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Advances in Biochemistry and Biotechnology

Review Article

Kovacic P and Somanathan R. Adv Biochem Biotechnol 3: 178.
DOI: 10.29011/2574-7258.000078

Biological Actions of Natural Phenolic Antioxidants: Reactive Oxygen Species and Oxidative Stress

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Citation: Kovacic P, Somanathan R (2018) Biological Actions of Natural Phenolic Antioxidants: Reactive Oxygen Species and Oxidative Stress. Adv Biochem Biotechnol 3: 178. DOI: 10.29011/2574-7258.000078

Received Date: 12 November, 2018; **Accepted Date:** 7 December, 2018; **Published Date:** 17 December, 2018

Abstract

This review deals with herbal medicines involving natural polyphenols, including, quercetin, luteolin, kaempferol, geralylated flavonoid, pycnogenol, bisflavonoid, rosmarinic acid, xanthohumol, pomegranate extract, epigallocatechin gallate, curcumin, and myricetin. Beneficial effects arise on generation of reactive oxygen species at low concentrations in accord with the unifying mechanistic theme based on electron transfer, reactive oxygen species, oxidative stress and antioxidants. Various other physiological effects are addressed, including inflammation, apoptosis and cell signaling.

Keywords: Antioxidants; Anticancer; Electron Transfer; Herbal Medicine, Oxidative Stress; Polyphenols; Radicals; Reactive Oxygen Species

Abbreviations

ROS	:	Reactive Oxygen Species
OS	:	Oxidative Stress
RNS	:	Reactive Nitrogen Species
ET	:	Electron Transfer
AO	:	Antioxidant

Introduction

The use of plants for healing purposes predates recorded history and has provided material to much of modern medicine. Many of present day drugs have their origin from plant sources e.g., aspirin from foxglove, quinine from chincona bark and morphine from opium poppy. Natural products from plants have provided the pharmaceutical industry with the most important sources of "Lead" compounds in the search for new drugs and medicines [1]. The search for new drugs from plants continues with many of the large-scale pharmaceutical companies.

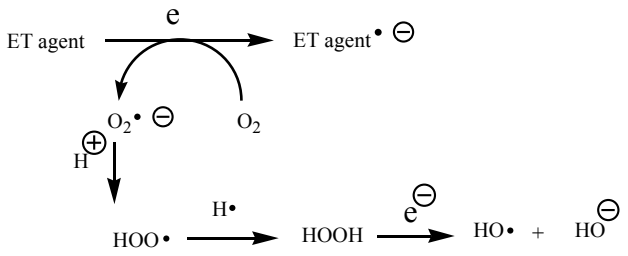
Chinese and Indian ayurvedic herbalism is the ancient herbal traditions that is currently practiced. It is based on "Yin" or cooling and "Yang" or stimulating or combination of both with various herbal materials. In addition, other ancient cultures in different parts of the world, such as Egyptian, Persian, Mayan and Aztec have also practiced herbal medicine.

About 20 years ago, a brief account of herbal medicines was reported [2]. Flavonoids, which are phenolic are known to be therapeutic agents, e.g., as anti-inflammatory, anti-ischemic and anti-thrombotic compounds. Ginko biloba, a Chinese herbal medicine of the flavonoid class, exerts AO action by rutin, quercetin, myricetin, and kaempferol. Tea possesses anticancer action, apparently due to the presence of catechins. The resin propolis has played a role in medicine, probably due to the presence of numerous phenolics. Herbal kampo medicines from Japan contain many AOs of the phenolic class. Nordihydroguairetic acid, from the creosote bush, inhibits lipid peroxidation.

Continuing on the same line, we recently reported naturally occurring mono-phenolic compounds as therapeutic agents and phenolic compounds in natural product spices and nutrients in relation to the unifying mechanism based on Electron Transfer (ET), Reactive Oxygen Species (ROS) and Oxidative Stress (OS) [3-6]. The small number of monophenolics involved consisted of thymol (thyme), carvacrol (thyme, bergamot), eugenol (clove, nutmeg, basil), gingerol (ginger) and capsaicin (peppers), vanillin (vanilla), and sesamol (sesame).

The prepondence of bioactive substances, usually as

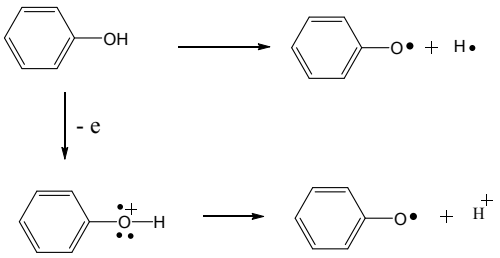
metabolites, incorporate ET functionalities. These may play an important role in physiological responses. The main group includes quinones (or phenolic precursors), aromatic nitro compounds, metal compounds and imines. Resultant redox cycling can occur, giving rise to OS through generation of ROS and diverse radicals (Scheme 1).



Scheme 1: Redox cycling with superoxide and ROS formation.

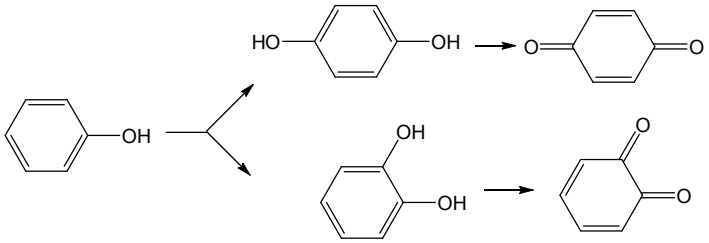
ROS and OS have been increasingly implicated in the mode of action of drugs and toxins. Phenols also display Antioxidant (AO) properties. There is a plethora of experimental evidence supporting the ET-ROS theoretical framework. This evidence includes generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, effect of exogenous AOs, and DNA oxidation and cleavage products, as well as electrochemical data. This comprehensive, unifying mechanism is consistent with the frequent observation that many ET substances display a variety of activities, such as multiple drug properties, as well as toxic effects [3]. Phenols are one of the principal operators in herbal medicine. Mode of action in conversion to quinones is illustrated in (Scheme 2). Phenolic ethers are also prevalent, which can undergo dealkylation to phenols.

A recent report on the High Through Put Screening (HTPS) of biologically active natural products and natural product drugs revealed the most hits were from molecules containing the catechol moiety, followed by p-dihydroxyphenols [7]. This is in compliance with our unifying theme of ET-ROS-OS associated with various illnesses. This prompted us to compile a list of natural products used in herbal medicine with the catechol structural motif. The present report deals with herbal medicines that perform many beneficial effects involving the polyphenolic class as AOs. The mechanism is shown in (Scheme 2).



Scheme 2: Mechanism of AO action.

Phenols act as pro-oxidants via conversion to quinones which generate ROS-OS via ET (Scheme 3). The effects can be beneficial at lower levels, but harmful with large amounts.



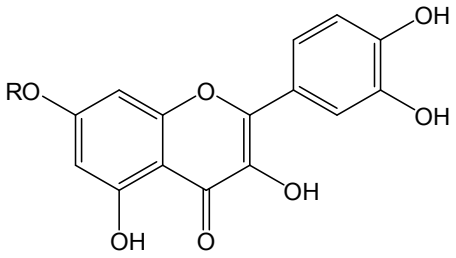
Scheme 3: Oxidation of phenol to o- and p- quinone.

Of the naturally occurring polyphenolic compounds, flavonoids are widely distributed and isolated from a wide range of vascular plants. Over 8000 individual compounds are known, which act as antioxidants, antimicrobials, photoreceptors, visual attractors, feeding repellants and for light screening [8,9]. Studies suggest that flavonoids exhibit biological activities, such as antiallergenic, antiviral, anti-inflammatory and vasodilating properties. The capacity of flavonoids to act as antioxidants in vivo has been the subject of several studies. As representative of the class of compounds, we have selected quercetin, luteolin, kaempferol, pycnogenol, rosmaric acid, curcumin, myricetin and polyphenols from tea for discussion of their biological properties in detail.

Quercetin

Quercetin (Figure 1), which occurs as free phenol or as D-glucoside, exerts medicinal effects, such as anticancer, anti-inflammatory and cyto-protective. Preventing OS is attributed to AO properties. Signaling pathways appear to be involved. The therapeutic potential includes neurodegeneration and anti-inflammation [10,11]. Hepato-protective and radical scavenging effects are exhibited by quercetin nanoparticles [12]. Chronic quercetin treatment exhibits antimanic and AO effects [13]. Quercetin exhibits AO and anti-fibroticin action in addition to prevention of cornea injury [14]. The flavonoid is classified as a cognitive enhancer in folk medicine. Treatment involves neurodegenerative disorders and cardiovascular diseases in which protective effects occur against OS mediated neuronal damage. The review puts focus on mechanism involving prevention of neurological disorders [15]. OS which is associated with aging, is the basis of neurodegenerative disorders for which polyphenols act as AO agents. The reaction mechanism is addressed for the vitro studies [16]. Anti-carcinogenic action is treated in another report [17]. An antidepressant effect is the topic of another study, in which hyperactivity was reduced. The effects are based on receptor inhibition and synthesis of NO. The AO effect contributes as evidenced by reduction of lipid hydro-peroxide levels [18]. The

report addresses amelioration of liver injury by reduction of OS and inflammation. Underlying mechanisms are treated based on OS and anti-inflammatory properties [19]. Rats with neurodegeneration by OS were treated with quercetin, in which AO activity counteracted the OS [20].



R= H Quercetin
R= 7-O-D-glucoside

Figure 1: Quercetin.

There was protection against renal and hepatic toxicity in rats. The beneficial role partly involves AO action [21]. Neuroprotective action of quercetin was studied. OS caused by free radicals contributes to the pathogenesis which is lessened by AO action [22]. Hepatotoxicity and OS underwent relief; AO action of the flavonoid plays a part [23]. Another study deals with the neuroprotective role. ROS are involved in the damaging effects of the illness resulting in OS which is decreased by the AO [24]. In a recent report quercetin showed potent anti-aggregation activity of amyloid-β peptide in Alzheimer's disease [25].

Luteolin

Luteolin, 3',4', 5,7-tetrahydoxyflavone (Figure 2), having the catechol structural moiety, is a flavonoid that is found to exist in many vegetables and medicinal plant species. Chinese traditional medicine uses plants rich in luteolin for treating hypertension, inflammation, and cancer. Having multiple biological effects, the phenol functions as an antioxidant as well as a pro-oxidant biochemically [26].

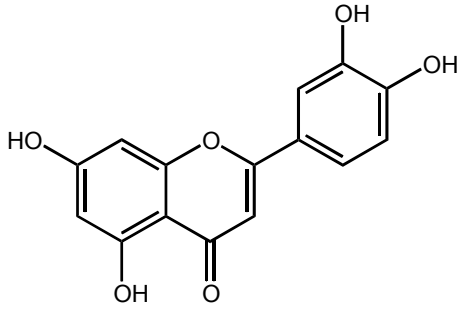


Figure 2: Luteolin.

Two 2008 reviews deal with the anticancer properties of luteolin, addressing apoptosis, inhibition of cell proliferation, metastasis and angiogenesis [26,27]. Furthermore, luteolin interacts with cancer cells by suppressing cell survival pathways via cell signaling [28], inhibiting apoptosis protein, and stimulating apoptosis pathways including the tumor suppressor p53. Luteolin induced ROS acts as potential cytotoxic agent to human colorectal cell line [29,30].

A study showed luteolin inhibits RNAs (RSK) and eradicates the cancer stem cell population [31]. It effectively blocks progestin-dependent human breast cancer tumor growth and stem cell-like phenotype in human breast cancer [32]. A similar study revealed retardation of growth by MCF-7 cells via inhibiting Insulin Growth Factor (IGF-1) mediated P13K-Akt pathway dependent ERα in human breast cancer stem cells [33].

Luteolin acts as a potential anticancer chemo preventive and chemotherapeutic agent in malignant melanoma cells [34]. Luteolin induces apoptosis in multidrug resistant cancer cells via ROS generation, DNA damage, activation of p53, NF-kB signaling pathways, activation of p38 pathway and depletion of anti-apoptotic proteins [35]. Glioma is one of the most common malignant tumors affecting the central nervous system. Drug screening using curcurmin, luteolin, chrysin and apigenin, showed suppression of the tumor cells [36].

Kaempferol

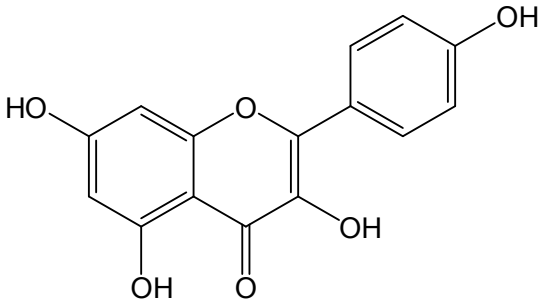


Figure 3: Kaempferol.

Kaempferol (Figure 3), a flavonoid in folk medicine, exerts a gastro protective effect. It was able to diminish the extent of ulcerated gastric areas in rodents [37]. Inflammation often is a healing response to many agents, such as pathogens. Kaempferol displays powerful anti-inflammatory properties which has been widely described in both in vitro and in vivo. The review describes this property in detail, in addition to mechanism, chemistry and toxic effects [38]. Kaempferol is used in treatment of many ailments. It possesses interesting AO and antimicrobial properties. Use is made in treatment of infections and damage from free radicals is lessened [39]. Plants containing kaempferol are known

to reduce the risk of cancer and cardiovascular diseases. There is a wide range of pharmacological activities, including AO, antimicrobial, anti-inflammatory, neuroprotective, antidiabetic, anti-osteoporotic, anxiolytic, analgesic and anti-allergic [40]. Metabolism is also discussed.

In addition to the above mentioned polyphenols and their biological actions, there are several recent reports of novel flavonoid compounds isolated from terrestrial plants. Natural geranylated flavonoid (Figure 4) isolated from *Paulownia tomentosa* fruits showed anti-inflammatory properties and inhibited cyclooxygenase and lipoxygenase activity; mechanism of anti-inflammatory effect is discussed [41].

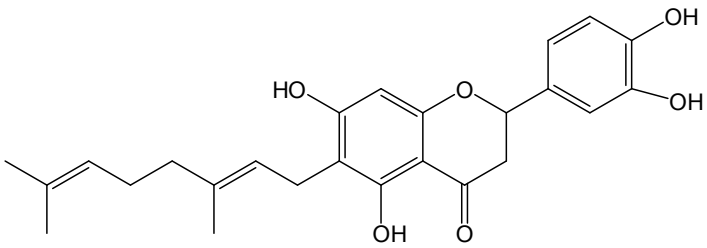


Figure 4: Geranylated flavonoid.

Parts of the plant *Epimedium brevicornum* are used in traditional Chinese herbal medicine as a cure for impotence, premature ejaculation, numbness hemiplegia, neurasthma, forgetfulness and tinnitus. Plant extract yielded several flavonoids, of which the prenylated flavonoid (Figure 5) exhibited cytotoxic activity against four human cancer cell lines [42].

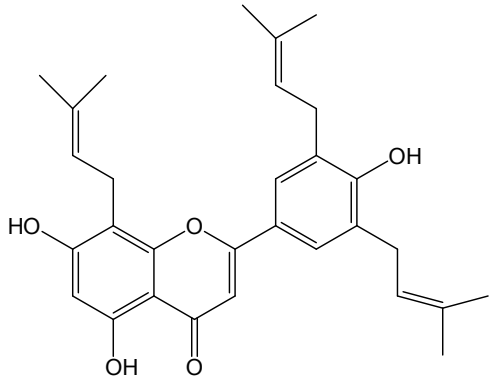


Figure 5: Prenylated flavonoid.

Pycnogenol

Pycnogenol (PYC) (Figure 6), a pine bark extract, is a procyanidin comprised of catechin and epicatechin subunits. PYC acts as a potent scavenger of free radicals [43]. There are other AO effects, including a role in the regeneration and protection of AO vitamins C and E. Anti-inflammatory activity has been demonstrated, as well as protection against UV radiation which produces harmful radicals. Phenolic acids produce a variety of beneficial effects. The AO action of anti-inflammation has been addressed [10,11]. PYC prevents ischemic-reperfusion injury from OS by decreasing DNA damage and increasing antioxidant status [44]. It showed neuroprotective action against oxygen-glucose deprivation/re-oxygenation-induced injury via NF-kB and ERK1/2 pathways in rat astrocytes [45]. PYC decreased selenite-mediated ROS in human lung carcinoma cells [46] and prevents complex organ dysfunction syndrome induced by oxidative damage by decreasing DNA damage and increasing the AO status and DNA repair capacity in rats [47]. A study showed a protective effect against OS mediated apoptotic changes caused by cisplatin-induced acute kidney injury [48]. PYC protects rats from OS produced by recurrent hypoglycemia [49].

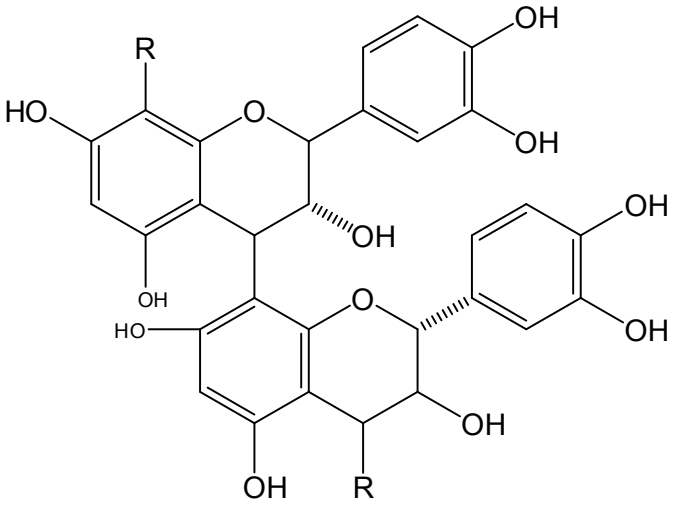


Figure 6: Pycnogenol.

Dietes bicolor (Iridacae) is an ornamental plant from Africa where it is used to treat diarrhea and dysentery. Among many flavonoids isolated from the species, the bisfalvonoid (Figure 7) exhibited anti-allergic activity by inhibiting antigen-induced β-hexosaminidase release and anti-inflammatory properties [50].

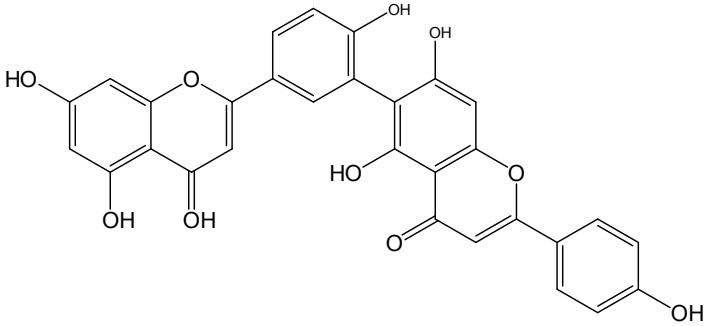


Figure 7: Bisflavonoid.

Rosmarinic Acid (RA)

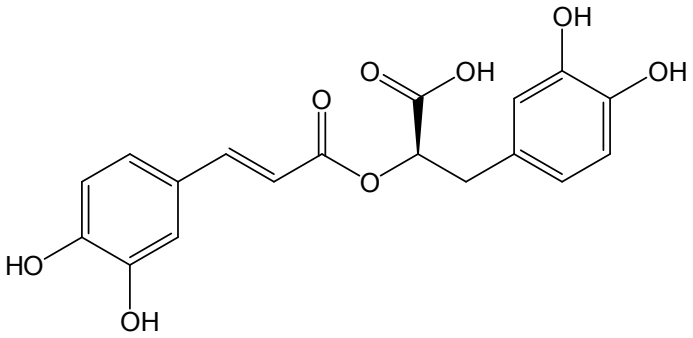


Figure 8: Rosmarinic acid.

Rosmarinic Acid (RA) (Figure 8), member of various medicinal plants, possesses AO and anti-inflammatory effects. In a study, the effects of RA on tracheal responsiveness in lung inflammatory cells and oxidant biomarkers in sensitized rats were evaluated [51]. Results were comparable to those of dexamethasone drug on sensitized rats. Ethanolic extracts of *Rosmarinus officinalis* L., as well as rosmarinic acid, showed anti-inflammatory effects in rat model with neuropathic pain [52]. RA was shown to delay the development of airway inflammation in cases of allergic asthma [53]. Anti-inflammation mechanism has been addressed previously [10;11].

A study revealed RA could serve as a hepato protective agent, and dietary supplementation may be beneficial in improving cholestasis-related liver injury via OS and down regulation of NF-kB, AP-1 and TGF-b1 signaling [54]. RA treatment ameoliorated damage caused by doxorubicin-induced testicular injury in rats [55]. A similar study showed action as an AO attenuated acetoaminophen-induced hepatotoxin in male rats [56]. Rosmarinic acid n-butyl ester protects cells against oxygen glucose deprivation-induced cell death, suggesting that the ester may be a promising drug candidate for the treatment of ischemia stroke. Supplementation with RA in rats protected them from deleterious effects caused by colon carcinogen 1,2-dimethylhydydazine; thus RA may be used as a potent chemo-preventive agent [53]. Rosmarinic acid inhibits inflammation and angiogenesis of hepatocellular carcinoma by suppressing NF-kB cell signaling in tumor bearing mice [57].

Xanthohumol

Xanthohumol (Figure 9) is isolated from *Humulus lupus* (Hops), and the antioxidant controls OS levels. Further consumption by diabetic animal's decreases inflammation and OS, allowing neovascularization control and improving diabetic wound healing [58].

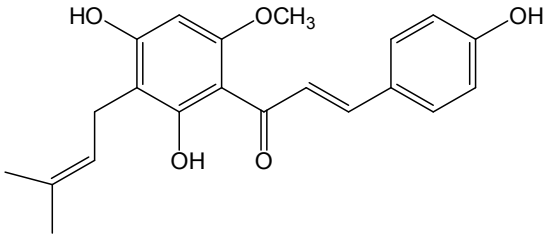


Figure 9: Xanthohumol.

Pomegranate Extract

Historically, pomegranate (*Punica granatum L*) has been used as a medicine for a variety of ailments in various cultures. In studies of human and murine models, pomegranate juice, peel, and oil have been shown to possess anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion, angiogenesis, anti-inflammatory, anti-atherogenic, and antioxidant activities [59-61].

The peel of pomegranate possesses a higher content of polyphenols. The fruit contains large amounts of ellagic acid and its derivatives (Figure 10), along with punicalagin (Figure11), a large polyphenol being the major constituent, possessing >50% of the antioxidant activity of pomegranate juice. Pomegranate also contains other polyphenols, such as anthocyanins, cyanidin (Figure 12), caffeic acid, coumaric acid and flavonols. Ellagic acid is metabolized by the colon microflora to form urolithins A and B that circulate in the blood stream reaching various organs, playing a role as antioxidant, and anti-inflammatory and anti-cancerous agents [60]. Four recent reviews deal with the role of pomegranate juice in breast cancer, colon cancer, pancreatic cancer, hepatocellular carcinoma, prostate cancer and human larynx epidermal carcinoma [59-61]. Mechanistically, as discussed in prior sections, the catechol can act as o-quinone precursor leading to ET-ROS-OS as part of the unifying theme.

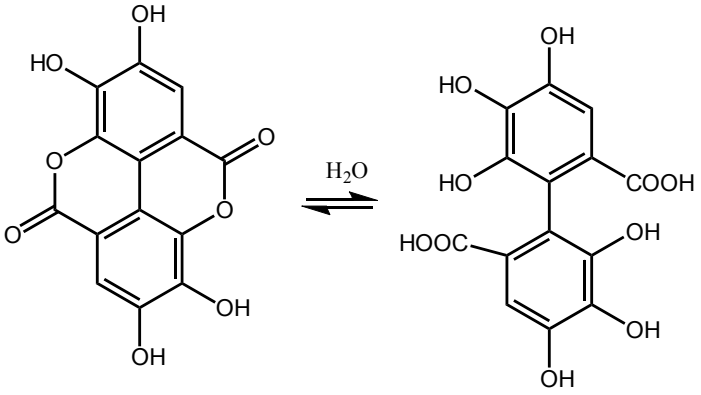


Figure 10: Ellagic acid (a) and hydrolysis product (b).

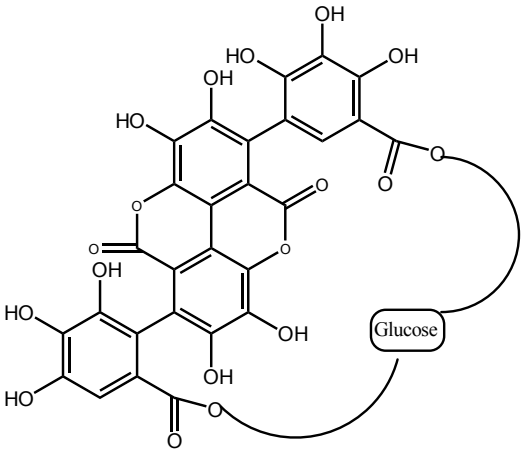
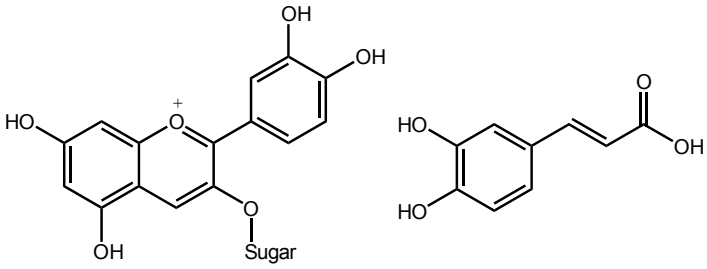


Figure 11: Punicalgin.



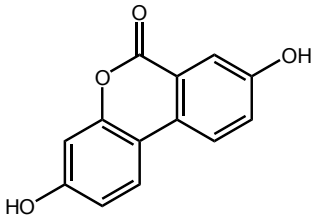


Figure 12: Polyphenols.

Epigallocatechin Gallate (EGCG)

EGCG (Figure 13) is a polyphenol prevalent in green tea. Clinical trials comprise the phenol alone or together with Pt drugs involving synergism against prostate and colon cancers. One mode of action entails induction of apoptosis in tumor cells and animal models, which can result from OS [62]. Increase in ROS occurs during gallate-induced apoptosis of hepatic cancer cells [63] The compound enhanced the production of radicals, both ROS and RNS [64]. A study was made of the drug effect on Leishmania [65]. Results suggest a mode of action involving ROS. The effect was reversed by catalase, providing evidence for ROS involvement.

In relation to the ET-ROS-OS unifying mechanism, the catechol portion can act as precursor of an o-quinone which is an ET agent capable of inducing ROS-OS which plays a role in cancer destruction.

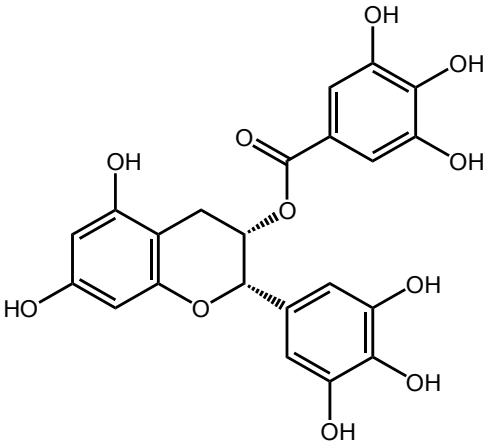


Figure 13: Epigallocatechin gallate.

Curcumin

Curcumin (Figure 14), the principal agent of turmeric, is also a component of the ginger family and curry powder. It is related structurally to capsaicin in being a phenol type, which undergoes tautomerism to the keto-enol form.

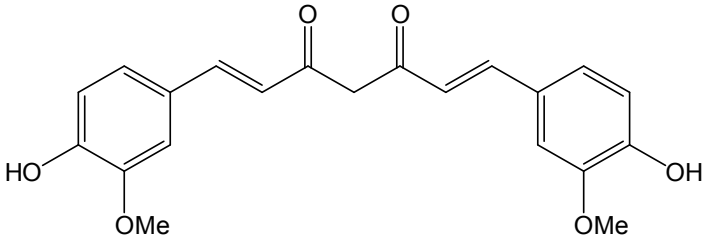


Figure 14: Curcumin.

The compound displays a broad spectrum of physiological and drug activities, of which representative examples are presented herein. In a study of chemo preventive and therapeutic effects, activity was shown as an anti-tumor, anti-inflammatory and anti-oxidant, capable of inducing apoptosis [66]. Mode of action is addressed in relation to carcinogenesis, gene expression and drug metabolism. Anti-inflammatory mechanisms are treated in a communication [67]. A brief review deals with antibacterial action, in addition to a broad range of other pharmacological properties, in which the mechanism involves multiple targets [68]. There is a report on anticancer properties and therapeutic activity [69]. Various biological aspects are involved including mutagenesis, Oncogenesis, apoptosis, tumorigenesis and metastasis. An anti-proliferation effect exists, in addition to metastasis. Turmeric is known to display antioxidant and antimicrobial properties [70]. A book reports on therapeutic use with attention to molecular targets

[71]. Beneficial effects are reported for skin diseases, inflammation and urinary diseases.

Since there is structural relation, the ET-ROS-OS theory treated in capsaicin should also apply with curcumin. There is also possible participation of the 1, 3-diketo structure in mechanism, e.g., metal chelation with subsequent ET. A study is reported on AO activity. The two phenolic OH groups play a major role [72]. Electron transfer reactions are involved. There is a protective effect conferred by the AO in Cd-induced OS and cardiovascular dysfunction [73]. A beneficial influence occurred with curcumin against Hg-induced OS in the liver [74]. The effect is attributed to free radical scavenging. These reports are representative examples of AO action.

Memory in people with Alzheimer's (AD) disease was improved [75]. The spice exerted various positive influences including AO and anti-inflammatory. Evidence supports involvement of OS, free radicals, metal toxicity and inflammation. Curcumin has been investigated in treatment of cancer, ulcers, arthritis, liver disease and atherosclerosis. A recent review entails a role in inhibiting stem cancer cells [5].

Myricetin

Myricetin (Figure 15), a polyether, is found in most herbal medicinal plants, which could exhibit AO properties. Enzymatically, the ether is dealkylated to the polyphenol; in support is a report dealing with the demethylation of polymethoxyflavones by human gut bacterium, *Blautia sp*. MRG-PMF1 [76].

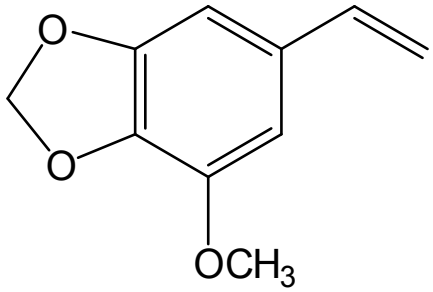


Figure 15: Myricetin.

An article deals with the effect of the herbal myriticin on memory loss in Alzheimer's (AD). Treatment reduces oxidative damage and increases AO enzyme activity. Also, there was decrease in iron which can be an ET agent [77]. Various bioactivities are demonstrated by myricetin. It ameoliorates liver fibrosis that was induced by carbon tetrachloride and may serve as a therapeutic agent [78]. Myricetin displays remarkable anticancer properties with few side effects. The underlying mechanism was investigated which appears to involve mitochondria [79]. Myricetin provides an anticancer effect by inducing mitochondrial-mediated apoptosis with involvement of human glioma cells. Other effects are ROS generation, inhibition of cell migration and cell cycle arrest [79]. Myricetin exerts various physiological effects; the mechanism involved in apoptosis is unclear. This is an example of an adverse effect by medicines which is common in the therapy field and deserves more attention. The effect can be harmful or beneficial [80].

Conclusion

Consumer spending on herbal products in the United States is estimated to be more than $5 billion per year. Interest in finding lead compounds from natural herbal medicines has intensified over the years. In this review, among the various biologically active molecules, we have focused on polyphenolic compounds, which exhibit AO properties, and is in keeping with our unifying theme of ET-AO-ROS-OS and their biological actions related to illnesses. All the compounds presented above are isolated from herbal plants used in Chinese and Indian Ayurvedic medicine, with potential therapeutic and biological properties.

Acknowledgement: Editorial support by Thelma Chavez is acknowledged.

Conflict of Interest: Authors acknowledge no conflict of interest.

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