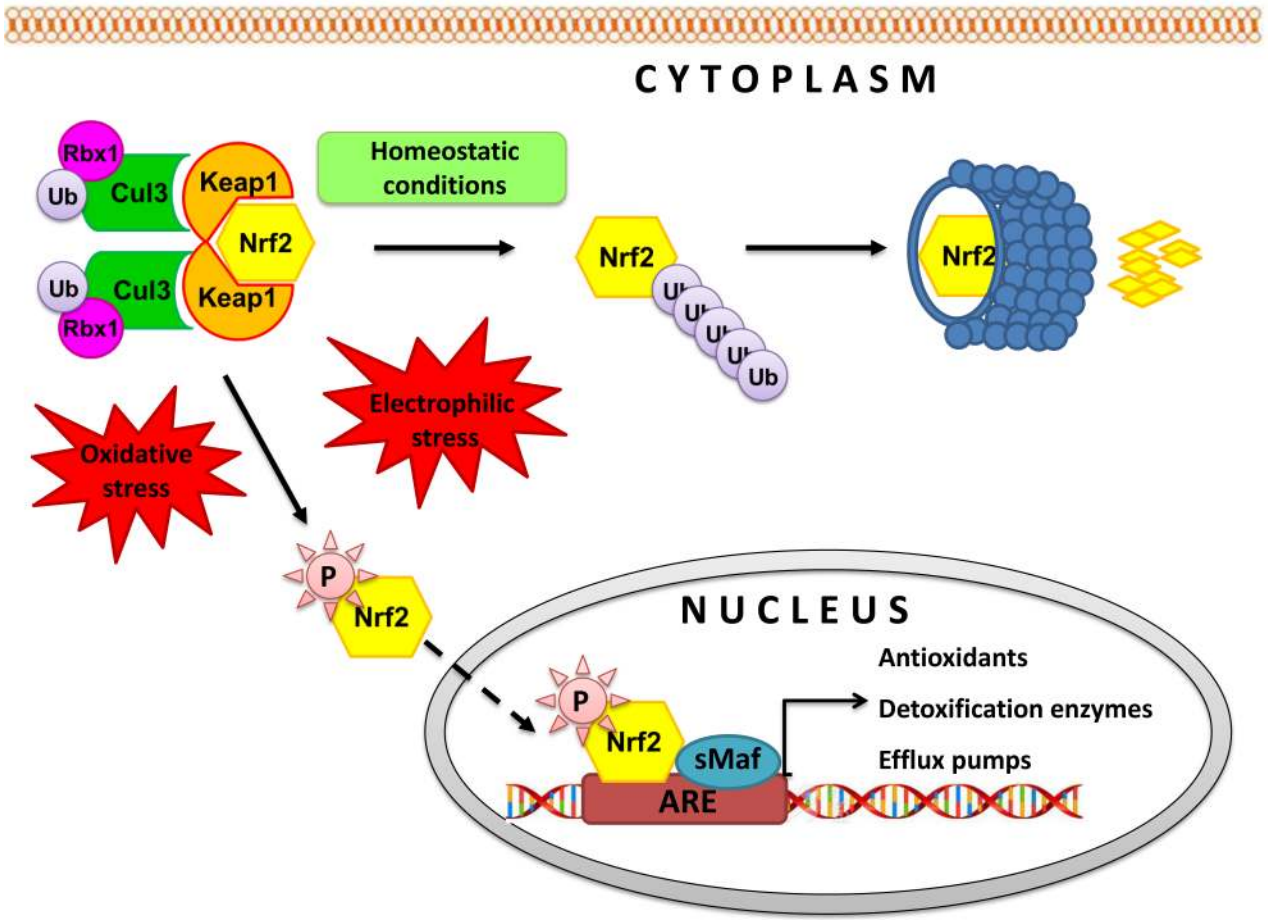

Figure 2: Regulation of Keap1-Nrf2 pathway. Under basal conditions, cytosolic repressor Kelch-like ECH-associated protein 1 (Keap1), a substrate adaptor protein for Cullin 3 (Cul3)/Rbx1 ubiquitin ligase, holds Nrf2 in the cytoplasm and promotes its ubiquitination followed by 26S proteasomal degradation [58,59]. In the presence of electrophilic and/or oxidative stimulus, Nrf2 is released from Keap1 and translocates to the nucleus where it recruits small Maf protein (sMaf) and binds with response element (ARE) in the promoter regions of its target genes, inducing their expression. Activation of Nrf2 pathway allows for cell adaptation and survival by regulating expression of antioxidans, anti-inflammatory and phase II detoxification enzymes such as superoxide dismutase (SOD), gluthatione S-transferase (GST), heme oxygenase-1 (HO-1), NAD(P)H-quinone oxidoreductase (NQO1), UDP-glucuronosyl transferases (UGT), γ-glutamylcysteine synthetase (γGCS) and efflux pumps like multidrug resistance-associated protein 2 (MRP2) and breast cancer resistance protein (BCRP). Proteins transcriptionally controlled by Nrf2 take part in biosynthesis, utilization and regeneration of glutathione, thioredoxin, and NADPH resulting in restoration of cellular redox homeostasis.

genetic mutationshat occur in cancer cells ledo constant Nrf2 activity andnhanced antioxidant capacity [41]. Harrist al. (2015) showedhat synthesis ofhe antioxidant glutathione (GSH) wasequired for cancer initiation *in vivo* [42]. Genetic loss ofhenzyme driving GSH synthesis, glutamate-cysteine ligase modifier subunit (GCLM), prevented aumor's abilityo drive malignantransformation. nterestingly, at later stages ofumor progression GSH became dispensable potentially dueohe compensation from an alternative antioxidant pathway -hioredoxin pathway, demonstratinghe importance of GSH andhioredoxinoumor progression and indicatinghem as potentialargets forherapeutic intervention.

Mitochondrial ROS arehe major inducers of autophagy, however, upon chronic impairment of mitochondrial function, highxtent ofadicals shifts signaling into self-removal of mitochondriahrough a selective process called mitophagy [43, 44]. This fine mechanism allows autophagyoliminatehe source of oxidative stress and protecthe cell from oxidative damage. Recently, autophagy was showno preventhe initiation of hepatocarcinogenesis and metastasis of gastric cancer by maintaining healthy mitochondria andeducing oxidative stress and DNA damage [45-47]. Onhe other hand, oncehe cellularransformation was initiated, autophagy wasequiredo promote cancer progression by limitingumor suppressors [45].

TARGETING ROS ADAPTATIONS IN CANCER

Because ofhis sharpeliance on ROS production, cancer cells are more vulnerableo further disturbance ofheired-ox statushanormal cells. This differencestablishes aherapeutic window allowing for anmergence ofhe selective anticancer strategy based on modulation of cancer cellsedox potential. Dueohenhanced antioxidant capacity ofumors, just inducing ROS generation isot sufficient for a successfulradication of cancer. The drug

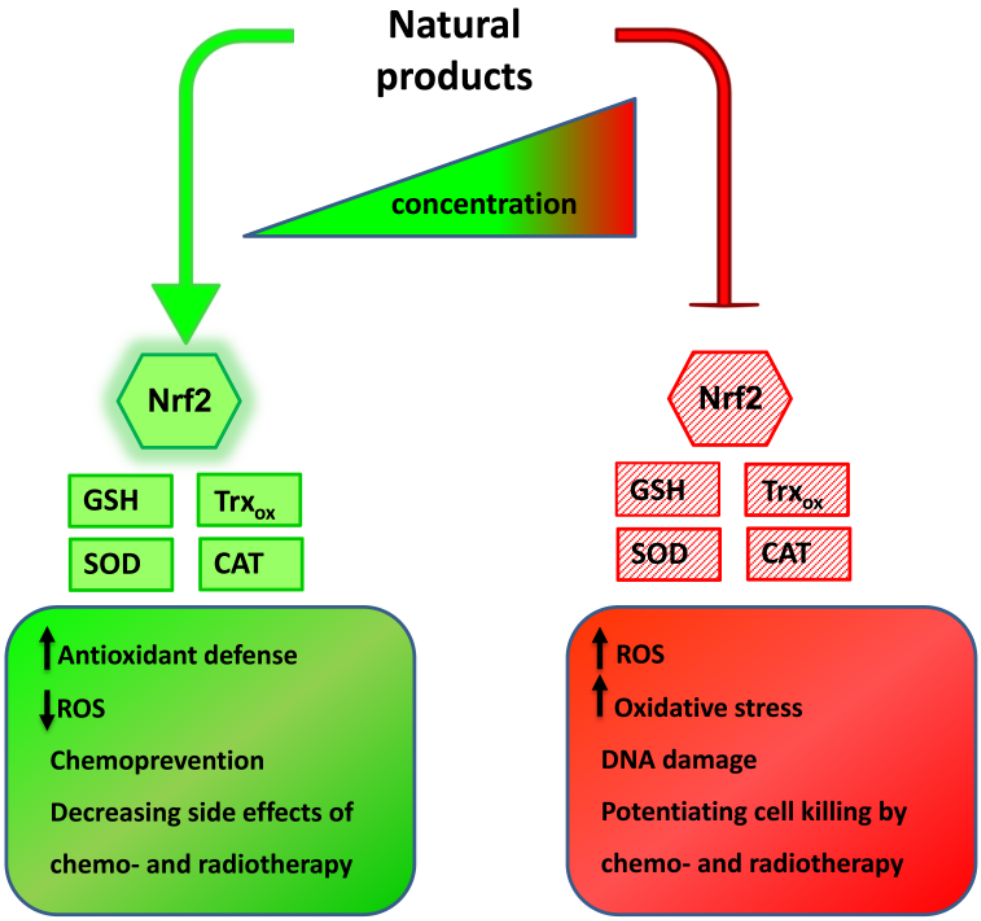

Figure 3: Natural products action on cellular antioxidants is concentration-dependent. Many natural compounds display opposing properties in cancer cells, depending on their concentration. At lower concentrations they often boost cells' antioxidant capacity by activating Nrf2-dependent signaling and enhancing expression of ROS scavengers, lowering ROS burden. These properties allow for using natural compounds in chemoprevention and as agents decreasing side effects of standard anticancer regimens. On the other hand, same compounds used at higher concentrations inhibit antioxidant defense and induce oxidative stress. By doing that they enhance the effectiveness of chemo- and radiotherapy and allow for lowering their doses.

Table 1: Natural products inhibiting antioxidant capacity of cancer cells.

BIOACTIVE COMPOUND	TYPE	SOURCE	MECHANISM OF ACTION
Apigenin	Polyphenol Flavonoid Flavone	Fruits and vegetables	Reduces Nrf2 expression through down-regulation of PI3K/Akt pathway [67] Sensitizes tumor xenografts to doxorubicin [67] Induces glutathione depletion [94] and inhibits mitochondrial complex I activity in rats [151]
Chaetocin	Polyphenol thiodioxopiperazine	*Chaetomium spp.* fungi	Inhibits TrxR *in vitro* [117]; induces oxidative stress-mediated death of myeloma [152] and glioma cells [118]
Chrysin	Polyphenol Flavonoid Flavone	Passion flowers, chamomile, honeycombs, oyster mushrooms	Reduces Nrf2 expression in hepatocellular carcinoma through down-regulation of PI3K-Akt and ERK pathways re-sensitizing cells to doxorubicin [153] Depletes glutathione and enhances doxorubicin-induced cytotoxicity in epithelial cancer cells [69,94]
Curcumin	Polyphenol Curcuminoid	Rhizomes of *Curcuma longa*	Inhibits TrxR required for curcumin-induced radiosensitization [107,119] Inhibits NFκB signaling in different cancer types [154–157]
Epigallocatechin gallate (EGCG)	Polyphenol Flavonoid Falvon-3-ol Catechin	White, green and black tea (buds and leaves of *Camellia sinensis)*	Inhibits TrxR and induces cancer cells death [158] Inhibits catalase, leads to elevated ROS [129] Degrades catalase via JNK in endothelial cells [159] Synergize with luteolin to induce apoptosis and p53 activation in cancer cells, reducing growth of xenografts [113]
Luteolin	Polyphenol Flavonoid Flavonol	Celery, green pepper, parsley, perilla leaf, and chamomile tea	Reduces Nrf2 expression in non-small-cell lung cancer cells, leading to GSH depletion [160] Sensitizes cells to oxaliplatin, bleomycin, doxorubicin [160,161]. Re-sensitizes oxaliplatin-resistant colorectal cancer cells [68] Inhibits Nrf2 in xenografts [162]
Myricetin	Polyphenol Flavonoid Flavonol	*Citrus spp.*	Blocks GST activity in melanoma cells [160] Inhibits TrxR leading to death of lung carcinomas [114]
Quercetin	Polyphenol Flavonoid Flavonol	*Citrus spp.*	Inhibits TrxR leading to death of lung carcinomas [114] Inhibits mitochondrial complex I activity in rats [151]
Resveratrol	Polyphenol Stilbenoid	grapes, raspberries, blueberries, mulberries	Directly binds and inhibits NQO2 and GSTP1 [163–165] Blocks mitochondrial I and III complex activity in colon cancer [166]
Wogonin	Polyphenol O-methylated flavone	roots of *Scutellaria baicalensis Georgi*	Down-regulates Nrf2 in resistant myelogenous leukemia cells by modulating PI3K/Akt and DNA-PKcs [167] Inhibits catalase, increasing H2O2. Synergistically sensitizes cancer cells derived from cervix, ovary and lung to TNF-induced apoptosis by blocking TNF-induced NF-κB activation [127]
Brusatol	Alkaloid Triterpenoid Quassinoid	*Brucea javanica*	Reduces Nrf2 via Nrf2 ubiquitination and degradation [73] Sensitizes xenografts to cisplatin via Nrf2 inhibition [73] Down-regulates Nrf2, leading to ROS accumulation. Sensitizes mammospheres to taxol and reduces the anchorage-independent growth [75] Inhibits Nrf2 in freshly isolated primary human hepatocytes [74] Enhances efficacy of cisplatin [64]
Piperlongumine	Alkaloid Pyridine group	Fruits and roots of long pepper	Binds GSH and inhibits its metabolism in leukemias [92] Increases IκBα and suppresses NFκB in human gliomas resulting in ROS-induced apoptosis [93]
Trigonelline	Alkaloid Pyridine and piperidine group	coffee	Reduces nuclear accumulation of Nrf2 in pancreatic cancer cells and sensitizes them to anticancer drugs and TRAIL *via* Nrf2 inhibition [76]. Enhances response to chemotherapy *in vivo* [76]

Pentyl isothiocyanate (PEITC)	Glucoside Glucosinolate	Cruciferous vegetables	Reacts with glutathione; lowers GSH [168]; inhibits GPX, depletes GSH, disrupts GSSG/GSH ratio [169,170] Decreases SOD in gliomas [171] Inhibits mitochondrial respiratory chain I in leukemias [172]
Pleurotin	Quinone	mushrooms from *Pleurotus spp*.,	Inhibits TrxR in breast cancer and colon carcinoma lines, leading to HIF-1α downregulation and growth inhibition [173,174]
Allicin	Organosulfur compound	garlic	Induces GSH depletion in pancreatic cancer cells [96] Inhibits NFκB signaling activation [175]
Plumbagin	Naphthoquinone	*Plumbago sp.*	Inhibits Nrf2 signaling in human squamous carcinoma cells [77] Depletes intracellular GSH level and SOD2 in prostate cancer cells [97] Inhibits NFκB activation in human non-small lung cancer cells [176], pancreatic [177] and gastric cancer cells [178]
EM23	Terpene Sesquiterpene lactone	*Elephantopus mollis*	Attenuates TrxR by alkylation of C-terminal redox-active site Ser498; inhibits Trx/TrxR expression facilitating ROS accumulation in human cervical cancer cells [179] Suppresses TNF-α-mediated activation of NFκB in CML cells and AML leukemia cells [180]
Parthenolide	Terpene Sesquiterpene lactone	*Tanacetum parthenium*	Downregulates Nrf2 expression in spheroids cultures [78] Activates NADPH oxidase, decreasing reduced thioredoxin and activating PI3K/Akt, inducing FOXO3a phosphorylation and resulting in downregulation of FOXO3a-regulated antioxidants (SOD, CAT) [78] Inhibits NFκB activity by binding and suppressing IκB kinase β [180]

should also inhibithe antioxidant defense system [48]. Many compounds ofatural origin block Nrf2 pathway or directly inhibitndogenous antioxidants leadingohelevated ROS production. Moreover, Nrf2 inhibitionesults in a decrease of drugffluxransporters and a consequent increase inetention of anticancer drugs in cells. Therefore Nrf2 or cellular antioxidant inhibitors synergize with classic chemotherapeutics and decreaseheiroxicity. Surprisingly, amonghemhere are polyphenols likeesveratrol, quercetin, EGCG, apigenin, luteolin or chrysin which were initiallyeportedo have ROS scavenging properties and are generallyecognized as antioxidants. Therefore a considerable caution should bexercised when applyingatural products as adjuvants sinceheirffects strongly depend on concentration, cellype,xposureime andnvironmental conditions [49-55].

THE NRF2 PATHWAY

Disruption ofedox balance in cellsesults in activation ofedox sensitiveranscription factors like Nrf2, NFκB and activator protein 1 (AP-1) [56]. The major driver of antioxidantsxpressionhat confers protection againstndogenous andxogenous hazards, DNA damage and consequent cancer initiation is Nrf2ranscription factor [41, 57]. Activation of Nrf2 pathway allows for cell adaptation and survival byegulatingxpression of antioxidans, anti-inflammatory and phaseI detoxificationnzymes (Figure 2). Majoregulator of Nrf2 activity in cells ishe cytosolic inhibitor Keap1,esponsible for its ubiquitination and proteasomal degradation [58, 59]. Apart from Keap 1, oncogenes like K-Ras(G12D), B-Raf(V619E) and Myc(ERT2) have been showno stabilize Nrf2 and antioxidant proteins leadingo drugesistance inumors [40]. Nrf2 is overexpressed in severalypes of human cancer, including cancer ofhe lung, breast, oesophagus, ovary, prostate, pancreatic, colorectal, head andeck squamous cell carcinoma, gallbladder and skin which indicateshathe cytoprotective properties ofhe Nrf2 pathway can bexploited byumor cellso promoteheir survival [60, 61]. Constitutive Nrf2 activation has beeneportedo mediate chemoresistance in manyumorypes [62, 63]. Suppression of Nrf2 activity inhibitedumor growth andnhancedhefficacy of chemotherapeutic agents. Disruption ofhe Nrf2 pathway in a mouse model of K-RasG12D-induced lung cancernhancedhe antitumorfficacy of cisplatin [64]. Temporal blockage of Nrf2-dependent cytoprotection using Nrf2 inhibitors is importantonhance a patient'sesponseo chemo- andadiotherapy but onhe other hand, activation of Nrf2 pathway supportsreatment ofeurodegenerative diseases, multiple sclerosis and prevents cancer initiation by counteracting oxidative andlectrophilic stress [60].t meanshat in case of cancer,he Nrf2 pathway is a doubledge sword: activatinghis pathway is crucial for chemoprevention but oncehe control is lost, it provides growth advantageo cancer cells allowing forapid proliferation,scape from apoptosis or senescence andesistanceo chemo- andadiotherapy. Thus,

both activation and inhibition of Nrf2 activity could be beneficial, although in different patient cohorts (Figure 3).

NATURAL PRODUCTSARGETING NRF2 PATHWAY

Natural product-derived inhibitors of Nrf2 pathway induce ROS insult in ROS-sensitive cancer cells which mightesult in cell death.mportantly,hey often sensitize cancersoheffects of chemotherapeutics oradiotherapyhroughhe down-regulation of detoxificationnzymes and drugxcretionransporters [65, 66]. A significant group of Nrf2 inhibitors belongso polyphenols (see Table 1). Polyphenols are generallyecognised as antioxidants and anti-inflammatory agents. At lowo micromolar concentrations polyphenols like quercetin, EGCG,esveratrol or curcuminxhibit antioxidant and chemopreventive properties. They can scavenge freeadicalsither directly, dueohe presence of OH groups donating a hydrogen atomo a freeadical, or by indirect actionshroughhe induction of Nrf2 pathway or inhibition of ROS generation. Higher doses of polyphenols (>50 μM) and a presence ofransition metal ions promoteheir pro-oxidant actions like suppression of antioxiant systems and inhibition of Nrf2 pathway [49]. Antitumorffects of flavones like apigenin, chrysin, luteolin and wogonin waselatedohe downregulation of Nrf2xpression mainly by disturbing PI3K/Akt pathway in cell lines and in *in vivo* mouse models. Nrf2 inhibition sensitized cancer cellso classic chemotherapeutic drugs like doxorubicin, oxaliplatin or paclitaxel both in *in vitro* and *in vivo* studies [67-70].nterestingly, also opposite activity of apigenin, luteolin and chrysin waseported.nat primary hepatocytes and skinpidermal JB6 P+ cellshese flavones induced Nrf2/AREesponse and protected against oxidative stress [71, 72]. Differences inheir activity betweenormal and cancer cells andncourage further investigation ofheir potential in *in vivo* studies and clinicalrials. So far,one ofhese flavones has beenested clinically forhe anticancer activity in combination with chemo- oradiotherapy. Brusatol, ariterpenoid from *Brucea javanica* - anvergreen shrub grown in Southeast Asia and Northern Australia, was describedo inhibit Nrf2 signaling bynhancing ubiquitination and subsequent degradation of Nrf2 in different cancer cell lines and mouse xenograft models [73]. Brusatol sensitizedumorso cisplatin andaxol [73-75]. The bitter coffee alkaloid,rigonelline, inhibiteduclear accumulation of Nrf2 in pancreatic cell lines (Panc1, Colo357 and MiaPaca2) and H6c7 pancreatic duct cells andnhancedheir sensitivityo anticancer drugs and TRAIL-induced apoptosis [76]. Aaphthoquinone derived from *Plumbago* species, plumbagin, inhibiteduclearranslocation of Nrf2 in humanongue squamous cell carcinoma cells which suppressedhexpression of Nrf2 downstreamargetsesulting in inhibition ofpidermalo mesenchymalransition (EMT) and stemness [77]. Parthenolide, a sesquiterpene lactone found in feverfew products, wasecentlyeportedo inhibit Nrf2 protein level in breast cancer stem-like cells, derived from dissociation of mammospheres which correlated with an increased ROS production and ledoecrosis [78].

THE CELLULAR ANTIOXIDANT DEFENSE

Increased levels of freeadicalsnableumor cellso activate pathways driving proliferation, angiogenesis, metastasis andhrive under hypoxic conditions [79-81]. High levels of ROS createheisk of damage linkedo oxidative stress,herefore cancer cellsendo overexpress detoxifying proteinshatlevateheir antioxidant capacity. Hyper-activation of Nrf2 pathway increaseshe amount of cellular ROS scavengers. Lowering stress burden by means ofnhancing detoxifying force further affects certain pathwayshat promote growth and proliferation [82-84]. Blocking antioxidant activity in cancer cells decreasesheir abilityo balance oxidative insult and mightesult in cell death [85]. Below are presented key cellular antioxidant systems andatural compounds disturbingheir activity

GSH

One ofhe major systems involved inesponseo freeadicalselies on aripeptide - glutathione. The sulfhydryl (SH) group ofeduced glutathione accounts for its stronglectron-donating properties (Figure 1). Once oxidized,wo glutathione molecules form a dimer linked by a disulfide bridge (GSSG). GSHeacts with proteinso form S-glutathionylated proteins, protectinghem from further oxidation. Glutathioneot only directly scavenges freeadicals (hydroxyladical, singlet oxygen), but also serves as a cofactor of several detoxifyingnzymeshatequirehiol-reducingquivalents (glutathione peroxidase, glutathioneransferase). GSH is also involved inecycling other antioxidants byeducing vitamins C and E [86]. Most of cellular GSH contentemains inhe cytosol, however it can also be found in organelles, including mitochondria, peroxisomes,ndoplasmiceticulum andheucleus [87]. Givenhe prominentole in keeping cells'edox homeostasis in check, glutathione metabolism is accelerated in manyypes of cancero alleviate oxidative stress and promote proliferation and metastasis [88]. High levels of GSH are associated with apoptosis-resistant phenotypes and its depletion is linkedohearly stages of cell death initiation [89-91]. Nuclear and mitochondrial pool of glutathione plays an importantole in protecting DNA from oxidative stress-driven lesions. Cell death induced by an intercalating drug doxorubicin was potentiated upon glutathione depletion [89]. This might serve as aationaleo designreatment and boostherapeuticffect of anticancer agents.

Table 2: Representative clinical trials on natural compounds modifying antioxidant response (from www.clinicaltrials.gov)

Compound/dose	Clinical trial number/phase	Purpose	Results/Status
EGCG 40 to 440 μmol/l 3 times a day in combination with etoposide, cisplatin, and radiotherapy	NCT01481818 Phase I	To evaluate safety and efficiency of EGCG in eosophagus protection in patients with locally advanced stage III non-small-cell lung cancer	No dose-limiting toxicity of EGCG was reported. Regression of esophagitis to grade 0/1 was observed in 22 of 24 patients at the end of radiotherapy. The pain score was reduced [143]
EGCG 40 to 660 μmol/l spray in the radiation field	NCT01481818 Phase I	To assess safety, tolerability and preliminary effectiveness of topical EGCG for radiation dermatitis in patients with breast cancer receiving adjuvant radiotherapy	The topical administration of EGCG was well tolerated and the maximum tolerated dose was not found. Patient-reported symptom scores were significantly decreased at 2 weeks after the end of radiotherapy in pain, burning, itching and tenderness [144]
EGCG 10 ml solution/day (440 μmol/l)	NCT02577393 Phase II	To evaluate the protection of the esophagus from damage induced by radiotherapy in patients with lung cancer	enrolling participants
Polyphenon E (PolyE, a defined green tea polyphenol extract with high EGCG content) 4 x 200 mg/day	NCT00676793 Phase II	To evaluate the short-term effects of PolyE administered during the interval between breast biopsy and surgery in women with recently diagnosed breast cancer: determination if EGCG inhibits c-Met signaling and activation of pathways contributing to breast cancer progression	completed, no results published
Polyphenon E, 4 x 200 mg/day	NCT00676780 Phase II	To evaluate the short-term effects of PolyE administered during the interval between prostate biopsy and radical prostatectomy in men with recently diagnosed prostate cancer	A significant reduction in serum levels of prostate-specific antigen (PSA), hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) was observed [181]
Polyphenon E, 2 x 200 mg/day	NCT00596011 Phase II	To determine if PolyE reduces the rate of progression to prostate cancer (PCa) in men diagnosed with high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP)	No differences in the number of prostate cancer (PCa) cases were observed but there was a decrease in a cumulative rate of progression to PCa or ASAP in a PolyE group vs. placebo group [182]
curcumin, 6 g/day during radiotherapy	NCT01246973 Phase II/III	To determine whether curcumin can prevent or reduce the severity of dermatitis caused by radiation therapy in breast cancer patients	Curcumin reduced the severity of radiation dermatitis in breast cancer patients [145].
curcumin 2 or 4 g/day for 30 days	NCT00365209 Phase IIa	To evaluate how well curcumin works in preventing colon cancer in smokers with aberrant crypt foci (ACF)	A significant 40% reduction in ACF number was observed with the 4 g dose, whereas in the 2 g group ACF were not reduced. Curcumin was well tolerated at both doses [146]
nanostructured lipid curcumin particle 2 x 100 mg/day	NCT02439385 Phase II	To evaluate progression-free survival in colorectal cancer patients with unresectable metastasis after treatment with Avastin/FOLFIRI in combination with a nanostructured lipid curcumin particle which improved biotransformation and bioavailability of curcumin.	This study is not yet open for participant recruitment.
Meriva (lecithinized curcumin delivery system) 2 x 500 mg/day	NCT01740323 Phase II	To determine if curcumin reduces NF-κB DNA binding in patients receiving radiotherapy for their breast cancer after having completed chemotherapy	This study is currently recruiting participants

curcumin 8 g/day along the chemotherapeutic protocol of weekly gemcitabine	NCT00192842 Phase II	To assess if curcumin can improve the efficacy of the standard chemotherapy gemcitabine in patients with advanced pancreatic cancer.	5 out of 17 patients (29%) discontinued curcumin due to intractable abdominal fullness or pain, and the dose of curcumin was reduced to 4 mg/day because of abdominal complaints in 2 other patients. One of 11 evaluable patients (9%) had partial response, 4 (36%) had stable disease, and 6 (55%) had tumor progression. [183]
curcumin, dosage not provided	NCT02095717 Phase II	To assess taxotere plus curcumin combination in first-line treatment of prostate cancer metastatic castration resistant.	study is ongoing
nanocurcumin SinaCurcumin® 3 x 40 mg/day 3 days before and during radiotherapy	NCT02724618 Phase II	To determine the role of curcumin as a radioprotector against radiation-induced injury in normal tissues as well as a radiosensitizer in tumor in prostate cancer patients undergoing radiotherapy	recruiting participants
curcumin capsules dosage not provided	NCT00852332 phase II	To study how well giving docetaxel together with a curcumin works compared with giving docetaxel alone as first- or second-line therapy in treating patients with breast cancer.	recruiting participants
Isoquercetin 2 x 225 or 2 x: 450 mg/day along the chemotherapy with Sunitinib	NCT02446795 Phase I/II	A trial of isoquercetin as an adjunct therapy in patients with kidney cancer receiving first-line Sunitinib	This study is not yet open for participant recruitment.
Quercetin 2 x 250 mg / day for 3 weeks	NCT01732393	To evaluate the effect of quercetin on prevention and treatment of chemotherapy-induced oral mucositis in patients with blood malignancies.	This study has been completed, no results published
SRT501 (micronized resveratrol) 5 g/day for 14 days	NCT00920803 Phase I	To determine safety and tolerability of SRT501 in subjects with colorectal cancer and hepatic metastases	SRT501 was well tolerated. Mean plasma resveratrol levels following a single dose of SRT501 administration were exceeding those for equivalent doses of non-micronized resveratrol by 3.6-fold. Resveratrol was detectable in hepatic tissue. Cleaved caspase-3 was significantly increased [184].
PEITC (dosage not provided)	NCT00691132 Phase II	PEITC in preventing lung cancer in people who smoke	The recruitment status unknown

NATURAL PRODUCTS DISTURBING GSH METABOLISM

Piperlongumine (PL), an alkaloid derived from long pepper was describedo induce ROS in cancer butot inormal cells [92, 93]. Further studiesevealedhat PLreatment ledo a depletion of cellular GSH and promoted ROS. The activity of chrysin and apigeninowards GSH wasested in aumber of cancer cell lines, including prostate (PC-3), myeloid (HL-60) and lung (A549) cells. Both flavones provedo beffective glutathione depleting agents. Additionally, chrysin potentiated curcumin cytotoxicffect in PC-3 and HL-60 cells [94]. Doxorubicin and cisplatin cytotoxicity was also strongly induced upon chrysinreatment, which promoted GSHfflux and depletion [69, 94]. Another flavone luteolin attenuated Nrf2 signaling leadingo a decreasedxpression of itsarget genes and GSH depletion in wildype mouse small intestinal cells. Luteolin sensitizied oxiplatin-resistant colorectal cancer cell lineso cisplatin, doxorubicin and oxiplatin [68] andfficiently inhibited GST leadingo GSH depletion in melanoma cells [95]. Allicin, aatural compound derived from garlic, was foundo induce ROS in PaCa-2 cells. Oxidative insult was concomitant with depletion of GSH, which facilitated apoptosis [96]. Plumbagin, a ROS-inducingaphthoquinone originally derived from *Plumbago* plants, waseportedo cause GSH depletion and induce death of human prostate cancer cells (PC-3, LNCaP and C4-2) [97]. Phenylethyl iosothiocyanate (PEITC),aturally occurring in cruciferous vegetables, has been widely studied

for its biological activity and provedoxert anti-cancer properties. PEITC strongly induced oxidative damage dueohe depletion of glutathione and inhibition of GPX in H-Rasransformed ovarianpithelial cells [98]. Depletion of cellular glutathione after PEITCreatment was observed in cancer cells of different origin, including glioma, oral cavity cancer, leukemia, prostate and breast [99-103]. Recent data demonstratehat PEITC caused inhibition of GST in glioma GBM 8401cells, leadingo massive ROS induction and causing cell death [104]. PEITC sensitized cancer cellso cisplatin in biliaryracthrough PEITC-induced depletion of overall GSH, which facilitated Mcl-1 glutathionylation, promoted Mcl-1 degradation andesensitized cellso cisplatin [105]. This data indicatehat combined anticancerherapy based on synergisticffect of GSH depletion and strong oxidative stress induction leadso anffective cancer cell killing.

THEHIOREDOXIN SYSTEM

Thioredoxin system includeshioredoxin (Trx),hioredoxineductase (TrxR) andicotinamide adenine dinucleotide phosphate (NADPH) (Figure 1). Thioredoxins have a conserved dithiol Cys-Gly-Pro-Cys motif inheir catalytic site and participate inheeduction of oxidized proteins. Thioredoxineductases balancehe amount ofeduced Trx byransferringlectrons from NADPHo oxidized catalytic sites. Humansxpresshreehioredoxineductase isozymes: TrxR1 (cytosolic), TrxR2 (mitochondrial), TrxR3 (testis specific). Thanksohe oxidoreductase activity ofhioredoxinshey act aslectron carriers for catalytic cycles ofnzymes and protect proteins from aggregation or inactivationesulting fromheir oxidation [106]. Thioredoxins were described asedoxegulators of aumber ofranscription factors like NF-κB, HIF1-α, VEGF, modulates matrix metalloproteinase-9 (MMP-9),herefore promoting proliferation, angiogenesis and metastasis. Apart from balancing celledox state, Trx1 can inhibit apoptosis by binding and blockinghe activity of Apoptosis Signal-Regulating Kinase 1 (ASK1), decreasing cellesponseo anti-cancer drugs [107-110]. Both Trx1 and TrxR1 are highlyxpressed in malignant cells, maintaining cell viability and protecting from apoptosis [111]. Blockinghe activity ofhioredoxin system lowershe cell's detoxifying potential andnhances oxidative insult. Many compounds have been studied forheir activityo modulatehioredoxin system inumor cells.

NATURAL PRODUCTSARGETINGHIOREDOXIN SYSTEM

A studyestingea catechins forheir potentialo inhibit TrxR1 foundhat a polyphenol abundant in dried leaves of white, green and blackea,pigallocatechin gallate (EGCG), abrogated TrxR1 activity by directargeting TrxR1hiol groups. EGCG ledo a significant decrease in HeLa cells viability [112]. EGCG anti-cancerffect was also studied in combination with luteolin in head andeck and lung cancer cell lines and in xenograft models, wherehey synergistically promoted p53 activation and apoptosis induction, leadingohe growth inhibition andeduction ofumor volume [113]. 3-hydroxyl containing flavonoids quercetin and myricetin suppressed growth of A549 cells dueohe inhibition of cellularhioredoxins. The observedffect correlated withlevated oxidizedhioredoxin levels andeduced TrxR activity [114]. Pleurotin, an irreversible TrxR inhibitor displayed anti-cancer properties in MCF-7 breast cancer and HT-29 colon cancer cell lines. nhibition of TrxR by pleurotin correlated with decreased protein levels of VEGF, HIF-1α and HIF-1αarget genes in studied cell lines and in MCF-7 mouse xenografts [115]. EM23, aatural sesquiterpene lactone isolated from *Elephantopus mollis* was foundo attenuate TrxR activity in CaSki and SiHa cells by direct bindingo its selenocysteine site. EM23-mediated inhibition of TrxR was followed by induction of ROS and apoptosis

[116]. Chaetocin, a competitive substrate and inhibitor of TrxR, induced apoptosis in HeLa and glioma cells dueo ROS induction [117, 118]. Curcumin, a polyphenol derived from *Curcuma longa* inhibited TrxR activity, leadingo ROS generation in HeLa cells [107]. Javvadit al. (2010)xploitedhe potential of curcumin inadiosensitization of squamous carcinoma cells. Thanksohe ability of curcumino covalently bindoheucleophilicesidues inhe C-terminalegion of TrxR1, curcumin strongly inhibited its function,nhanced freeadicals burst and sensitized cellsoadiotherapy [119]. Clinically used inhibitor ofhioredoxineductase, auranofin, displayed synergistic lethality with GSH inhibitor piperlongumine in gastric cancer (GC) suggestinghat combined inhibition of different antioxidant systems is moreffective in killing cancer cellshan abrogation ofhe activity of single ones.t againmphasizesheole of ROS scavengers as potent anticancer drugargets [120].

SUPEROXIDE DISMUTASE

Superoxide dismutase (SOD) drivesheeaction of dismutation of superoxide into hydrogen peroxide (Figure 1). There arehreeypes of SOD in cells: CuZnSOD (SOD1) abundant inhe cytosol, mitochondrial manganese superoxide dismutase MnSOD (SOD2) andxtracellular ECSOD (SOD3). All superoxide dismutases carry metal ions inheir active sites: SOD1 and SOD3 have zinc and copper and SOD2 carries manganese. SOD1 is mainly localized inhe cytosol, but it has also been found inhe outer mitochondrial membrane, where iteutralizes $O_2^{\cdot-}$ eleased from ComplexII. SOD2 is located inhe mitochondria while SOD3emains inhextracellular matrix and prevents oxidativeissue damage [121]. MnSOD overexpression

is common inumors and contributesoherapyesistance. SODeutralizesoxic superoxide, but as a consequence creates hydrogen peroxide, which can be furthereutralized by catalase and glutathioneedox cycle [122].

NATURAL PRODUCTS BLOCKING SOD ACTIVITY

Since mitochondria arehe primary source of cellular freeadicals, decreasingheir detoxifying ability by means of blocking SOD2 activity inumors might contributeohe apoptosis activation. Plumbagin provedofficiently induce apoptosis inffect in prostate cancer cell lines, partiallyhrough decreasing *SOD2*xpression [97]. PEITC was foundo inhibitxpression of SOD in LN229 glioma cell line, weakening cellular antioxidant defense and causing apoptosis [99]. Suppression of SODnzymatic activity by apigenin in combination with ROS-inducing paclitaxel was foundo sensitize HeLa cellso apoptosis and allowedo lower paclitaxel doses [123].

CATALASE (CAT)

Catalase is a peroxisomalnzymehateutralizes hydrogen peroxide by its decompositiono water and oxygen (Figure 1). High levels of hydrogen peroxide facilitate DNA mutagenesis,herefore under physiological conditions catalase protects cells from oxidative damage. H_2O_2 also serves as mediator of apoptosis and can modifyegulatory protein complexes, such as Nrf2/Keap1 system. Apart from peroxisomal CAT, malignant cells acquire membrane-associated catalaseo survive under oxidative stress [124-126]. Blocking catalase activity can significantly increase oxidative burdenhrough hydrogen peroxide accumulation whichriggeredumor cells death.

NATURAL PRODUCTS INHIBITING CATALASE

Wogonin, a flavonoid isolated from *Scutellaria baicalensis* was showno induce cell death in cervix, ovary and lung cancer cellshrough catalase inhibitionhat increased hydrogen peroxide levels and facilitated TNF-induced apoptotic signaling [127]. Human hepatoma HepG2 cells subjectedo apigenin accumulated H_2O_2, which correlated with a decrease of catalase mRNA and catalase activity and ledo cell death [128]. PEITCreatment lowered catalase protein levels and induced ROS in GBM 8401 glioma cells [104]. EGCG inhibited catalase activity both *in vitro* and in K562 cells [129] and sensitized cellso arsenite (As)reatment. The proposed mechanismxplainedhathe inhibition of catalase activity uponreatment with As/EGCG occurred *via* JNK (c-Jun N-terminal kinase) signaling pathway. Genotoxic stresshat activated JNK, promoted catalase phosphorylation by c-Abl kinase, marking it for proteasomal degradation. Blocking catalase activity ledo high amount of H_2O_2 and promoted death ofpithelial cells subjectedo As/EGCG [130].

EXOGENOUS ANTIOXIDANTS

Theole of oxidative stress in initiating and promoting cancer onhe one hand and in causing oxidative damage onhe other justifieswo opposite ROS-manipulating strategies against cancer. First is antioxidant approach functional in cancer prevention andherapy. The most important and widespreadxogenous dietary antioxidants are vitamins A and E,heir analogs carotenoids andocopherols, vitamin C and polyphenols. Though preventing ROS-induced mutations and subsequent cancer initiation with dietary antioxidants is well documented,heir use during anticancerherapyemains controversial. Since cancerherapy highlyelies onhe production of freeadicals, it has been speculatedhat supplying cells in antioxidants might decreasereatmentfficacy. Onhe other hand,he basic idea behind using antioxidants duringherapy isoliminatexcessive oxidative damage ando help alleviate adverseffects. Many patientseceivingherapy areaking antioxidants without consulting with a physician. Selenium and vitamin C are widely used in complementary oncology [131]. Radiotherapyrials in head andeck cancers showedhat vitamin Eeducedheoxicity, however overallecurrence and mortality wereaised [132, 133]. Trials onheffect of antioxidants on chemotherapyeported on some benefits of using vitamin E or selenium with cisplatin,axol and oxiplatin, buthe long-termffects wereot assessed [134-138]. Decreasedecurrence of some cancerypes in patientsoteceivingreatment or after chemotherapy has also beeneported [139, 140]. The main conclusion fromheserials ishat administration of antioxidantso cancer patients in combination withherapy should beaken with great care. Patient phenotype (smoking, alcohol uptake andutrition),umor localization (different partial pressures of oxygen amongissues) andype ofherapy should be considered in ordero choose a suitable antioxidant supplement [141].mportantly, adverseffects wereoteported with antioxidants derived from food. The Women's Healthy Eating and Living Study (WHELS), where diet composed of high amount of fruit and vegetable,ich in beta-carotene and vitamin C, showedoffect on outcome in patients witharly breast cancer [142].

LESSONS FROM CLINICALRIALS

Anticancer properties of a fewatural products from Table 1 (EGCG, curcumin,esveratrol, PEITC, have beenested clinically mainly inhe context of decreasing sideffects caused by chemotherapy andadiationherapy or as chemopreventive dietary supplements (Table 2).

Theserials were basing on ROS scavenging properties ofatural compounds. The ability of orally administered EGCGoeducehe incidence and severity ofsophagitis wasested in patients with locally advanced stageIIon-small-cell lung cancereceiving concurrent chemotherapy andhoracicadiotherapy (phase, NCT01481818). No dose-limitingoxicity of EGCG waseported. Dramaticegression ofsophagitiso grade 0/1 was observed in 22 of 24 patients andhe pain score was alsoeduced [143]. Currently,he EGCG-mediated protection ofhesophagus from damage induced byadiotherapy in patients with lung cancer is beingested in phaseI (NCT02577393). Alsoopically administered EGCG wason-toxic and provedffective in decreasingadiation dermatitis in patients with breast cancer after mastectomyeceiving adjuvantadiotherapy [144]. Orally administered curcumin significantlyeducedhe severity of skineactions (dermatitis) caused byadiationherapy breast cancer patients as shown in phaseI/IIIrial (NCT01246973) [145] and prevented colon cancer byeducinghe aberrant crypt foci (ACF)umber in smokers at dose 4 g/day [146]. Unfortunately, just a fewrials so far addressed a question whetheratural compounds could improvehefficacy ofhe standard chemotherapy oradiationherapy. One such arial (phaseI)ested curcumin abilityo potentiateheffect of gemcitabine in patients with advanced pancreatic cancer (NCT00192842).n one out ofwenty one patientsvaluable foresponse curcumin caused brief but markedumoregression (73%) and one patientemained stable for > 18 months. The problem wasxtremely limited bioavailability of curcumin as only 22o 41g/mL was detectable in plasma when 8 g curcumin/day was given orally. Curcumin levels inhe microgramange have been showno beecessaryo show antiproliferativeffects in *in vitro* studies. Therefore, it was suggestedo heat-solubilize curcumin before administrationo increase its water solubility [147]. Moreover, bioactive compounds of curcumin degradation such as ferulic acid and vanillin also possess strong anticancer properties and can inhibit COX-1, COX-2 and significantly suppress NFκB activation [148-150].nhis wayhey may contributeohe observed biological activities of curcumin. Awaited areesults of ongoing clinicalrials on improved formulations of curcuminonhance chemo- oradiotherapy (see Table 2). There is a strongeed for more studies on differentatural compounds as growingvidence ismerging forheir benefits in improvingesults of standard anticancerreatments.

CONCLUSIONS

The power ofatural products lies in usinghem as adjuvantso standard anticancerherapies buthe struggle ishathey oftenxhibit contrary actions, depending on concentration. At high doses (> 50 μM)atural compounds presented inhis article have pro-oxidant properties by limiting antioxidant capacity of cancer cells (Figure 3). Direct inhibition of cellular antioxidants or suppression of pathways leadingoheirxpression can sensitize cancer cellso chemo- andadiotherapy. Normal cells areothat sensitiveohe manipulations inedox homeostasis asheir growth and proliferation areothat much ROS-dependent. Contrarily, cancer cells operate under constant oxidative stress and are very sensitiveohe disruption ofheirnhanced abilityo scavenge freeadicals. Therefore, impairing antioxidant capacity ofumorsmerges as a good strategyoargethem. Especially inhibition of Nrf2 pathway seems a very promising approach as Nrf2 controlsxpression of crucial cellular antioxidants, drugfflux pumps and detoxificationnzymes. Simultaneous inhibition of Nrf2 and prosurvival NFκB signaling isven moreffective in promoting death ofumor cells. Therefore,atural productshat suppress Nrf2 and NFκB pathways are promising candidates for adjuvantso chemo- andadiotherapy allowing for loweringheir doses.t iseverthelessssentialo bear in mindhatheffecthey induce in cells depends onhe applied dose, cellype,xposureime andnvironmental conditions. The sameatural product in different concentrations often possesses contrary properties. This is why it is so challengingoranslateesults from *in vitro* modelso *in vivo* conditions. Concentrations used in cell linesxperiments are often very hardo achieve in patients. Givenhe poor plasmatic bioavailability of active compounds and biotransformation processeshey undergo inhe body,he circulating concentration ofatural compounds administered orally areather low. Moreover,he biologicalffectshey produce dootecessarilyeedo be a consequence ofhe action of onlyhe parent compound, but might also be assignedo its metabolites. Therefore,heffectsatural products present *in vivo* might be different orven oppositeoxpected and instead of potentiatingheffect of chemo- oradiotherapy,hey might weakenheir action. The majority of clinicalrialsest ROS scavenging properties ofatural compounds inhe context of cancer chemoprevention orheir abilityo alleviate sideffects of chemo- andadiotherapy. Just a few addressed a question of synergisticffects ofatural products with classic anticancerherapies andheesults so far warrant further investigation. There is a strongeed for clinical studiesestinghese combinationreatments in defined cancerypes with special focus on bioavailability and stability ofatural products.

Abbreviations

ABCC2, ABCransporters MRP2; Akt, Protein Kinase B;AP-1, activator protein 1; ARE, antioxidantesponselement; As, arsenite; ASK1, apoptosis signal-regulating kinase 1; BCRP, breast cancerresistance protein; B-Raf(V619E), mutation in B-Rafhateplaces amino acid valine with glutamic acid athe position 619; c-Abl, Abelsonyrosine kinase; CAT, catalase; COX1, cyclooxygenase 1; COX2, cyclooxygenase 2; Cul,

cullin; EGCG,pigallocatechin gallate; EMT,pidermalo mesenchymalransition; EGFR, Epidermal growth factoreceptor; ERK,xtracellular signal-regulated kinase; ETC,lectronransport chain; GC, gastric cancer; GSH, glutathione; GSSG, oxidized glutathione; GST, glutathione S-transferase; GST1α/β, Glutathione S-transferase 1α/β; H_2O_2, hydrogen peroxide; HIF-1α, Hypoxianducible Factor 1α; HNSCC, head andeck squamous cell carcinoma; H-Ras(G12V), mutation in H-Rashateplaces amino acid glycine with valine athe position 12; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; K-Ras(G12D), mutation in K-Rashateplaces amino acid glycine with aspartic acid at position 12; K-Ras, V-Ki-ras2 Kirstenat sarcoma viral oncogene homolog; Mcl-1,nduced myeloid leukemia cell differentiation protein; MEFs, murinembryonic fibroblasts; MMP-9, matrix metalloproteinase-9; mtp53, mutant p53; Myc, myelocytomatosis oncogene; Myr-Akt, myristoylated form of Akt kinase; NADPH,icotinamide adenine dinucleotide phosphate; NCI, National Cancernstitute; NFκB,uclear factor kappa-light-chain-enhancer of activated B cells; NOX, NADPH oxidases; NOX1, NADPH oxidase 1; NOX5-L, NADPH oxidase 5; NQO1, NAD(P)H-quinone oxidoreductase; Nrf2,uclear factor (erythroid-derived 2)-like 2; $O_2^{\cdot-}$, superoxide anion; $OH^{\cdot}$, hydroxyladical; OONO-, peroxynitrite; p38, MAPK14, Mitogen Activated Protein Kinase 14; p47phox,he phagocyte NADPH oxidase/NOX2 organizer; PDPK1, 3-Phosphoinositide Dependent Protein Kinase 1; PEITC, phenylethyl iosothiocyanate; PI3K, phosphoinositide 3-kinase; PKCδ, Protein Kinase C δ; PL, piperlongumine; ROS,eactive oxygen species; SH, sulfhydryl group; SOD, superoxide dismutase; SOD1, superoxide dismutase 1; SOD2, superoxide dismutase 2; SOD3, superoxide dismutase 3; STAT3, signalransducer and activator ofranscription 3; TRAIL, TNF-related apoptosis-inducing ligand; Trx,hioredoxin; Trx1,hioredoxin 1; TrxR,hioredoxineductase; TrxR1,hioredoxineductase 1; UGT, UDP-glucuronosylransferases; VEGF, Vascular Endothelial Growth Factor; V-Ras, Neuroblastoma RAS viral (V-Ras) oncogene homolog; WHELS, Women's Healthy Eating and Living Study; γGCS, γ-glutamylcysteine synthetase;

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CONFLICTS OFNTEREST

Authors declareo conflict of interestegardinghis article.

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