Therapeutic Effect of Natural Compounds in Targeting ROS-Induced Cancer 102

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Abstract

Every cell within the body maintains homeostasis for the production of energy through mitochondrial oxidation. This homeostasis is disturbed by high metabolic activity, mutations in cellular organelles (mitochondria, lysosomes, and peroxisomes), and crosstalk with infiltrating immune cells. These changes increase the level of reactive oxygen species (ROS) that activates oncogenes or suppresses the tumor suppressor genes through disrupted signaling pathways. The conventional administered therapies against cancer have incomplete efficiency, usually followed by severe repercussions such as drug resistance and tumor relapse. Therefore, an alternative approach has been adopted to replace these therapeutic models in which phytochemicals supplementation increases the chemotherapeutic efficiency in the treatment of ROS-induced cancer. Since these compounds are employed because of their wide-scale bioavailability and their synergism, this demonstrates a gradual decrease in tumorigenesis. In this chapter, we have summarized the plant-derived natural compounds based on their active

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role in modulating oxidative stress and cancer. Also, this chapter describes ROS's impact on inducing oxidative stress and its regulation through the body's innate defenses. These defense mechanisms include modulation through various genes and proteins, which tend to curb the stress level through their antioxidant activity. Mainly, the chapter provides a specific therapeutic role of the natural compounds to regulate ROS. The natural compounds have been categorized based on their function in the classes such as polyphenols (flavonoids and nonflavonoids), other polyphenols (diarylheptanoid (curcumin), and vitamins), alkaloids, terpenoids, quinones, and miscellaneous compounds like essential oils, isothiocyanates, and minerals. The combinations of these phytochemicals can be used to regulate ROS's level for cancer treatment.

Keywords

Cancer · ROS · Oxidative stress · Polyphenols · Antioxidant · Prooxidant

Introduction

A plethora of exhaustive studies and approaches have been conducted and developed to elucidate the mechanisms of cancer progression. Despite this, the mortality rate of cancer is increasing every year worldwide (Manda et al. 2015). The healthy cells produce energy in the form of ATP by the metabolic process of oxidative phosphorylation (OxPhos) (Ralph et al. 2010a), wherein the oxidation of substrates such as pyruvate or lactate, free fatty acids, glutamine or glutamate, and ketone bodies takes place (Ralph et al. 2010b). However, glucose uptake in cancer cells is high and produces lactate in the presence of oxygen. This glycolysis/respiration ratio represents the difference between cancer and healthy cells, known as the Warburg Effect. The metastasis, cancer growth, and recurrence of several types of cancers are mostly due to cancer stem cells (CSCs). These CSCs possess stemness properties, maintain intratumor heterogeneity, and are resistant to radiotherapy and chemotherapy (Phi et al. 2018). Also, the reactive oxygen species-(ROS) induced stress is absent in CSCs, and they possess different machinery of metabolism compared to the non-CSCs. ROS are highly reactive oxygen-containing chemical species such as hydroxyl radical ($OH^{\bullet}$), singlet oxygen ($^1O_2$), and superoxide anion radicals ($O_2^{\bullet -}$) (Jackson and Loeb 2001). Mechanistically, the organelles like lysosomes and peroxisomes maintain the intracellular ROS level, but mitochondria majorly contribute this regulation through electron transport chain (ETC). The ETC channel is composed of four complexes, namely I, II, III, and IV. Electrons released from these complexes react with oxygen within the intermembrane mitochondrial space and matrix, reducing it to form superoxide radicals (Ralph et al. 2010a).

Furthermore, the proapoptotic proteins, Bax, or Bak on mitochondria, induces the mitochondrial outer membrane permeabilization (MOMP) forming pores (Raghav et al. 2012a, 2019). The higher ratio of Bax/Bcl-2 (proapoptotic/antiapoptotic proteins) induces apoptosis and causes the rupture of the membrane (Raghav et al.

2012b). Subsequently, the superoxide free radicals are then transported into the cytoplasm through these pores, where they are transmuted into hydrogen peroxide H_2O_2. The H_2O_2 levels within the cells are now maintained in two ways, either transported out of the cell to maintain the permissible baseline level of H_2O_2 within the cell or oxidized back into H_2O molecules through the Haber-Weiss reaction. This production and maintenance of ROS are due to an imbalanced reduction of oxygen in mitochondria by cellular enzymes like NADPH oxidase, angiotensin II, lipoxygenase, and MPO, or external exposure such as pollution, excess intake of alcohol and tobacco, heavy metals, drugs, UV light or irradiation (Wu et al. 2006). Although low levels of ROS are required by each cell to sustain its homeostasis and maintain the cell cycle, ROS levels higher than the permissible limits can cause massive insult to cellular organelles and DNA. Interestingly, enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX), maintain the redox balance between the reducing and oxidizing species, which regulate cancer cell's proliferation and signaling pathways (Raj et al. 2011). The upregulation of naturally occurring antioxidants like glutathione (GSH) also neutralizes the mutilating effect of ROS (Hanot et al. 2012), failure in which causes DNA damage, lipid peroxidation, and disrupted cell cycle, all ultimately culminating in tumorigenesis.

Thus, it is essential to maintain the ROS homeostasis to overcome the cell's cytotoxicity (Noh et al. 2015). ROS is involved in the initiation, promotion, and progression of cancer (Goetz and Luch 2008). The initiation of cancer demonstrates the DNA mutation, and the promotion represents the apoptosis inhibition that leads to abnormal proliferation of mutated cells. However, the progression is associated with alteration in functional activity. Aside from ROS's role in cancer promotion, it effectively regresses cancer (Diehn et al. 2009; Maraldi et al. 2009). For this purpose, radiotherapy, and phototherapy have been observed to increase ROS's level in cancer cells, which causes sudden death of cells due to high oxidative stress. This elevated ROS level activates cyt c release from the mitochondria that induces apoptotic and necrotic cell death in human carcinoma cells (Rojo et al. 2014). Therefore, it is required to develop new approaches for targeted drug designing, which would deplete high oxidative stress and increase antioxidant levels to eradicate cancer.

The present chapter discusses the regulation of ROS-induced cancer and the biological effect of polyphenols like flavonoids and nonflavonoids, alkaloids, terpenoids, quinines, and other miscellaneous antioxidants such as vitamins, minerals, isothiocyanates, and essential oils. The nonenzymatic important players that control this redox loop are vitamins and minerals, which serve as essential antioxidants. Hereby, this chapter encapsulates a detailed account of all the phytochemicals that have been most exploited to study their roles in the treatment of ROS-induced cancer (Fig. 1).

Natural Compounds in Regulation of ROS Generation

Even though the body has its defense mechanism to fight off the oxidative stress within the system, yet the stress level might become grueling and out of control. The body will then need exogenous sources of antioxidants/prooxidants to keep the stress levels in check and maintain homeostasis. Through years of studies, the most

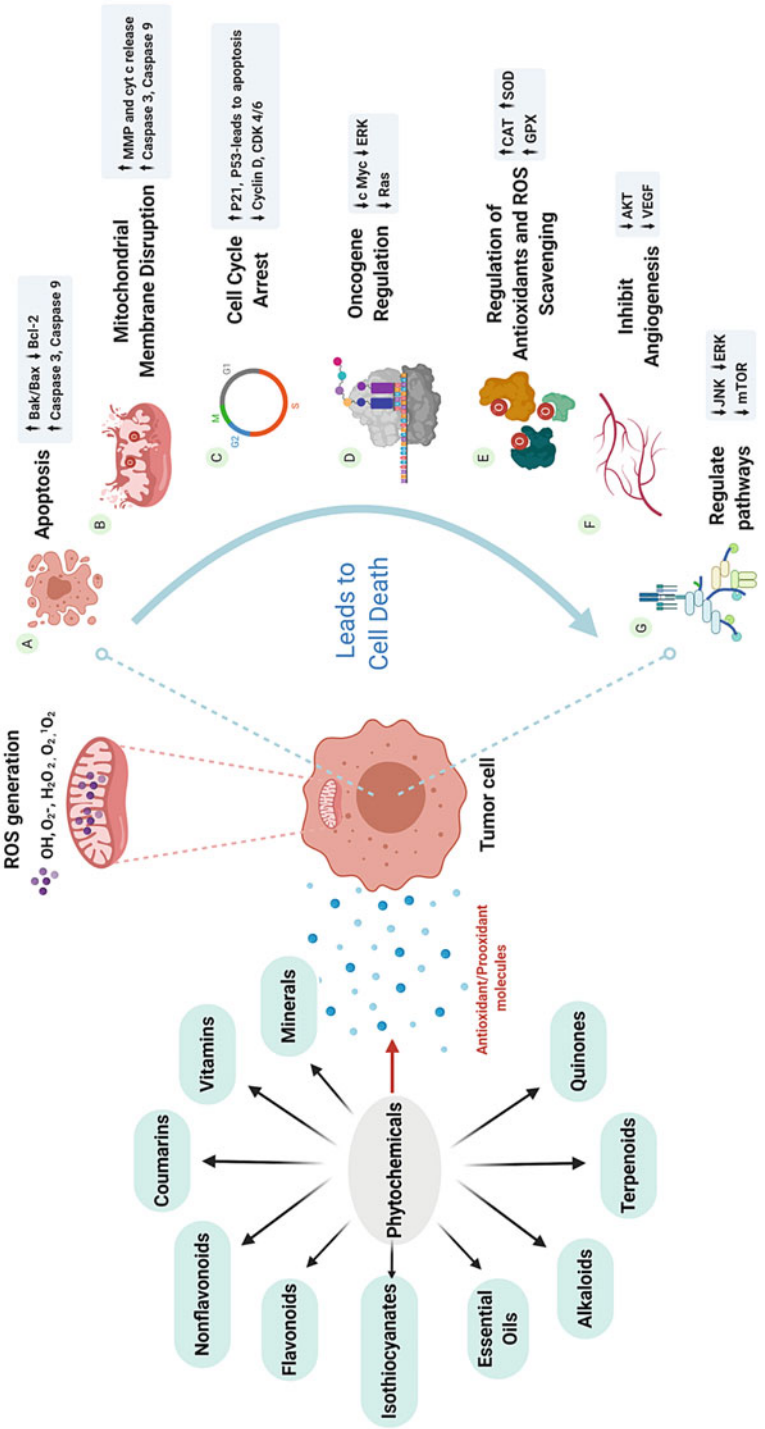


Fig. 1 (continued)

commonly occurring phytochemicals have been discovered and associated in not only tumor prevention but also been modified for therapeutic interventions (Pandey and Rizvi 2009). The commonly explored phytochemicals have been summarized as follows (Table 1).

Polyphenols

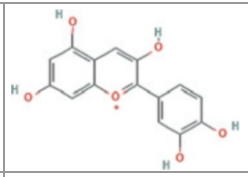
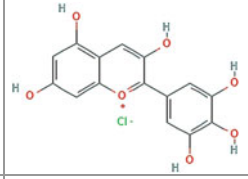
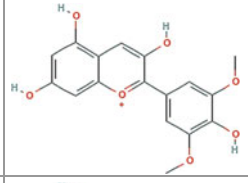
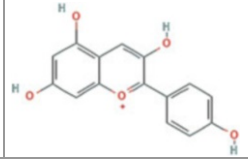
Polyphenols are naturally occurring plant-derived compounds of the ubiquitous family and found abundantly in vegetables, beverages, fruits, and cereals (Firuzi et al. 2004). The polyphenols perform dual functions of antioxidants and pro-oxidants, and their structures possess multiple aromatic or a phenolic ring. The antioxidant polyphenols scavenge ROS containing hydroxyl groups on aromatic rings in mammals, reducing oxidative stress in cancer cells. In contrast, prooxidant polyphenols, including vitamins, have shown similar or even better effects. These natural polyphenols are broadly categorized into two main classes of compounds, viz., flavonoids and nonflavonoids (Table 1).

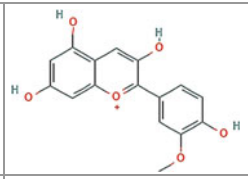
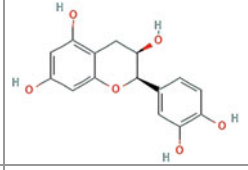
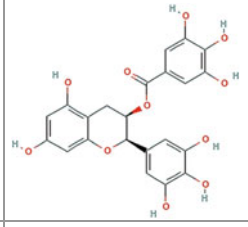
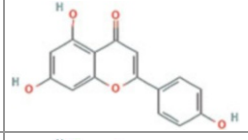
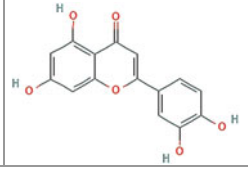
Flavonoids

Flavonoids are natural dietary antioxidants, and their derivatives have a remarkable contribution to prevent cancer (Ahn-Jarvis et al. 2019). The epidemiological analyses reported that an abundant flavonoids diet helps to prevent cancer (Ahn-Jarvis et al. 2019). According to pharmacokinetics study, the liver and GI are the primary sources of flavonoids metabolism, wherein methylation, sulfation, and glucuronidation abolish their hydroxyl group (Jung et al. 2003). Thus, this section summarizes the effects of ROS on cancer, which is regulated through flavonoids.

Fig. 1 Overall representation of anticancer effects of phytochemicals. A typical tumor cell is under oxidative stress due to accumulation of ROS (Reactive oxygen species) such as H_2O_2 (Hydrogen peroxide), O_2 (Oxygen molecule), $O_2^{\cdot -}$ (Superoxide anion radical), $^1O_2$ (Singlet oxygen), and OH^- (Hydroxyl free radicals) free radicals. Natural compounds released by phytochemicals drive tumor cells toward cell death via their antioxidant or prooxidant activity through different mechanisms. (**a**) Apoptosis elevates the expression of proapoptotic proteins, Bak, Bax, and suppressing antiapoptotic protein Bcl2 (B-cell lymphoma 2), which activates caspase 3 and caspase 9, leading to programmed cell death. (**b**) Mitochondrial membrane polarization (MMP) disruption occurs in the mitochondrial membrane that leads to the release of cyt c (cytochrome complex) into cytoplasm that activates caspases inducing cell death. (**c**) Cell cycle arrest activates tumor suppressor genes (p21 and p53), and suppression of Cyclin D and CDK 4, CDK 6 (Cyclin-dependent kinase) activity that blocks the cell cycle and halts tumor cell proliferation. (**d**) Oncogene regulation inhibits oncogenes (c Myc, ERK, Ras). (**e**) Regulation of free radicals through ROS scavenging activity of the compounds controls the oxidative stress within the tumor cell by upregulating antioxidant enzymes CAT (catalase), GPX (Glutathione peroxidase), and SOD (Superoxide dismutase). (**f**) The angiogenesis inhibition initiated by downregulating Akt levels and inhibiting VEGF (Vascular endothelial growth factor) activity. (**g**) The proliferation of tumor cells is controlled through the inhibition of ERK (Extracellular signal-regulated kinase), JNK (c-Jun N-terminal kinase), and mTOR (mammalian Target Of Rapamycin) pathways. Image is created using BioRender.com.

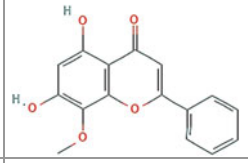
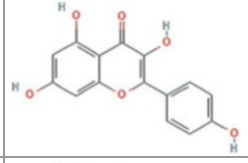
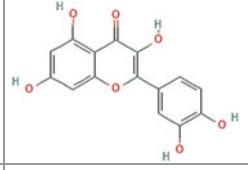
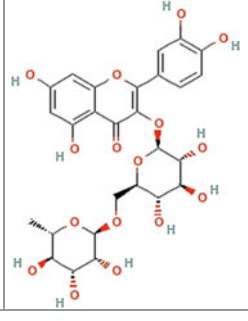
Table 1 Natural compounds are having antioxidants and prooxidant properties classified into flavonoids, nonflavonoids, other phenolic compounds, alkaloids, terpenoids, quinones, and miscellaneous compounds with their anticancer mechanism via ROS scavenging, apoptosis and regulating multiple pathway and genes. The Structure and molecular formula of each compound were retrieved from PubChem

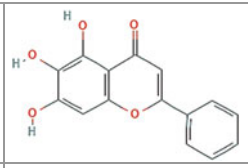
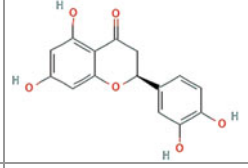
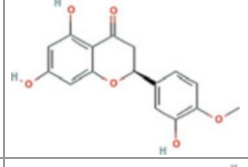
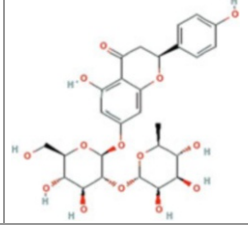
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
Polyphenols						
Flavonoids						
1	Anthocyanidin	Cyanidin	$C_{15}H_{11}O_6$+		Inhibits tumor formation via its anti-angiogenic property	20494645
		Delphinidin	$C_{15}H_{11}O_7$ ($Katio_n$)		Repairs/protects DNA. Anti-angiogenic	25533011
		Malvidin	$C_{17}H_{15}O_7$+		Stimulates apoptosis causing tumor growth regression	25533011
		Pelargonidin	$C_{15}H_{11}O_5$+		Anti-angiogenic that causes inhibition of tumor growth	25533011

		Peonidin	$C_{16}H_{13}O_6+$		Stimulates apoptosis inhibiting tumor growth	25533011
2	Flavan-3-ol	Epicatechin	$C_{15}H_{14}O_6$		Antioxidant. Acts as ROS scavenger by inhibiting HAT enzyme, p-JNK and p38 activity	26180580
		Epigallocatechin-3-gallate (EGCG)	$C_{22}H_{18}O_{11}$		Proapoptotic. Activates caspase pathway and Nrf2, suppresses STAT3 pathway, and upregulates Bax and Bak levels	19602054, 24910845
3	Flavone	Apigenin	$C_{15}H_{10}O_5$		Proapoptotic, arrests cell cycle at G2/M phase and suppresses Nrf2 activity	26180580
		Luteolin	$C_{15}H_{10}O_6$		Proapoptotic. Arrests cell cycle at G2 phase	21601631

(continued)

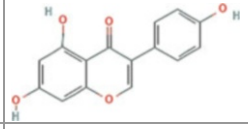
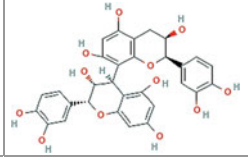
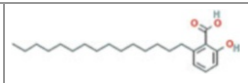
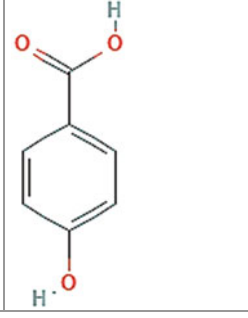
Table 1 (continued)

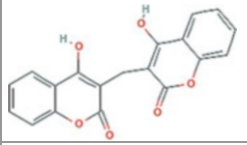
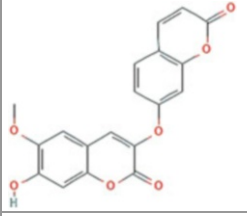
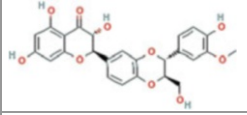
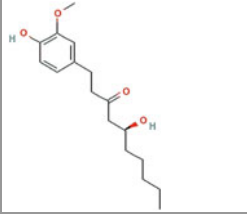
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
		Wogonin	$C_{15}H_{10}O_5$		Inhibits apoptosis through MMD-intrinsic death pathway, and p53 and PUMA activation	24910845
4	Flavonol	Kaempferol	$C_{15}H_{10}O_6$		Induces apoptosis through STAT3, p53, and caspases' activation	25147152
		Quercetin	$C_{15}H_{10}O_7$		Proapoptotic. Free radicals deplete GSH, causing cyt c release due to MMP. Bax and Bak elevated and Bcl-2 and Bcl-xL suppressed	26167193
		Rutin	$C_{27}H_{30}O_{16}$		Induces apoptosis through STAT3, p53, and caspases activation	32823876

5	Flavonone	Baicalein	$C_{15}H_{10}O_5$		Proapoptotic. Caspase 3, 9 activation by cyt c release. p53 and BAX levels increase and Bcl2 reduces	22381695
		Eriodictyol	$C_{15}H_{12}O_6$		Prooxidant. Elevates ROS levels. Causes cytotoxicity by NFkb suppression	21824100
		Hesperetin	$C_{16}H_{14}O_6$		Prooxidant. Elevates ROS levels. Causes cytotoxicity by NFkb suppression	33265939
		Naringin	$C_{27}H_{32}O_{14}$		Prooxidant. Elevates ROS levels. Causes cytotoxicity by NFkb suppression	32979141

(continued)

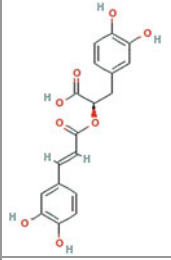
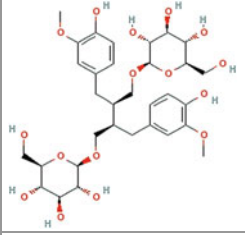
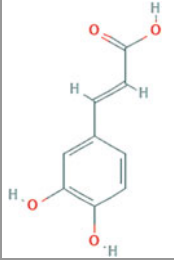
Table 1 (continued)

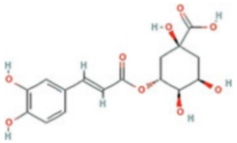
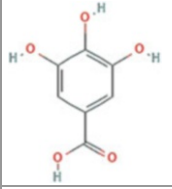
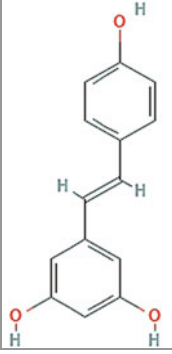
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
6	Isoflavones	Genistein	$C_{15}H_{10}O_5$		Proapoptotic. Causes cell cycle arrest by suppression of 3a-4 mediated metabolism, inhibiting oxidative metabolism	26180580, 23680455
7	Proanthocyanidins	Procyanidin B2	$C_{30}H_{26}O_{12}$		Prooxidant. Induces apoptosis and inhibits metastasis	25533011
Nonflavonoids						
8	Benzoate	Anacardic acid	$C_{22}H_{36}O_3$		Suppresses tumor promotion by inhibiting NFkb and Tip50HAT activation	23041058
9	Benzoic acid	p-Hydroxybenzoic acid	$C_7H_6O_3$		Antioxidant. ROS scavenging activity	32245245

10	Coumarins	Dicumarol	$C_{19}H_{12}O_6$		Cytotoxic to cancer cells by upregulating ROS levels	28617852
		Daphnoretin	$C_{19}H_{12}O_7$		Scavenges ROS. Suppresses DNA and protein synthesis	23680455
11	Flavonolignans	Silibinin	$C_{25}H_{22}O_{10}$		Induces apoptosis by MMP disruption that activates caspases. Acts on ERK ½, NF-KB,c-JUN, c-FOS pathway	22735354
12	Guaiacol	Gingerol	$C_{17}H_{26}O_4$		Induces apoptosis by inhibiting NFkB signaling pathway and p38-MAP kinase	30009484

(continued)

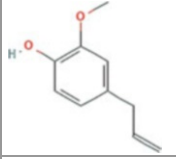
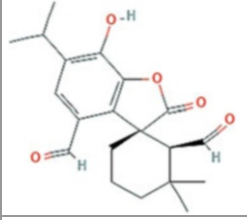
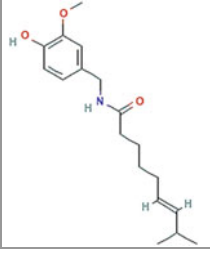
Table 1 (continued)

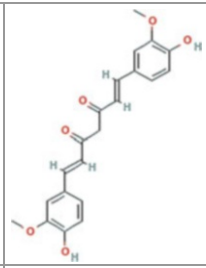
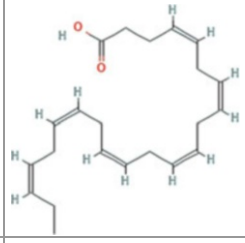
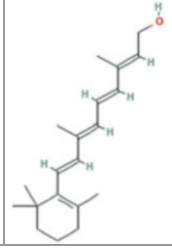
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
13	Hydroxycinnamic acid	Rosmarinic acid	$C_{18}H_{16}O_8$		Antioxidant. Protects the membranes against oxidative damage	19619938
14	Lignans	Secoisolariciresinol diglucoside (SDG)	$C_{32}H_{46}O_{16}$		Proapoptotic. Arrests cell cycle at G2/M phase and inhibits STAT3 activity	28990504
15	Phenolic acid	Caffeic acid	$C_9H_8O_4$		Proapoptotic at high concentration and antiapoptotic at low concentration	25533011

		Chlorogenic acid	$C_{16}H_{18}O_9$		Induces apoptosis by DNA methylation and activation of p38	28990504
		Gallic acid	$C_7H_6O_5$		Elicits protection against colon carcinogenesis by preventing DNA damage	25533011
16	Stilbenoid	Resveratrol	$C_{14}H_{12}O_3$		Both Prooxidant and Antioxidant. Proapoptotic due to disruption of MMP and the release of cyt c. Scavenger of free radicals	23041058

(continued)

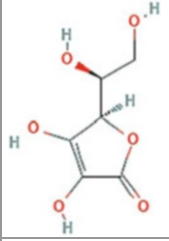
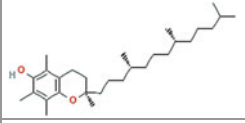
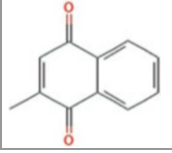
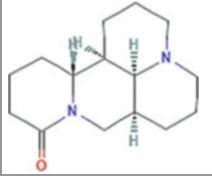
Table 1 (continued)

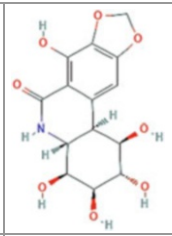
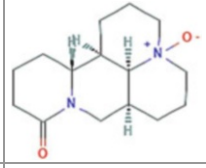
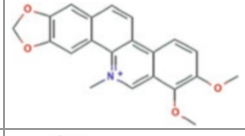
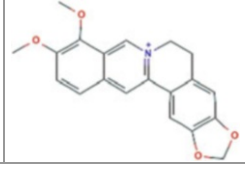
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
Other phenolic compounds						
17	Allylbenzene	Eugenol	$C_{10}H_{12}O_2$		Induces apoptosis by induction of membrane permeability transition, reduction of bcl-2, and cytochrome c	25003106
18	Benzofurans	Rosmadial	$C_{20}H2_4O_5$		Protects the membranes against oxidative damage	25533011
19	Catechol	Capsaicin	$C_{18}H_{27}NO_3$		Proapoptotic. Disrupts ETC system via MMD. Activates intrinsic death pathway	24910845

20	Diarylheptanoid	Curcumin	$C_{21}H_{20}O_6$		Both Antioxidant and Prooxidant. Scavenges ROS radicals and upregulates antioxidant enzymes. Cyt c release due to MMP disruption causes apoptosis	26167193, 25597786, 23916858
21	Vitamin	DHA	$C_{22}H_{32}O_2$		Cytotoxic. Produces an anticancer secondary metabolite 3-mercaptopropionaldehyde	21774786
		Vitamin A	$C_{20}H_{30}O$		Antioxidant. Prevents Lipid peroxidation	24790705

(continued)

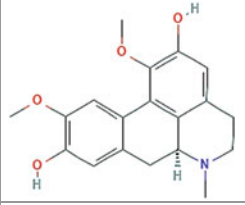
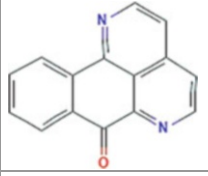
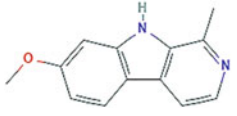
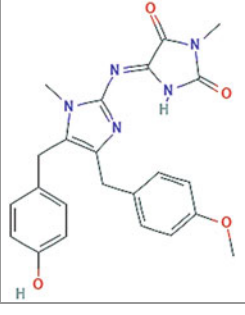
Table 1 (continued)

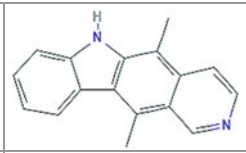
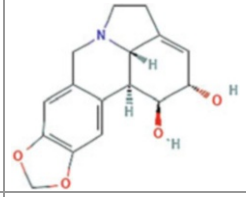
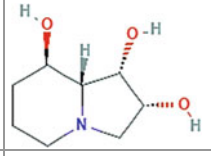
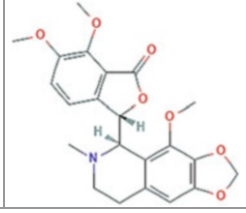
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
		Vitamin C	$C_6H_8O_6$		Antioxidant. Reduces skin malonaldehyde, glutathione, and protein thiols content	24790705
		Vitamin E	$C_{29}H_{50}O_2$		Antioxidant. Proapoptotic. Arrests cell cycle at G1 phase. Protects lipids peroxidation	24004441, 24790705
		Vitamin K3	$C_{11}H_8O_2$		Cytotoxic agent, that generates ROS through redox reaction	26961313
Alkaloids						
22	Allomatrine	Matrine	$C_{15}H_{24}N_2O$		Proapoptotic. Causes decrease in ratio of Bcl-2/Bax, mitochondrial membrane disruption and caspase -3 activation	32477114

23	Amaryllidaceae	Pancratistatin	$C_{14}H_{15}NO_8$		Activates the MMD- intrinsic death pathway, which decreases ATP. Activates Bax, P53 and Caspase	24910845
24	Ammothamnine	Oxymatrine	$C_{15}H_{24}N_2O_2$		Induces apoptosis by increasing oxidative stress that disrupts mitochondrial membrane	21774786
25	Benzophenanthridine	Chelerythrine	$C_{21}H_{18}NO_4$		Proapoptotic causes cell cycle arrest in S phase. Disrupts MMP, causes cyt c release and caspase activation	29780252
26	Benzylisoquinoline	Berberine	$C_{20}H_{18}NO_4+$		Both prooxidant and antioxidant. Scavenges ROS and stabilizes DNA triplexes. Proapoptotic, triggers mitochondrial caspase release	23680455, 23916858

(continued)

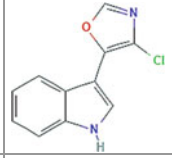
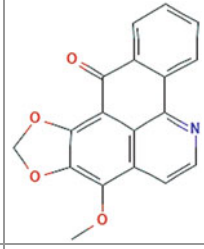
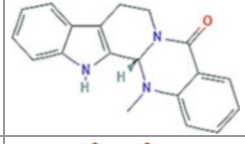
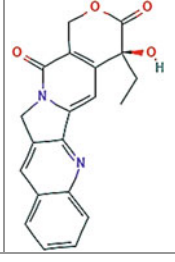
Table 1 (continued)

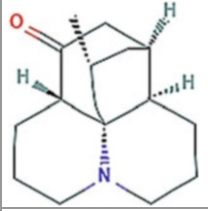
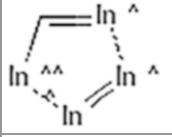
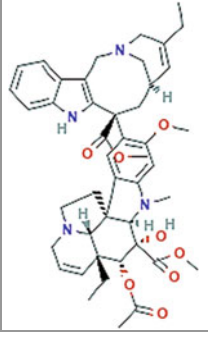
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
		Boldine	$C_{19}H_{21}NO_4$		Anti-inflammatory and cyto-protective	24944509
27	Copyrine	Sampangine	$C_{15}H_8N_2O$		Prooxidant, inhibits telomerase activity which inhibits cell proliferation	26637046
28	Harmala	Harmine	$C_{13}H_{12}N_2O$		Proapoptotic. Downregulates Bcl-2, Mcl-1, and Bcl-xl without affecting Bax. Mitochondrial disruption and caspase 3, 9 activation	27625151
29	Imidazole	Naamidine-A	$C_{23}H_{23}N_5O_4$		Induces apoptosis by mitochondrial disruption and activation of caspases 3, 8 and 9	19369860

30	Indole alkaloid	Ellipticine	$C_{17}H_{14}N_2$		Proapoptotic. Cell cycle arrest when intercalates with DNA and inhibits topoisomerase II. Activates ERK and JNK pathways	25107543
31	Indolizidine	Lycorine	$C_{16}H_{17}NO_4$		Induces apoptosis by activation of caspase-3 and 9. Negative regulation of Mcl-1 and degradation of PARP	23932729
		Swainsonine	$C_8H_{15}NO_3$		Proapoptotic. Causes decrease in ratio of Bcl-2/Bax, mitochondrial membrane disruption, and caspase -3 activation	31781485
32	Isoquinoline	Noscapine	$C_{22}H_{23}NO_7$		Proapoptotic. Enhances Bax expression and reduces Bcl-2 expression, MMP disruption causing cyt c release	32791146

(continued)

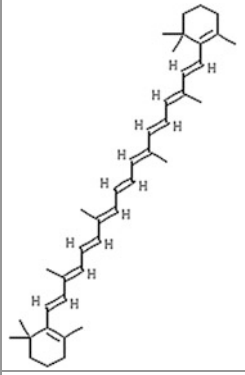
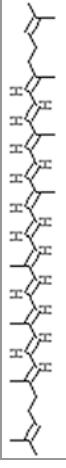
Table 1 (continued)

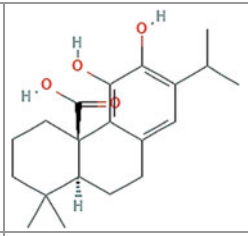
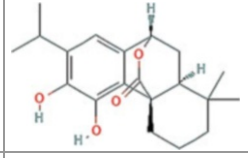
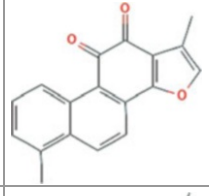
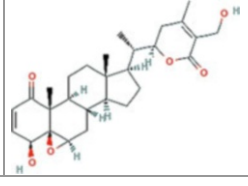
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
33	Oxazole	Streptochlorin	$C_{11}H_7ClN_2O$		Induces apoptosis by activation of Bax and FasL, MMP disruption, Caspase-3 activation, and degradation of PARP	25931814
34	Oxoaporphine	Oxoisoaporphine	$C_{18}H_{11}NO_4$		Prooxidant. Induces apoptosis. Disrupts mitochondrial membrane causing release of cyt c	31892146
35	Quinazoline	Evodiamine	$C_{19}H_{17}N_{30}$		Proapoptotic. Activates Bax and p53, downregulates Bcl-2 and caspase activation. Cell cycle arrest in G2/M phase	32863934
36	Quinoline	Camptothecin	$C_{20}H_{16}N_2O_4$		Induces apoptosis through Fas activation through ROS	21774786

37	Quinolizidine	Lycopodine	$C_{16}H_{25}NO$		Prooxidant and proapoptotic. Causes mitochondrial disruption followed by release of cyt c and caspase-3 activation	31852250, 19786013
38	Vinca alkaloid	SK228	$CHIn_4$		Proapoptotic. Causes decrease in ratio of Bcl-2/Bax, mitochondrial membrane disruption and caspase -3, 9 activation	22285910, 22015944
		Vinorelbine	$C_{45}H_{54}N_4O_8$		Prooxidant. Activates JNK regulated DNA damage. Causes Mitochondrial membrane disruption and caspase activation	30245856

(continued)

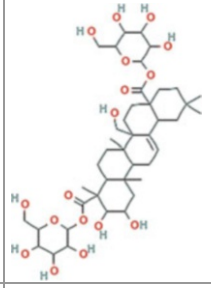
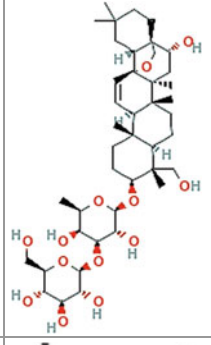
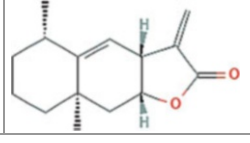
Table 1 (continued)

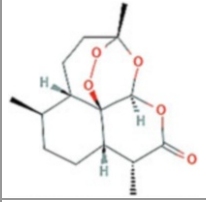
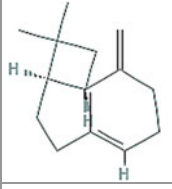
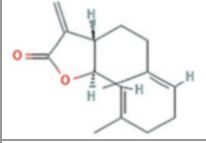
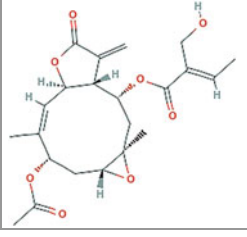
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
Terpenoids						
39	Carotenoid	Carotene	$C_{40}H_{56}$		Antioxidative. Acts as ROS scavenger	24790705
		Lycopene	$C_{40}H_{56}$		Antioxidant. Scavenges ROS, inhibits lipid peroxidation and DNA damage	21615277

40	Diterpene	Carnosic acid	$C_{20}H_{28}O_4$		Protects the membrane against the free radicals generated	25533011
		Carnosol	$C_{20}H_{26}O_4$		Shields the membrane against free radicals-induced oxidative stress	25533011
		Tanshinone	$C_{18}H_{12}O_3$		Prooxidative. Induces apoptosis, cell cycle arrest at G2/M phase. Activates caspase-3 and 9	23916858
41	Lactone	Withaferin A	$C_{28}H_{40}O_{10}S$		Antioxidative. Elevates levels of antioxidant enzymes like catalase, SOD, and glutathione	25949858

(continued)

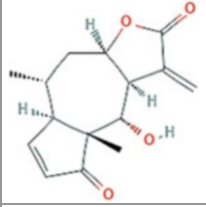
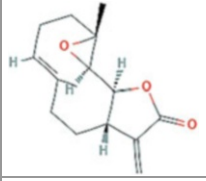
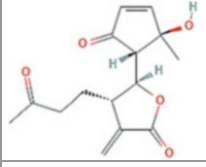
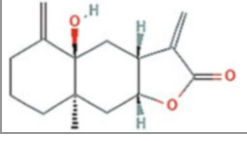
Table 1 (continued)

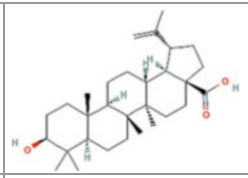
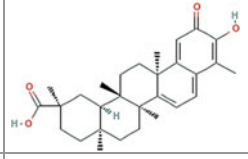
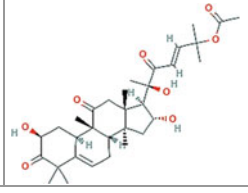
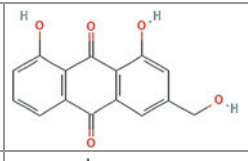
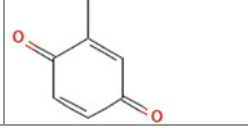
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
42	Saponin	Ginseng	$C_{42}H_{66}O_{17}$		Proapoptotic. Suppresses Nrf2-dependent pathway	21774786
		Saikosaponin	$C_{42}H_{68}O_{13}$		Prooxidant. Induces apoptosis, through oxidative stress	21774786
43	Sesquiterpene lactone	Alantolactone	$C_{15}H_{20}O_2$		Prooxidative. Causes GSH depletion and mitochondrial dysfunction	25656627

		Artemisinins	$C_{15}H_{22}O_5$		Cytotoxic, by generating carbon-centered free radicals. Proapoptotic by MMP loss and GSH depletion	21774786, 25656627
		Beta-Caryophyllene	$C_{15}H_{24}$		Prooxidative via ROS generation and PI3K/AKT/mTOR/S6K1 signaling-dependent apoptosis	25003106
		Costunolide	$C_{15}H_{20}O_2$		Induction of apoptosis under ROS generation due to Jnk activation and MMP loss that leads to cyt c release	25656627
		Eupalinin A	$C_{22}H_{28}O_8$		Prooxidant. ROS generation causes MMP disruption	25656627

(continued)

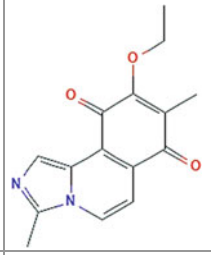
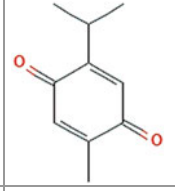
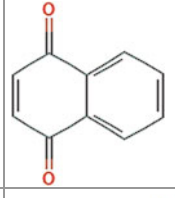
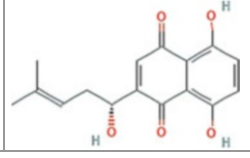
Table 1 (continued)

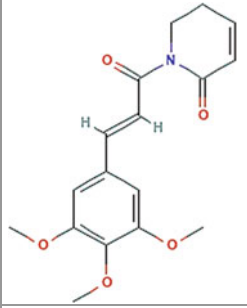
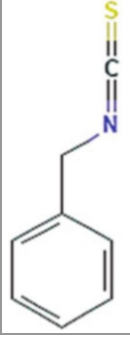
S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
		Helenalin	$C_{15}H_{18}O_4$		Induces apoptosis by disruption of MMP and caspase activation	25656627
		Parthenolide	$C_{15}H_{20}O_3$		Induces apoptosis under JNK activation. MMP loss leads to cyt C release and GSH depletion	25656627
		Salograviolide A Iso-seco-tanapartholide	$C_{15}H_{18}O_5$		Prooxidative. Causes ROS generation that disrupts mitochondrial membrane potential	25656627
		Telekin	$C_{15}H_{20}O_3$		Prooxidative. ROS generation that causes mitochondrial membrane potential disruption	25656627

44	Triterpenoid	Betulinic acid	$C_{30}H_{48}O_3$		Both prooxidant and antioxidant. Decreases tumorigenic miRNAs by ROS production. Also shows ROS scavenging activity	23680455
		Celastrol	$C_{29}H_{38}O_4$		Anti-inflammatory and cytotoxic. Decreases cyclin E, D1 levels. Activation of p53, JNK, caspase 3 and 9 and increase in TSG expression	23916858
		Cucurbitacin	$C_{32}H_{46}O_9$		Antioxidant. Scavenges ROS. Inhibit JAK and STAT pathway	23680455
Quinones						
45	Anthroquinone	Aloe-emodin	$C_{15}H_{10}O_5$		Proapoptotic. Causes cell cycle arrest at G2/M phase and ALP activation	17257888
46	Benzoquinone	Toluquinones	$C_7H_6O_2$		Both Prooxidant and Antioxidant. Can scavenge ROS and also cause cytotoxicity in tumor cells	17876050

(continued)

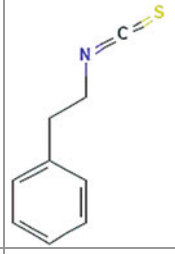
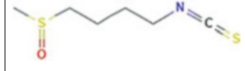
Table 1 (continued)

S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
47	Isoquinoline	Cribrostatin 6	$C_{15}H_{14}N_2O_3$		Proapoptotic by ROS production that suppresses cancer cells' proliferation	20169400
48	Benzoquinone	Thymoquinone	$C_{10}H_{12}O_2$		Dual response, proapoptotic in glioblastoma via cyt c release, antiapoptotic in gastric carcinoma by decreasing caspase activity	27573448
49	Naphthoquinone	Naphtho (1,2-b) furan-4,5-diome	$C_{10}H_6O_2$		Proapoptotic. Cell cycle arrest, Inhibition of PI3K/Akt/mTOR pathway and downregulation of Bcl-2	22381695
		Shikonin	$C_{16}H_{16}O_5$		Anticancer. Inactivates NFkb	22381695

Miscellaneous natural compounds						
50	Dioxolane	Piperlongumine	$C_{17}H_{19}NO_5$		Induces apoptosis by p53 independent pathway, post-oxidative stress caused due to ROS generation	24910845
51	Mineral	Zinc	Zn	Zn	Under deficiency creates a tumor microenvironment. Accumulation is tumorigenic due to overexpression of estrogen receptor	28353636
52	Isothiocyanates	BITC	C_8H_7NS		BITC inhibits the proliferation of cells via inhibiting the ERK-1/2, JNK, and regulating the focal adhesion kinases	28423628

(continued)

Table 1 (continued)

S.No.	Classification	Compounds	Molecular formula	Structures	Mechanism of action	PubMed ID
		PEITC	C_9H_9NS		Proapoptotic. Activates JNK and depletes GSH due to MMP disruption	28423628
		Sulforaphane	$C_6H_{11}NOS_2$		Induces apoptosis under JNK activation. Disrupts MMP that depletes GSH. Inhibits PI3K and ERK1/I	23999506, 18671201
53	Essential Oils	Aniba rosaeodora	–	–	Selectively induces apoptosis, advantageous against cancer cells	25003106
		Artemisia lavandulaefolia	–	–	Causes mitochondrial stress and caspase-activated apoptosis	25003106
		Boswellia sacra	–	–	Selectively induces apoptosis in cancer cells	25003106
		Salvia libanotica	–	–	Inhibits tumor growth	25003106
		Zanthoxylum schinifolium	–	–	Prooxidative. Induces apoptosis via ROS generation	25003106

Majorly, these flavonoids are classified into six sub-classes, including proanthocyanidins (procyanidin B2), anthocyanidins or anthocyanins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin), flavones (luteolin, apigenin), isoflavones (genistein), flavonol (kaempferol, quercetin, rutin), flavan-3-ol (epigallocatechin-3-gallate, (−)-epicatechin, catechin), and flavanone (eriodictyol) (Gibellini et al. 2015; Hollman and Katan 1999).

Proanthocyanidins

The proanthocyanin such as procyanidin B2, is a free-radical scavenger that significantly induces apoptosis and inhibits the proliferation in the 4T1 cell line (mouse breast cancer) (Li et al. 2014). Later, the results of an *in vivo* study where 4T1 cells were injected subcutaneously in Balb/c mice and treated with proanthocyanins were found corroborating with *in vitro* findings. These results exhibited the efficacy of proanthocyanins to exterminate breast cancer and also inhibit metastasis.

Anthocyanidin or Anthocyanin

Anthocyanin is an anti-angiogenic compound rich in berries, which possesses anticarcinogenic properties. This compound inhibits the growth of blood vessels leading to reduced tumor formation. Grape seed proanthocyanidin has been studied to be proapoptotic and even inhibit metastasis in human breast carcinoma cells (Li et al. 2014).

Flavones

Flavones are glycosylated forms of luteolin and apigenin, present in abundance in celery and parsley (Shay et al. 2015). The flavones are cytostatic compounds having the parent structure, 2-phenyl-4H-1-benzopyran-4-one, which prevent proliferation of and stimulate apoptosis in human colon cancer cell line, HT-29.

Apigenin is a flavone commonly found in garlic, cabbage, guava, bilimbi fruit, celery, French peas, bell pepper, and wolfberry leaves. Apigenin causes G_2/M phase cell cycle arrest and inhibits tumorigenesis in colon carcinoma cell lines (SW480, Caco-2 and HT-29). Also, it inhibits chemo-drug-induced ROS-mediated drug resistance in lung cancer, and triggers proapoptotic activity by suppressing NF-κB activation as reported in the prostate, liver, and pancreatic cancer. Luteolin is also found in certain spices like oregano and encourages apoptosis through G_2 cell cycle arrest (Shay et al. 2015).

Isoflavones

Genistein is an isoflavone commonly found in legumes and soybean seeds, and has been used in treating breast cancer, since it inhibits estrogen receptor β, 20-fold higher than estrogen receptor α (Chenand Chien 2014). Therefore, isoflavones are structurally similar to estrogen hormone, hence competing with it to bind at the estrogen receptor and called phytoestrogen. Among all the other polyphenols, genistein is a nontoxic isoflavone, proven to be a potential anticancer agent, though inferior *in vivo* bioavailability, and the low water solubility makes it less efficient for solid tumors. However, at low doses, it leads to more tumor growth and chemo-

resistance in breast cancer. It has been reported to show proapoptotic activity in liver and lung cancer as well via cell cycle arrest (Shay et al. 2015).

Flavonol

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is an example of flavonol found in various plants (broccoli, tea, grapes, cabbage, kale, beans, strawberries leek, endive, and tomato). This antioxidant has shown an increased inhibitory effect on ROS due to more hydroxyl groups. Kaempferol exhibits anti-proliferative activity and induces apoptosis by modulating the targets such as STAT3 and p53, activation of caspases, and ROS production. The synergistic effect of conventional chemotherapeutic drugs and kaempferol reduces the toxicity caused by chemotherapy (Rajendran et al. 2014).

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) has shown anticancer activity and performs dual activities (prooxidant and antioxidant). This ubiquitous natural compound is present in tea, vegetables, onions, nuts, fruits, red wine, and seeds. The effect of quercetin on mitochondrial oxidative phosphorylation is the main topic of interest because of its explicit accumulation in the mitochondria and inhibition of ATP synthase (Gibellini et al. 2015). A similar effect as kaempferol has been shown by quercetin, wherein it scavenges the mitochondrial ROS (O_2^- and H_2O_2) by a high number of hydroxyl groups and conjugated π orbitals. Subsequently, the reaction between quercetin and O_2^- generates an unstable product, semiquinone radicals that cause DNA damage, lipid peroxidation, and production of H_2O_2, later reacting with H_2O_2 decreases the peroxidase level. Quercetin induces apoptosis by upregulating the expression of the proapoptotic protein Bax and downregulating expression of the antiapoptotic protein Bcl-2. This change in protein expression triggers the loss of mitochondrial membrane potential (MMP), subsequently releasing cytochrome c from mitochondria and activating caspase-3 and caspase-7.

Hydroxyethylrutosides (oxerutins) are semi-synthetically derived hydroxyethyl esters prevailing naturally as flavonol rutin (or rutoside). Hydroxyethylrutosides are widely used to treat chronic venous diseases, which decreases hyperpermeability and edema. The commercial drugs, Venoruton, Relvene, and Paroven are the mixtures of hydroxyethylrutosides and have been prescribed for chronic venous disorders (Aziz et al. 2015).

Flavan-3-ol

Epigallocatechin-3-gallate (EGCG) is abundantly found in green tea and used to treat colon cancer. EGCG upregulates the expression of the antioxidant promoting gene, nuclear factor-erythroid-2-Related Factor 2 (Nrf-2). Also, EGCG activates caspase-3/7 that inhibits the expression of Bcl-2, XIAP, and survivin, and induces apoptosis in CSCs isolated from the human prostate tumor. In nasopharyngeal carcinoma, EGCG inhibits the STAT3 pathway, reducing tumor growth initiation and progression (Shay et al. 2015).

(−)-Epicatechin is associated with the group of flavan-3-ol, commonly found in cacao and cacao-based products (green tea and dark chocolate. However, the seaweed like Halimada (Chlorophyceae) contains a high level of polyphenols, such as

(−)-epicatechin and EGCG. Besides, synergistic use of (−)-epicatechin and chemotherapy has shown an improvement in radiotherapy received by MAP kinase mutated patients (Shay et al. 2015). This improvement is due to the 4-hydroxyl groups of (−)-epicatechin, which can scavenge and neutralize the increased ROS in cancer cells. Also, it suppresses the androgen receptor activation and gene transcription that inhibits the proliferation potential of prostate and breast tumors. Mechanistically, inhibiting histone acetyl-transferase (HAT) activity reduces prostate cancer cell viability, while (−)-epicatechin significantly inhibits p38, p-JNK, and cleaved caspase-3 levels when used in combination with radiation treatment.

Catechins, on the other hand, are chemo-preventive agents for prostate cancer, though they have poor efficiency when used in chemotherapy against prostate cancer (Shay et al. 2015).

Flavanone

Flavanones are found abundantly in the fibrous part of citrus fruits compared to their juice. The citrus fruits such as naringin, hesperetin, and eriodictyol are the major source of flavanones. The flavanones suppress NF-κB and increase the ROS level to induce cytotoxicity in cancer cells (Shay et al. 2015).

Nonflavonoids

Nonflavonoids include stilbenes or stilbenoids (pterostilbene and resveratrol), phenolic acid (gallic acid, chlorogenic acid, vanillin acid, ellagic acid, ferulic acid, nordihydroguaiar, methyl gallate, salicylic acid, caffeic acid, and sinapic acid), hydroxycinnamic acid (rosmarinic acid, p-hydroxybenzoic acid, protocatechuic acid, and p-coumaric acid), hydroxybenzoic acids, flavonolignans (silibinin), coumarins (dicumarol, daphnoretin, esculetin, fraxetin, aesculetin), and lignans (secoisolariciresinol diglucoside (SDG)) (Table 1) (Tungmunnithum et al. 2018).

Stilbenes or Stillbenoid

Resveratrol (3,5,4′-trihydroxystilbene) is a phytoalexin, a robust antioxidant abundantly found in red wine, grapes, blueberries, and raspberries. Resveratrol has two isoforms, “cis” and “trans”, and it upregulates the expression of oxidative phosphorylation and mitochondrial biogenesis genes to enhance the mitochondrial function (Lee et al. 2013). Resveratrol effectively scavenges hydrogen peroxide, hydroxyl radical ($OH^{\bullet}$), and superoxide anion, through hydrogen atom transfer and SPLET (Sequential proton loss electron transfer) mechanisms. It is also a chelator of transition metals like copper and iron, which inhibit lipid peroxidation and increase glutathione. The cancer-preventive and cytoprotective effect of resveratrol have been displayed because of its antioxidant activity in several types of cells such as keratinocytes, cardiomyocytes, neurons, brain tissue, and adipocytes. At high concentration, it overwhelms the expression of Bcl-2, which subsequently releases cytochrome c that triggers caspases to induce apoptosis in human carcinoma cells (D’Archivio et al. 2008). Resveratrol has been considered for evaluation in ongoing clinical trials for lymphoma and colon cancer. The combination of resveratrol and

5-fluorouracil (5-FU), compared to 5-FU alone, significantly inhibits the tumor in H22 hepatocarcinoma lymphoma, and colon cancer.

Phenolic Acid

The phenolic acids are present abundantly in red berries like strawberry and cranberry, black radish, mango, tea, coffee, and onion. The derived phenolic acids, including gallic acid, caffeic acid, coumaric acid, ferulic, and gentisic acid are abundantly found in argan oil, olive oil, oats wheat, berries, coffee, and artichokes. Primarily, it has been studied in the *in vitro* melanoma model that the phenolic acids and their derivatives inhibit NF-κB and ROS enzymes (lipoxygenases and XOD) that suppress ROS production and promote antiapoptosis (D'Archivio et al. 2008).

Gallic acid decreases lipid peroxidation and inhibits the DNA damage that prevents colon cancer. Gallic acid significantly increases the number of antioxidants such as SOD, catalase, glutathione reductase and glutathione peroxidase but reduces glutathione in rats. Synergistically, the gallic acid and ECGC chelate the transition metals that decrease toxicity due to ROS, and also activate tumor suppression genes like p21, p53, and Bax.

Caffeic acid works in a dose-dependent manner, being proapoptotic at higher concentration and antiapoptotic at a lower concentration, hence making caffeic acid not a very reliable intervention due to its non-reproducible results.

Hydroxycinnamic Acids and Hydroxybenzoic Acids

Polyphenols such as rosmarinic acid, p-hydroxybenzoic acid, p-coumaric acid, protocatechuic acid have contributed to Lycopus lucidus and tea antioxidant potential measured using DPPH and NO scavenging assays (Lee et al. 2013).

Flavonolignans

Silibinin (silybin) is a natural bioactive component of flavonolignans and has proved to be a potential agent to suppress angiogenesis and growth in the colon, liver, bladder, prostate, and lung cancers. Silibinin upregulates the association of p27/CDK4 and p21/CDK4 complexes while downregulating the E2F1/DP1complex association inhibited by phosphorylation of retinoblastoma in HuH7 cells. Additionally, silibinin arrests the cell cycle at G_1 and G_2-M phase in HepG2 cells and Hep3B cells, respectively, and decreases the expression of cyclin-dependent kinase, (CDK) 2, CDK4, cyclin D1, D3, and E, which collectively increase the level of Kip1/p27 (Varghese et al. 2005).

Coumarins

Coumarin-derived antioxidant, dicumarol, increases the oxidative stress, inducing ROS and cytotoxicity in human pancreatic cancer cells. It mediates oxidative stress within the tumor cell by affecting the ETC in mitochondria, which leads to production of free radicals O_2^- and H_2O_2, culminating in apoptosis (Martin-Cordero et al. 2012).

Lignans

Lignans are formed when residues of cinnamic acid form a dimer. Since they are analogous to human estrogen, they are also called phytoestrogens (Sharma et al. 2018). Lignans are found abundantly in flaxseed and sesame, but not so prevalent in fruits and vegetables. Secoisolariciresinol diglucoside (SDG) is an essential lignan and abundantly found in flaxseed that shows antitumor activity by reducing the high estrogen level in breast and prostate cancer. Sesame oil is a rich source of lignans that shows cell cycle arrest at G_2/M phase and STAT3 inhibition that drives the tumor cells toward apoptosis.

Other Polyphenols

Polyphenols, including diarylheptanoids (curcumin) and vitamins (A, C, E, and K3), have been studied to effectively regress cancer by regulating the oxidative stress levels within tumor cells (Liu et al. 2018). Although these two classes primarily effectuate an antioxidant effect through the mechanism of ROS scavenging, recent studies show that these polyphenols actually act as double-edged sword, showing both prooxidant and antioxidant activity as summarized in Table 1.

Diarylheptanoid

Curcumin

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a diarylheptanoid polyphenol that is isolated from rhizomes of Curcuma longa (turmeric) commonly used as a spice. Curcumin effectively scavenges the hydroxyl radical ($OH^{\bullet}$), O_2^-, and H_2O_2 (Borra et al. 2014). As to its direct role in reacting with ROS, it upregulates the expression of cytoprotective and antioxidant proteins indirectly through Nrf-2. Curcumin suppresses cancer growth by inhibiting *in vitro* and *in vivo* cell proliferation and was found nontoxic to humans. Furthermore, curcumin increases apoptosis through p53-pathway and the upregulation of Bax expression in human cancer cells. Curcumin inhibits proliferation and induces apoptosis; it also suppresses mammosphere formation in several cancers due to G_2/M phase cell cycle arrest. Turmeric-derived compound, diferuloylmethane, has potent anti-inflammatory and antioxidant properties and has been recommended to be included in the diet for the treatment of inflammatory lung disease. Currently, curcumin-based phase-I/II trials are ongoing for the treatment of pancreatic, colorectal cancer, and multiple myeloma (Borra et al. 2014).

Vitamins

Vitamins are essential nutrients not synthesized sufficiently in the human body, thus required for intake from exogenous sources. Vitamins are antioxidants, including vitamins A, C, E, and K considered safe and can be administered in larger doses over a longer duration. Vitamins have the advantage of being recycled back into their

active forms after ROS detoxification, which improves their bioavailability compared to other antioxidants (Liu et al. 2018).

Carotenoid (Vitamin A or Retinol, Fucoxanthin)

Vitamin A (retinol) is a β-carotene derivative formed in the liver known to prevent lipid peroxidation. This vitamin belongs to the retinoid family and is considered a weaker antioxidant as proved by the obtained non-significant difference of progression-free survival between vitamin A treated and chemotherapy-alone patients. The weight and number of tumors formed are effectively reduced on the administration of natural form of vitamin A (retinyl palmitate), while vitamin A drug (13-cis-retinoic acid) only decreases the weight of the generated skin tumors within mice. Nevertheless, the topical application of 13-cis-retinoic acid and retinyl palmitate has a synergistic effect of inhibiting the growth of skin papillomas and is proved effective against skin cancers (Liu et al. 2018).

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble potent reducing antioxidant found mostly in citrus fruits as the oxidized form, L-ascorbic acid. It acts primarily by reacting with hydroxyl and lipid peroxyl free radicals, transforming them into H_2O and getting self-oxidized into dehydro-L-ascorbic acid (Liu et al. 2018). Vitamin C protects cell membranes peroxidation efficiently and scavenges H_2O_2, superoxide, $^1O_2$, peroxyl radicals, and hydroxyl radical. Under the Warburg effect, GLUT isoforms are overexpressed in the cancer cells' membranes, which increases the glucose uptake by the tumor cells and permits the preferential uptake of dehydro-L-ascorbic acid. This oxidized form of vitamin C is an essential iron scavenger that promotes the reduction of ferric ions into ferrous ions through cellular metalloenzymes. Nonetheless, its oral administration does not affect ultraviolet (UV) radiation-induced erythema in patients. Vitamin C also reduces skin malonaldehyde, glutathione, and protein thiols content, though it increases collagen production, improves inflammatory skin conditions, and protects against the damaging effect of UVA and UVB rays (Pandey and Rizvi 2009).

Dehydroascorbic Acid (DHA)

DHA is the oxidized form of ascorbic acid and is also abundantly present in the human diet. DHA selectively targets the cancer cells to eliminate the growing tumors in the mouse models. In this approach, DHA reacts with homocysteine thiolactone, a chemical present in cancer cells, and converted into a cytotoxic compound, 3-mercaptopropionaldehyde (Song and Kim 2016).

Vitamin E

Vitamin E is a lipid-soluble vitamin, prevalent either as tocopherols or tocotrienols. Its variants have four isoforms, which differ in the locus and quantity of methyl groups present on the aliphatic chain. The level of vitamin E was found reduced in UVR-induced oxidative stress conditions, whereas its treatment to the cells reduces the amount of sunburn. Likewise, lower levels of vitamin E compared to control

have been observed in breast cancer. Tocopherols is a lipid-soluble derivative of tyrosine, found in plasma membranes that reacts with peroxide radicals and singlet molecular oxygen ($^1O_2$), and protect lipids against peroxidative damage. Vitamin E has both antioxidant and UV absorptive properties, which protect against UV-induced skin photodamage (Liu et al. 2018).

Also, Tocotrienol acted as an antioxidant and have antitumor or proapoptotic properties. The chemistry of this antioxidant property involves the donation of hydrogen ions from its side-chain methyl groups to the ROS, which hence terminates the serial peroxidation of lipids and hydroxyl ions. It promotes epigenetic modifications and demonstrates the antitumor activity by G_1 phase cell cycle arrest in pancreatic, colon, cervical, and bladder cancer (Liu et al. 2018).

The combination of Tocotrienol with antitumor drugs like simvastatin decreases the self-renewal ability through inhibiting STAT3 levels within the CSCs in breast cancer (Liu et al. 2018).

Vitamin K3

The single-electron reduction of vitamin K3 produces semiquinone that again gets oxidized back to vitamin K3 in the presence of oxygen. This reduction of vitamin K, combined with chemotherapeutic drugs, produces ROS that causes oxidative stress and cytotoxicity in cancer cells (Badave et al. 2016).

Alkaloids

Alkaloids are a class of nitrogen-containing organic molecules. Most of the alkaloids have been extracted from natural herbs and serve as a rich reservoir for drug discovery, owing to their anti-proliferation and anti-metastasis activity (Habli et al. 2017). Among the alkaloids discovered so far, the extensively studied molecules, sampangine, boldine, quinoline, ellipticine, and berberine, are summarized in Table 1.

Sampangine

Sampangine is a class of polycycles copyrine alkaloids, naturally present in the Cananga odorata, Anaxagorea dolichocarpa, and Duguetia hadrantha stem bark. These molecules exert their anticancer activity through the generation of ROS, inhibition of telomerase activity, and DNA interaction to form G-quadruplex (G4) complexes at telomere, where they block telomerase hybridization and catalytically elongate the telomere, and inhibits cell proliferation (Rodriguez-Arce et al. 2020).

Boldine

Boldine (boldo tree extract) stands out due to its higher polyphenol content and has various characteristics such as anti-inflammatory, hepatoprotective, cryoprotective, and choleretic property. It induces apoptosis by downregulating Bcl-2 and Hsp70,

while upregualting Bax protein levels. It is also known to activate caspase 3/7 and caspase 9 that leads to cell death ultimately (Paydar et al. 2014).

Quinoline

Camptothecin is a quinoline alkaloid that exhibits antitumor and antileukemia effects. It also activates Fas to induce apoptosis through ROS and oxidative stress pathways in highly resistant medulloblastoma (a malignant brain tumor). Its analogs have also been studied to be proapoptotic in myeloid leukemia cells by activating protein kinase Cδ through proteolytic action (Kovacic and Somanathan 2011).

Pyridocarbazole

Ellipticine is an antineoplastic pyridocarbazole and intercalates within DNA and is an efficacious inhibitor of mammalian topoisomerase II. Ellipticine alkaloid elevates oxidative stress that breakdown mitochondrial transmembrane potential and releases cytochrome c, leading to apoptosis in human melanoma cells. It induces oxidative stress by arresting cells at G_2/M phase and disrupting mitochondrial potential that leads to ROS generation, and ultimately apoptosis by AIF release through caspase-independent pathway (Saeidnia and Abdollahi 2013).

Isoquinoline

Berberine is a derivative of isoquinoline alkaloid isolated from Chinese medicinal herb Huanglian and shows antineoplastic activities against various cancers. Berberine triggers mitochondrial-dependent apoptosis that activates caspase release and decreases Bcl-XL, Bcl-2, and Bid expression in hepatocellular carcinoma (Saeidnia et al. 2013).

Terpenoids

Terpenoids is another class of chemo-preventive natural compound, mostly isolated from traditional Chinese herbs (Huang et al. 2012; Yang et al. 2020). Based on their structure, the terpenoids have been classified into five major classes, namely, triterpenoids (betulinic acid, oleanolic acid, celastrol), lactone sesquiterpenoids (artemisinin, parthenolide), saponins (ginseng), caretonoids (carotene, lycopene), and diterpernoids (tanshinone) (Table 1).

Triterpenoid

Triterpenoids such as betulinic acid, its derivatives (methyl ursolate, β-boswellic acid, and celastrol), and synthetic analogs (glycyrrhetinic acid [2-cyano-3,11-dioxo-18β-oleana-1,12-dien-30-oc acid (CDODA)] and oleanolic acid [2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO)]) are effective anticancer agents that exhibit antiproliferative activities. These compounds induce ROS generation, and sequentially decrease miR-27a, miR-20a/miR-17-5p expression in several cancer cell lines (Saeidnia and Abdollahi 2013).

Celastrol or tripterine is a Chinese herb extract and an antioxidant of quinine methide triterpenoid, which demonstrates anticancer, and anti-inflammatory effect. Celastrol decreases the levels of cyclin E and cyclin D1 while it increases the levels of p21 and p27 that collectively inhibit the hepatic tumor cells' growth (Hu et al. 2013).

Lactone Sesquiterpenoid

Lactone sesquiterpenoid is a plant-derived compound that induces oxidative stress and acts as cytotoxic/anticancer activity. Increased production of ROS promotes the characteristics of cancer development and progression in healthy cells. Oppositely, increased ROS initiates apoptosis through the mitochondrial-dependent pathway and suppresses cancer progression. Generally, Lactone sesquiterpenoid decreases the high level of GSH to induce apoptosis in cancer cells (Gach et al. 2015).

Artemisinins is an antimalarial compound known to have cytotoxic effect in tumors. Artemisinins elevate ROS by accommodating an endoperoxide (–C–O–O–C–) bridge that undergoes cleavage to generate carbon-centered free radicals. This culminates in apoptosis by inducing oxidative stress, cell cycle arrest, and autophagy (Kovacic and Somanathan 2011).

Parthenolide is a sesquiterpene-derived compound known to exhibit the anti-inflammatory and anticancer activity. Parthenolide suppresses proapoptotic genes through inhibition of the transcriptional activity of NF-κB and STAT genes or by direct inhibition of associated kinases (IKK-β) (Takai et al. 2013).

Saponins

Saponin derivatives are currently being accepted as anticancer agents. Saikosaponin is a derivative known to sensitize cancer cells to cisplatin through oxidative stress-mediated apoptosis, making its combination with cisplatin a practical therapeutic approach.

Ginseng is another derivative known to function as a cancer preventive agent, especially for human gastric and breast carcinomas. It acts on the Nrf-2 pathway by ameliorating suppressing oxidative stress within the cancer cells (Takai et al. 2013).

Carotenoid

Carotene is an antioxidant carotenoid that scavenges the oxidative stress-induced ROS, though its oral consumption for skin treatment has some adverse effects. Carotene is used for photoprotection and effective against UV-induced erythema, but it is found futile against severe UV irradiation. The increased dose concentration and duration of carotene are required for the successful treatment of severe skin diseases (Godic et al. 2014).

Lycopene is a tomato-derived carotenoid-based antioxidant that scavenges ROS and prevents lipid peroxidation and DNA damage. The combination of lycopene with other antioxidants would likely play a pivotal role in anticancer treatment (Kelkel et al. 2011).

Diterpenoids

Compounds under this classification consist of four isoprene subunits. Tanshinone shows anticancer activity by intercalating with the DNA of the tumor cell and upregulating TNFα, which induces ROS production followed by apoptosis. It has also been observed to inhibit metastasis by reducing MMP2 and MMP9 levels, which synergizes with its prooxidant effect (Hu et al. 2013).

Quinones

Quinone (Table 1) moieties are most commonly present in many drugs, such as doxorubicin, anthracyclins, mitoxantrone, daunorubicin, saintopin, and mitomycin used to treat solid cancers (Ziech et al. 2012).

Cribrostatin 6

Cribrostatin 6 generates large amounts of ROS within the treated cells, which potentially induces apoptosis, not followed by any defined cell cycle arrest (Cui et al. 2014).

Naphthoquinone

Napthoquinones are naphthalene derivatives having two carbonyl oxygen atoms, in which 1,4-naphthoquinone is the most stable naphthoquinone derivative. Additionally, Lawsone, Shikonin, Juglone, Plumbagin, Naphthoquinoidal and Menadione are the most prevalent derivates of naphthoquinone (Ziech et al. 2012). *In vivo* and *in vitro* studies have reported that the Plumbagin or 5-hydroxy-2-methyl-1, 4-naphthoquinone (extracted from roots of the plant Plumbago zeylanica L.), a yellow-colored secondary metabolite of the quinone family, has antioxidant and anticancer properties. This compound shows better antitumor activity when administered synergistically with a chemotherapy drug. However, the mechanism of action differs in different cancer subtypes, in lung cancer it arrests the cell cycle at G_2/M phase in tumor cells and inhibits PI3K/Akt/mTOR pathway. Likewise, in HER2 positive cells, it also causes cell cycle arrest at G_2/M phase and initiates mitochondria-mediated apoptosis, while it potently targets both receptors for positive and negative tumors in breast cancer.

Nonetheless, it shows antitumor activity by inhibiting Bcl-2, which leads to apoptosis on its regimen along with taxol in the case of triple-negative cancers. Plumbagin directly suppresses the generated ROS in mitochondria to inhibit tumor progression in cervical cancer, while it indirectly suppresses ROS by inhibiting STAT3 to induce apoptosis in gastric and esophageal cancer. Another quinone of interest is Shikonin, the bioactive component of Zicao, a root derivative of the plant Lithospermum erythrorhizon. Its vigorous anticancer activity has been observed in various cancer subtypes, including leukemia, gastrointestinal, pancreatic, lung, and breast cancer, primarily by a different mode of ROS generation, and by acting on PI3K/Akt/mTOR pathway, that ultimately leads to apoptosis (Ziech et al. 2012).

Thymoquinone

Thymoquinone is a natural bioactive compound obtained from the black seeds of Nigella sativa L, having a monoterpene structure. The protective effect of Thymoquinone is studied in different cancers such as breast, colorectal, prostate, lung, glioblastoma, and fibrosarcoma. All these studies have shown to decrease angiogenesis via modulating the VEGF through Akt and extracellular receptor kinase pathway. Interestingly, this compound exerts both apoptotic and antiapoptotic activity, like in gastric carcinoma, it significantly reduces the activity of caspase-3 and caspase-9, whereas, in glioblastoma cells, it induces apoptosis via elevating Bax and cytochrome c (Zhu et al. 2016).

Toluquinones

Toluquinones (triprenylated toluquinones and toluhydroquinones) induce apoptosis in esophageal cancer cell lines. These compounds scavenge ROS and are capable of killing cancer cells (Whibley et al. 2007).

Miscellaneous Natural Compounds and Products

Essential Oils (EOs)

EOs are lipophilic and concentrated hydrophobic liquids of aromatic plants, they easily penetrate inside the cell (Blowman et al. 2018; Gautam et al. 2014). Essential oils and their constituents such as Citral, Carvacrol, Thymol, Myrcene, α-humulene, perillyl alcohol (POH), Geraniols, β-caryophyllene, d-limonene have been considered as antioxidants and used in cancer therapy. The anticancer effect of EOs involves increasing ROS levels and cell cycle arrest, inducing apoptosis, modulating DNA repair, anti-metastasis, and anti-angiogenesis, anti-proliferative capacity in cancer cells. Furthermore, EOs and their constituents have indicated cytotoxic effects in leukemia, breast, colon, liver, lung, prostate, mouth, and brain cancer. Correspondingly, EOs regulate MAPK-pathway, transcription factors (NF-κB and AP-1), tumor suppressor proteins (p53 and Akt), and detoxification enzymes (glutathione peroxidase, glutathione reductase, SOD, and catalase). Table 1 contains important EOs which regulates ROS in cancer cells.

Boswellia Carteri (Frankincense Oil) EO

The constituents of this EO modulates the expression of apoptosis-related genes, CDKN1A, NUDT2, GAD45B TNFAIP3, SGK, IL6, IER3, and DEDD2 in bladder cancer cells. Also, this EO downregulates Bcl-2 and upregulates Bax genes, which activates caspase-9 and caspase-3 and stimulates apoptosis in human oral epidermoid carcinoma KB cells (Gautam et al. 2014).

Artemisia Lavandulaefolia EO

This EO's main compound, 1,8-cineole, induces apoptosis, which involves mitochondrial and MAPKs pathways. EO constituents cleave an indicator of apoptosis,

poly(ADP-ribose) polymerase-1 (PARP) in mouth cancer KB cells (Gautam et al. 2014).

Salvia Libanotica EO

This EOs' principal constituent such as linalyl acetate, terpineol, and camphor and their combinations effectively inhibits proliferation through a caspase-dependent pathway in HCT-116, colon cancer cell lines (p53+/+ and p53−/−), though no significant changes have been noted in standard intestinal cell line. Additionally, EOs and their constituent inactivate PARP-1 protein induces the release of caspases and then cancer cell death (Gautam et al. 2014).

Boswellia Sacra EO

The Boswellia sacra EOs induces PARP cleavage that leads to apoptosis in MDA-MB-231 cells. Also, it influences the Akt protein expression that regulates a tumor suppressor protein (p53) (Gautam et al. 2014).

Aniba Rosaeodora (Rosewood) EOs

This EO derivative increases ROS generation that induces apoptosis in cancer cells. The ROS accumulation leads to depolarisation of mitochondrial membrane, followed by caspase activation and phosphatidylserine externalization on the tumor cells, which leads to apoptosis (Gautam et al. 2014).

Zanthoxylum Schinifolium EO

This EO targets the cancer cells, liver (HepG2) to induce apoptosis wherein, it decreases the levels of glutathione, cellular antioxidants, and increased ROS production has been found. The extract of EO from this plant is known to trigger caspase-independent apoptosis, as seen in hepatocellular carcinoma (Gautam et al. 2014).

Minerals

Minerals are an essential component for the proper functioning of the antioxidant machinery of the body (Table 1). Most of the minerals act as cofactors of antioxidant enzymes like zinc for SOD and selenium for GPX. As immunoproteins they play an essential role in regulating oxidative stress with cancer cells (Lee 2018; Hariharan and Dharmaraj 2020).

Zinc

Zinc is a cofactor for antioxidant enzyme SOD, that induces the synthesis of metallothionein and sequesters to reduce hydroxyl radicals within the cytoplasm. It also acts as a suppressor of oxidative stress that inhibits the NOX enzyme, and TNFα-induced NF-κB pathway. Zinc deficiency has been associated with the risk of breast cancer, as the oxidative stress increases macrophage infiltration, creates a pro-tumor microenvironment, and its accumulation within the cell leads to overexpression of estrogen receptor, ultimately causing mutations within the mammary gland and triggering carcinogenesis (Lee 2018).

Selenium

Selenium is an immunonutrient that is a part of selenocysteine, which is a component of GPX and TXR enzymes. These enzymes, with the aid of selenium derivatives called selenoproteins are responsible for maintaining the oxidative state of the cell by scavenging ROS. It has also been observed that organic selenium compounds show better anticancer activity than their inorganic counterparts. Recent studies have reported that organic selenium derivatives comprise nucleophilic molecules that also play an essential role in controlling metastasis, with minimal systemic effects (Hariharan and Dharmaraj 2020).

Isothiocyanates

Glucosinolates are naturally occurring secondary metabolites present in the cruciferous plants, which hydrolyzes to form isothiocyanates. The main classes of glucosinolate are Benzyl Isothiocyanates (BITC), which are mostly seen in cabbage, garden cress; Phenethyl Isothiocyanates (PEITC), which are present in watercress, turnip; and sulforaphane present in abundance in green vegetables like broccoli (Table 1) (Lin et al. 2017; Sestili and Fimognari 2015).

BITC

Benzyl Isothiocyanate (BITC) has various effects on different cancers. In the case of blood cancer, BITC inhibits cell proliferation by inhibiting the c-Jun N-terminal Kinase (JNK), ERK-1/2, and regulating the focal adhesion kinases. In contrast, in the case of breast cancer, BITC targets p53 activation and suppresses the tumor formation, while in brain tumor, BITC downregulates protein kinase C, which plays a significant role in cell signaling and inflammation (Lin et al. 2017).

PEITC

Phenethyl Isothiocyanate (PEITC) controls oxidative stress in the cell through thiol modification, particularly affecting the GSH antioxidant system. PEITC inhibits GPX by extruding the GSH out of the cell, which leads to overproduction of ROS, consequently damaging mitochondria leading to apoptosis in the cancer cells. Its preferential selection for the cancer cells makes it a suitable candidate for clinical studies. In combination with rapamycin, it is quite effective in eradicating Akt-activated tumor cells, as observed in preclinical studies, but found ineffective in treating Akt-induced chemo-resistant cells (Lin et al. 2017).

Sulforaphane

This is a bio-compound found in broccoli as L-sulforaphane (SFN) and identified as a chemo-preventive agent by activating phase II antioxidant enzymes. Sulforaphane, an isothiocyanate, has been studied extensively to induce apoptosis through cell cycle arrest, disruption of microtubule polymerization, and by sensitizing cells to TRAIL factor in lung carcinoma tumor cells. Emerging evidence suggests that it also acts as an HDAC inhibitor, as HDAC acts as an oxidative stress sensor and plays an essential role in cancer progression (Sestili and Fimognari 2015).

Conclusion

It is well established that the oxidative status of the cell forms the ground for the overall functioning of a tumor cell (Hanahan and Weinberg 2011). Since the tumor cell is capable of maneuvering its oxidative status by compromising the standard scavenging mechanisms of a non-tumor cell, this mechanism summarizes that the overall ROS production is upregulated in a cancer cell as compared to a normal cell (Liou and Storz 2010). Conventional interventions like chemotherapy and radiation are not full proof due to the significant concern that they might hamper the ROS levels in a normal cell and turn into tumorigenic (Liou and Storz 2010). The irradiated patients can be supplemented with combinations of dietary antioxidants, which would likely minimize collateral damage. These antioxidants function primarily to downregulate the ROS levels in the tumor cells through regulation of ROS-related apoptotic signaling pathways like PI3K/AKT, MAPK/JNK/p38, JAK/STAT, and ER stress pathways. Importantly, phytochemicals like genistein and daidzein act as a double-edged sword and promotes the overproduction of intracellular ROS, which can be toxic to both the healthy and neoplastic cells (Bonomini et al. 2015). Therefore, for the wide-scale application of these phytochemicals in fighting cancer by targeting oxidative stress of the cancer cells, many factors must be taken into consideration, like study model, dose concentration, and exposure period. This approach can mark the future of therapeutics as an alternative intervention model.

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