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An overview on natural antioxidants for oxidative stress reduction in cancers; a systematic review

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Abstract

Tumor cells have deviated pathway that lead to increased constant state levels of free radicals and consequently lead to DNA damage, and then activates signaling pathways that causes unlimited growth, the inability to differentiation, and the malignant phenotype. Some studies have demonstrated that antioxidants can inhibit free radicals generation and repress oxidative damage and can prevent the creation of most diseases like cancer. There are some studies that investigated the mechanism and regulative effects of herbal extract antioxidant carcinogenesis prevention; they have documented that antioxidant effects and the inhibition of cancer development depends on a number of basic cellular mechanisms by phenolic compounds including a spectrum of cellular basic machinery. This systematic review aimed at providing an overview on the relevant data available in antioxidant activity of herbal products for cancer prevention and treatment. In this regards, Web of Science and PubMed databases were searched by the application of Endnote software for the publications about the role of herbal antioxidants on cancer; published from 2000 to February 2016. This study can/might provide a new horizon on the design of anticancer herbal medicines.

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Introduction

Based on the new data it is confirmed that oxidative stress and following inflammation are critical components of tumor initiation and progression (1,2). Oxidative stress is recognized as pro-oxidant/antioxidant imbalance situation (3); it demonstrates an unequal condition between reactive oxygen species (ROS) such as hydroxyl peroxide, superoxide and hydroxyl radicals, biological system's ability inclination to detoxify the reactive intermediates, and maintenance the created damage (4-7). In pathological condition, lipid peroxidation and DNA damage free radicals generation is enhanced as a consequence of cellular damages, and also antioxidant defense mechanisms are overwhelmed. Oxidative stress in different frequent pathologies, such as cardiovascular diseases, neurodegenerative disorders, and cancers critical is an important pathophysiological mechanism (8,9).

Generally, oxygen radical's superoxide is generated within the mitochondria in cancer cells and consequently reduced to hydrogen peroxide and hydroxyl radicals.

Key point

Natural antioxidant agents have role in reducing agents, hydrogen donors, quenchers of singlet oxygen, delay oxidative reactions, and significantly terminate oxidative chain reactions by removing the free radical intermediates. Natural antioxidant can promote the arrest of cell cycle and death of cancer cells.

These species cause damage DNA, genome instability, cell proliferation, tumors formation, and sustain promotion (10-12). Besides, in this process the mitochondrial respiratory chain increases the production of nitric oxide (NO) and subsequently reactive nitrogen species (RNS) under hypoxic conditions in cancer cells. Nitrite, nitrate, and peroxynitrite as RNS are the byproducts of NO metabolism and they can further generate other reactive species such as reactive aldehydes-malondialdehyde and 4-hydroxynonenal by inducing great lipid peroxidation that lead to cellular damage enhancement (13). Then, in signaling

pathways for metabolic protein exchange, ROS and RNS-induced imbalances lead to contrary effects to recruit deficiency abnormal proteins and compounds that causes tumorigenic processes (14,15).

In fact profound knowledge on the relationship between carcinogenesis, oxidative stress, and antioxidant reactions may suggest a broadly approved rationale for the progression of antioxidant medicines in order to reach to more efficient removal of free radicals and therapy of carcinogenesis. Antioxidant/detoxifying compounds have a protective mechanism against oxidative stress that reduce reactive species (16,17); they can protect normal cells from endo-/exogenous oxidative damage and minimize coetaneous carcinogenesis chance effectively (18,19). Further studies about the exploration of natural products have demonstrated that herbal medicines can be applied as a medicine for several human diseases such as cancer around the world population (20-28); it takes wide range of the pharmaceutical industry market in this field.

The aim of this review is to present an overview on the relevant data available in antioxidant activity of herbal products for prevention and treatment of cancer.

Materials and Methods

For this systematic review, PubMed and Web of Science databases were searched by the application of Endnote software from 2000 to June 2016. The search terms were Medicinal plant, Herb, Herbal medicine, phytochemical, or Herbal drugs and cancer when were accompanied with Reactive oxygen species, Reactive nitrogen species, or reactive nitrogen species (RONS). After searching, similar articles identified in same databases were deleted. The title and abstract of 38 articles that involved the search terms were reviewed. Then articles that did not have the study's inclusion criteria and full text were excluded. Around, 23 articles related to the herbal antioxidant effect on cancer were selected and different parts of each article were fully reviewed. Finally, the data were extracted of them.

Results

Medicinal plants as modulator of oxidative stress in cancer cells

Maytenus emarginata is an evergreen tree, which belongs to Celastraceae family and grows in a wide range of climates, from tropical to subpolar zones. Generally, around the world *M. emarginata* has been applied for fever, asthma, rheumatism, and gastrointestinal disorders worldwide (29). The results have confirmed that high flavonoid, isoflavonoid glycosides, and sesquiterpene pyridine alkaloids content in methanolic extract of *M. emarginata* possibly could be responsible for high antioxidant activity and significance ROS-scavenging activity. Besides, several antioxidant compounds show cytotoxicity against human tumor cell lines (KB, A-549, HCT-8, RPMI-795 1, and TE-67 1) have reported in studies (30,31).

Ocimum sanctum belongs to Lamiaceae family and it is known as one of the Indian native plants. Studies have demonstrated that *O. sanctum* has a wide range of health usefulness and pharmacological effects such as free radical scavenging, anti-hypertensive, analgesic, anti-pyretic, anti-allergic, immunomodulatory, radioprotective, and anti-carcinogenic efficacies. The presence of apigenin and ursolic acid as two common pentacyclic triterpenoid derivatives, in addition to protective effect against free radicals by inhibiting the activity of aromatase (estrogen synthase) can reduce the human breast cancer risk (32-34).

A daisy-like perennial plant like feverfew (*Tanacetum parthenium*) is found commonly in gardens and along roadsides that belongs to the Asteraceae family. Traditionally, feverfew has been applied as a herbal treatment to reduce fever and to treat women's ailments, inflammatory conditions, and headaches (35). Feverfew includes sesquiterpene lactones, flavonoids, and volatile oils biologically active derivatives. Parthenolide is one of the sesquiterpene lactones compounds by evaluating oxidative stress above a tolerable threshold and also by interfering with sulfhydryl groups of cellular molecules; it can suppress melanoma progress and maintenance (36,37).

Additionally, *Graptopetalum paraguayense* is a traditional Chinese herb from Crassvlaceae family. Studies have demonstrated that extract hepatic disorders, lower blood pressure, brain function, and relieve pain can be alleviated by *G. paraguayense* (38). Polyphenolic compounds, such as flavonoids and anthocyanin in the extracts of the leaves of *G. paraguayense* in vitro studies have demonstrated the scavenge free radicals and exhibit antioxidant and anti-proliferative effects against human cancers. Besides, *G. paraguayense* has shown anti-cancer and high cytotoxic effects by down-regulation the presentation levels of several onco-proteins in hepatocellular cancer cell line (HepG2) (39).

Traditional Arabic-Palestinian plants analysis has been shown that *Arum palaestinum* Boiss and *Coridothymus capitatus* have a maximum cytotoxic activity against cancer cell lines among several extracts. Also, *Teucrium capitatum* can be an efficient scavenger of O_2 in breast cancer cell line (MCF-7). Reported studies have demonstrated that total antioxidant activity and free radical scavenging activity were strongly related to flavonoid content and total phenolic groups (40).

Swertia chirata or *Kirata-tikta* as a species from Gentian family is an Indian medicinal plant that famous for its multipurpose therapeutic such as febrifuge, antihelminthic, and scanty urine remedy. Numerous studies have demonstrated that superoxide scavenging properties of *S. chirata* extraction is due to the range of its chemical constituents such as xanthones and also their derivatives, lignans, alkaloids, terpenoids, flavonoids, secoiridoids, and iridoids (41,42). Moreover, according to the depletion in generation of ROS and also lipid peroxidation in liver by *S. chirata* methanol extract, in mice skin exposed to carcinogenic agents multiplicity of papillomas is reduced (43).

Alstonia scholaris (commonly named devil tree) belonging to the Apocynaceae family is an evergreen tree with white and strongly perfumed flowers. The systemic consumption

of *A. scholaris* decoctions prevent liver disorders, indigestion and decrease fever and also has an effects on blood purifier and affords cardioprotective. Anti-cancer, anti-microbial, anti-oxidant and anti-inflammatory properties of *A. scholaris* extract are probably due to the presence of steroids, flavonoids, triterpenoids and more extensively alkaloids (44). Anti-cancer properties of lupeol acetate alkaloid of *A. scholaris* extract in vivo studies have demonstrated that this compound can reduce the risk of skin cancer in CD-1 mice via antioxidant activities and regulation of inflammatory pathways (45). Accordingly, *Coriandrum sativum, Foeniculum vulgare, Berberis aristata, Achillea millefolium*, *Prunus domestica*, and *Matricaria chamomilla*, significantly that are Pakistan medicinal plants show antioxidant activity. Studies have shown that these medicinal plants can be ideal source of phytochemicals that strongly inhibit cytokine generation and can show cytoprotective effects, significantly (46,47). According to these studies, anti-inflammatory and antioxidant effects of selected medicinal plants can demonstrate the strong inhibitory activity against ROS generation and inflammatory cytokine production such as IL-8 in *Helicobacter pylori*-infected gastric epithelial cells. Besides, these plants traditionally are used as chemoprevention against peptic ulcer or gastric cancer (46).

Rosemary (*Rosmarinus officinalis*) is a useful plant belongs to Lamiaceae family that it has strong anti-inflammatory and antioxidant activities. Its main compounds include carnosic acid, carnosol, methyl carnosol, rosmarinic acid, and ursolic acid. The carnosic acid (as the most abundant diterpene) and carnosol via the capacity to chelate iron, and scavenger peroxyl free radicals have long been related to the oxidative stress and lipid peroxidation (48,49). In vitro studies have revealed that carnosol is a probable agent in the inhibition of prostate cancer formation and progression in athymic nude mice with 26% decrease in serum prostate-specific antigen (PSA) levels in comparison to control (50).

Curcumin is a well-known medicinal plant isolated from the rhizome of turmeric (*Curcuma longa* that it belongs to the Zingiberaceae family (51). The performed studies on radical-production and radical-scavenging activities of curcumin have revealed that this compound act not only as antioxidants but also as prooxidants. Curcumin derivatives have electron donor groups (methoxy groups and ß-diketone functional group) that increase antioxidant activity of these polyphenolic compound rather than the other flavonoids (52). In vitro studies have shown that curcumin can suppress proliferation in cancer cells via apoptotic, anti-inflammatory, and antioxidant properties. Indeed it can induce G2/M phase cell cycle arrest and apoptosis in HepG2 (53).

Moreover, KIOM-C belongs to East Asia including *Radix paeoniae* Alba, *Radix scutellariae,* and *Radix angelicae* Gigantis, *Platycodon grandiflorum*, *Zingiber officinale*, and *Lonicera japonica* Thunb. as a new herbal medicine. This herbal medicine among the available phytochemicals via synergy and reciprocal action can focus on multiple cellular pathways and inhibit the invasive potential of malignant tumor cells (54). The available components in this herbal cocktail can elicit antitumor effects against fibrosarcoma cell line (HT1080), and also efficiently block lung metastasis in C57BL/6J mice (55). Table 1 shows the phytochemical components of KIOM-C which can induce cytotoxic effects in cancer cells.

Another rich source of phytochemicals is edible flowers that are gained from 97 families and most of them are potential sources of pharmaceuticals. Some phytochemical compounds in edible flowers can strongly reduce the risk of cancers (Table 2) (64). Flavonoids are one of the most important mediators that have been existed in many edible plants such as carrots, peppers, celery, and olive oil. They can show significant effects against cancers. In B-ring catechol group and C2-C3 double bond in conjugation with an oxo group at C4, two classical antioxidant structural features of flavonoids are involved that it can significantly present the antioxidant activity. Luteolin as an example for famous flavonoid in edible plants can have proper antioxidant activities and as a consequence reduce the proliferation of human colon carcinoma cell line (HCT-15) (65).

Table 1. Cytoprotective compounds of KIOM-C herbal cocktail

Medicinal plants	Ecological features	Phytochemical components	Ref.
Radix scutellariae	A flowering plant from Lamiaceae family	Flavonoids including baicalin, baicalein, wogonin, and wogonoside	(56)
Radix glycyrrhizae	A flowering plant from Fabaceae family	Flavonoids and pentacyclic triterpene saponins including liquiritin, liquiritigenin, isoliquiritigenin, liquiritin apioside, and glycyrrhizin	(57)
Radix paeoniae Alba	A perennial plant from Ranunculaceae family	Monoterpene glycosides, galloylglucoses and phenolic compounds	(58,59)
Platycodon grandiflorum	A habitual plant from Campanulaceae family	Platycosides (saponins) with a structure containing a triterpenoid aglycone and two sugar chains	(60)
Radix angelicae Gigantis	A member from Apiaceae family	Pyranocoumarin decursin and its isomer decursinol angelate (DA)	(61)
Zingiber officinale	A aromatic herb from Zingiberaceae family	Gingerols and shogaols	(62)
Lonicera japonica Thunb	A flowering plant from Caprifoliaceae family	Anthocyanins, proanthocyanins and other flavonoids	(63)

Table 2. Some founded phytochemical compounds in edible flowers with anticancer activity

Phytochemicals in edible flowers	Example	Source	Ref.
Flavonols	Qercetin, kaempferol, isorhamnetin and myricetin	Hangzhou white chrysanthemum, wild chrysanthemum, roselle, xibei tree peony, cactus, and etc.	(66)
Flavanols	Catechin, epicatechin, epicatechin gallate, and epigallocatechin gallate derivatives	Rose, water lily, and day lilyand roselle	(66)
Flavones	Luteolin, apigenin, acacetin, chrysoeriol, and their glucosides	Hangzhou white chrysanthemum, wild chrysanthemum, sweet-scented osmanthus, honeysuckle, and roselle	(67)
Anthocyanins	Glycosides, peonidin, pelargonidin and cyaniding	Roselle, tree peony, and Chinese rose	(68)
Phenolic acids	Chlorogenic acid, caffeic acid, caffeyolquinic acid, protocatechuic acid, and gallic acid	Roselle, honeysuckle, day lily, hangzhou white chrysanthemum, and rose	(69)

Natural antioxidants and their mechanisms of function

Oxidative DNA damage outcomes such as DNA strand breaks (70), oxidative DNA base modifications (71), and DNA-protein cross links (72) has been established by ROS and therefore lead to the initiation, promotion, and progression of cancer (52). Clinical studies with new basis demonstrated that imperfections of essential proteins in signaling cascade are responsible for transferring normal cells to cancer cells.

Antioxidants are applied as molecule via admission or donating an electron that this process can neutralize the effects of free radical. Studies related to the mechanism and kinetics of antioxidants present new strong mechanism including; first; scavenger of reactive oxygen and nitrate species, and also decreasing the levels of free radicals such as NO, nitrite, hydrogen peroxide and superoxide anion. Second; suppressor of nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), NADPHoxidase (NOX), lipoxygenase (LOX), myeloperoxidase (MPO) activity and inflammatory factor generation such as NF-κB, cytokines and interleukins (3) decreasing RONS induced protein and DNA damage (73). There is a need for global practices to identify critical antioxidant for modulating signaling pathways and targeting the programmed cell death without adverse effects to normal cells. Herbal phytochemical compounds have a significant role in anti-oxidative defense and regulation of redox that signal without the stimulation of the immune system or progress in the quality of life (74). It should be mentioned that biological property of medicinal plants strongly depends on their types of phytochemical compounds to reduce cancer risk via their anti-oxidant and anti-tumorigenic properties (75). In this review, we focused on the selected herbal derivatives that act as natural antioxidants and mentioned their possible mechanisms in cancers prevention.

One of vital proteins is APE1/Ref-1 that acts as an essential significant regulator of several transcription factors such as c-Jun, hypoxia-inducible factor 1a (HIF-1a), activator protein-1 (AP-1), tumor-suppressor protein p53, nuclear factor kappa B (NF-kB), and paired box gene 8 (PAX8); and also it is involved in various cellular processes such as cell survival, growth signaling and inflammatory pathways (76). Besides, the formation of ERK, JNK/stress-activated protein kinase and p38 MAP kinase proteins family is based on the mitogen-activated protein kinases (MAPKs) that are broadly involved in pro-inflammatory responses. Many kinds of MAPK pathways participate in stress signaling and contributes to the control of many cytokine genes and activate in response to radiation, environmental stress, and other stimulators such as growth factors (77). Moreover, the cyclooxygenase (COX) enzyme modulate the conversion of arachidonate and present in formation of prostanoids, including thromboxane and prostaglandins. COX activity leads to the products such as prostaglandins mediate pathogenic mechanisms, that includes the inflammatory response (78). The suppression of COX, especially COX-2 is related to the blocking the prostaglandin cascade might affect the growth of malignant cells via inhibiting proliferation and angiogenesis (79).

According to the above mentioned items, cyclooxygenase catalyzes the conversion of the free fatty acids to prostanoids; it is an early response gene when stimulated by serum, mitogens, tumor promoters, cytokines and endotoxins. According to reported studies, a possible mechanism of *O. sanctum* phenolic extract against cancer cells is the suppression of COX-1 and COX-2. Besides, MAPK signaling blocking, NF-κB and AP-1 activation, and finally the expression of responsive gene is another function of these phenolic compounds (80,81). Interestingly, phenolic phytochemicals of *O. sanctum* such as flavonoids can paradoxically demonstrate pro-oxidant activity under certain experimental conditions and by induction of unendurable amounts of ROS in cancer cells initiates apoptosis via MAPK activation (82).

An important modulator of susceptibility to carcinogen-induced carcinogenesis is Nrf2 that is a member of basic region-leucine zipper (bZIP) proteins. Nrf2 links to the antioxidant response element (ARE) that consequently leads to the enhanced expression of phase II detoxifying/antioxidant enzymes including glutathione S-transferase (GST), Catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD).Similarly, *S. Chirata* Buch.Ham, and *Curcumin* phytochemicals are reported in studies as strong activators of Nrf2 that adjust the resistance enzymes via the activated Nrf2 signaling pathway (83,

84). Moreover, some edible flowers extract such as protocatechuic acid and delphinidin 3-sambubioside via the stimulation of Nrf2 antioxidant response, P53 phosphorylation, and p38 MAPK/FasL cascade pathway can induce cell apoptosis and adjust the ROS-mediated mitochondrial dysfunction pathway (85-87).

Major molecular mechanisms of action of phenolic compounds include down regulation of mutant p53 protein, cell cycle arrest, tyrosine kinase inhibition, inhibition of heat shock proteins, reduction of NF-kB and APE-1 activity, inhibition of PI3K, STAT3 and IGF1R signaling pathways are known as (88). Moreover, flavonoids as hydroxylated phenolic substances that widely presented in *Alstonia scholaris, Tanacetum parthenium, Maytenus emarginata,* edible flowers and Traditional Arabic Palestinian plants extracts exert their antioxidant effect via suppression of ROS formation either by inhibition of enzymes or by chelating trace factors involved in free radical production and upregulation or the protection of antioxidant defenses (89).

According to the published articles, *G. paraguayense* flavonoids and partly anthocyanin via radical-scavenging capability extracts have a role to protect cells against lipid peroxidation. Besides, the reinforcement of PTEN expression and decreased AKT phosphorylation at Ser473 is another mechanism of *Graptopetalum paraguayense* phenolic extract that induced apoptosis in hepatocyte cancer cells (39,90).

Carnosol (as a phenolic diterpene) via down-regulation of Bcl-2, 5-adenosine monophosphate-activated protein kinase (AMPK) pathway, pro-caspase 8, PI3K/Akt pathway, and upregulation of Bax induce cell cycle arrest and modulates occurrence of apoptosis in a PC3 cell line. *Carnosol* play as antagonist activity against androgen receptor (AR) and estrogen receptor a (ERa) according to the time-resolved fluorescence resonance energy transfer investigation and also it can act as disruptor of both receptors in prostate cancer cells (50).

Conclusion

The results of this review article demonstrated that many kinds of medicinal plants have been identified as potential modifiers of cancer and presented important breakthroughs in cancer prevention and/or treatment. It can be mentioned that oxidation chain reaction imperfection can be corrected by irreversible cellular injury that leads to the cell death. Investigations documented that bioactive and safe phenols, mainly flavonoids, from some medicinal plants have antioxidant properties and exert anti-tumor, anti-carcinogenic, anti-mutagenic, antibacterial, antiviral, and anti-inflammatory effects. Natural antioxidant agents have role in reducing agents, hydrogen donors, quenchers of singlet oxygen, delay oxidative reactions, and significantly terminate oxidative chain reactions by removing the free radical intermediates. In summary, activation and/or inactivation of transcription factors, regulation of inflammatory such as prostaglandin cascade and COX1/2 expression and subsequently pathways are the major mechanisms to treat cancer cells by the application of medicinal plants. Subsequently, signaling pathways via modulation of vital cell growth and proliferation cascades such as MAPK, ERK and JNK herbal antioxidant promote the arrest of cell cycle and death of cancer cells.

Authors' contribution

Searching the data and preparing the primary draft conducted by NGD, MAS and MRMS. MAS and TL edited the manuscript. All authors read and sign the final paper.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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