UNIFYING MECHANISM INVOLVING PHYSIOLOGICAL ACTIVITY OF SPICES: ELECTRON TRANSFER, REACTIVE OXYGEN SPECIES, OXIDATIVE STRESS, ANTIOXIDANTS, REDOX CHEMISTRY, AND FOODS

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ABSTRACT
This review deals with mode of action of spices. Those studied, involving principal ones and parent substances, together are the following: capsaicin (pepper, tabasco, jalapeño), curcumin (tumeric, ginger, curry), anethole (anise, fennel), myresticin (nutmeg, parseley, dill), sesamin (sesame) and piperine (pepper). These are in the phenolic and phenolic ether class, whereas allicin alone is in the disulfide category. Evidence supports the unifying mechanism of electron transfer, reactive oxygen species and oxidative stress for the seven. The disulfide is closely related via redox reaction without electron transfer. This review is an extension in relation to the unifying mode of action. Physiological and medical effects are treated

Keywords: Mechanism of action of spices, capsaicin, curcumin, sesamin, anethole, myresticin

INTRODUCTION
In early history, spices played an important role in trade, economy and exploration, as well as food flavoring and preservation, plus medicinal. A few years ago, a brief report was made on phenolic, natural product spices in relation to the unifying mechanism based on electron transfer (ET), reactive oxygen species (ROS) and oxidative stress (OS) ¹. 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) (Fig, 1).

The preponderence of bioactive substances, usually as metabolites, incorporate ET functionalities ². These may play an important role in physiological responses. The main group includes quinones (or phenolic precursors). 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

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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. Phenols are one of the principal operators in spices. Mode of action in conversions to quinones is illustrated in Scheme 2. Phenolic ethers are also prevalent, which can undergo dealkylation to phenols.

**Scheme 2: Oxidative conversion of phenol to quinones**

The literature contains reports on phenolic ethers acting as precursors of phenols. A quite relevant one involves the spice capsaicin which undergoes demethylation to a catechol type which is subject to subsequent oxidative transformation to an o-quinone 1. Two possible routes exist, namely, acid catalyzed cleavage or oxidative radical dealkylation, the latter being the most likely. Scheme 3 provides the mechanism for the radical mode.

**Scheme 3: Radical mechanism for phenol formation**

This review is an extension of the prior one. Most of the spices fall in the phenols and/or the phenolic ether class. Physiological and medical effects are treated, in addition to the ET-ROS-OS mechanism.

**Capsaicin**

Capsaicin (Fig.2) is the main ingredient of various spices, such as pepper, chilli, and cayenne, tabasco and jalapeno. A recent book presents a detailed account of various aspects with emphasis on therapy 3. The receptor, transient receptor potential vanilloid type-1 (TRPV1), responds to other stimuli including heat, protons and vanilloids. TRPV1 is involved in the control of pain and inflammation. The receptor is a non-selective cationic channel comprising expressed cells with excitable membranes, involving neurons which are capable of generating and propagating action potentials. Brain TRPV1 is associated with a wide array of functions and behavior in the central nervous system (CNS), including learning, memory and addiction. A section deals with capsaicin in the treatment of neuropathic pain. Studies indicate a role for the spice as an ant-obesity drug. Afferent nerves appear to play a role. Research supports the antitumor effects of capsaicin via induction of apoptosis. Apparently, the mechanism involves Ca increase, activation of transcription factors, disruption of mitochondrial membrane transition potential and generation of ROS which is in accord with the ET-ROS-OS unifying theme. The spice acts as therapy in dermatology involving neurogenic pain.

**Figure 2: Capsaicin.**

Many of the physiological effects of capsaicin are based on the nervous system. A review presents a unifying electrochemical theme in the mechanism of the nervous system operation 4. A study of metabolites from capsaicin provides insight concerning mechanistic aspects, particularly in support of the ET-ROS-OS unifying theme. 5. Oxidation by cytochrome P450 and peroxidase enzymes produced quinone methide and quinone products in addition to aromatic hydroxylation. Biomolecular coupling of free radical intermediates also occurred. The quinone metabolites can serve as ET agents in the formation of ROS and OS. The generated free radicals may play a role in the cytotoxic properties and pro-carcinogenic
effects. The chemoprotective influence can be attributed to AO property of the phenolic portion.

Extensive literature exists involving ROS-OS to capsaicin action. In many cases, there is a connection with apoptosis as discussed in the following. The association may result from involvement of caspase-3 and formation of calcium ions. AOs, such as catalase and a thiol type, largely prevented apoptosis generated by capsaicin-induced OS. In another case, apoptosis resulted from participation of mitochondria in formation of OS from capsaicin participation. The possible involvement of NADPH oxidase in ROS production during the process was examined.

There are considerable other articles on influence of ROS-OS in capsaicin systems. The chili components enhanced uptake of glucose in muscle cells via ROS involving the AMPK/p38 MAPK pathway. Increased inflammation and OS from lipid peroxidation may interfere with cell processes, possibly leading to cell death. Data indicate that certain receptors control the transduction of ROS by capsaicin-sensitive lung tissue. A report deals with nerves sensitive to capsaicin and ROS in the pathology of gastric ulcers. ROS mediated the development of hyperalgesia induced by capsaicin. The ROS-OS aspect plays a role in various other aspects of the physiological activity of capsaicin. There is a lessening of death of cancer cells via generation of ROS and depolarization of mitochondria. Reports deal with involvement in the neural area.

Substantial literature addresses use of capsaicin as an AO agent. It served as a powerful AO in lowering OS and blood LDL levels. The spice constituent effectively decreased the generation of ROS.

### Curcumin

Curcumin (Fig.3), 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 and undergoes tautomerism to the keto-enol form.

![Curcumin](image)

The compound displays a broad spectrum of physiological and drug activities, of which representative examples are presented herein. In a study of chemopreventive and therapeutic effects, activity was shown as an anti-tumor, anti-inflammatory and anti-oxidant, capable of inducing apoptosis. Mode of action is addressed in relation to carcinogenesis, gene expression and drug metabolism. Anti-inflammatory mechanisms are treated in a communication. A brief review deals with antibacterial action, in addition to a broad range of other pharmacological properties. The mechanism involves multiple targets. There is a report on anticancer properties and therapeutic activity. Various biological aspects are involved, including mutagenesis, oncogenesis, apoptosis, tumorogenesis and metastasis. An anti-proliferation effect exists, in addition to metastasis. Turmeric is known to display antioxidant and antimicrobial properties. A book reports on therapeutic use with attention to molecular targets. 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 to curcumin. Phenols are known AO agents. 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 major roles. Electron transfer reactions are involved. There is a protective effect conferred by the AO in Cd-induced OS and cardiovascular dysfunction. A beneficial influence occurred with curcumin against Hg-induced OS in the liver. 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. The spice exerted various positive effects, 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.

### Gingerol

Gingerol (Fig. 4), is an active ingredient of ginger and is chemically related to capsaicin. The spice also contains 8-, 10- and 12- gingerols. It and the analogs are active against cancer cells including those of blood and lung, as well as other organs.

Since the structure is similar to that of capsaicin, the chemical aspects should be related. Hence, the ET-ROS-OS theme could be applied to ginglers, including any AO effects.

![Gingerol](image)

### Anise

Anethole (Fig. 5), a flavoring compound with an aromatic ether structure, is the principal active ingredient of anise and fennel. Anethole possesses a sweet taste and is used in alcoholic drinks, seasoning, confectionary applications and oral hygienic products. The compound is a powerful antimicrobial agent against bacteria, fungi and yeast. In antifungal action, it increases the effectiveness of phytochemicals. Antihelmintic activity is exhibited in gastrointestinal nematodes of sheep. Nemoanticidal action occurs against plant nematodes. Anethole is an effective insecticide against the mosquito and other insects. It also has activity as an estrogen and is present in the...
liquor absinthe. Production of certain illicit drugs involves anethole as precursor.

**Figure 5: Anethole**

**Myristicine**

Myristicine (Fig. 6), a phenolic ether is present in nutmeg, parsley and dill. It is a psychotic drug functioning as an anticholinergic and providing hallucinogenic effects, as well as intoxication. Recreational use has caused poisoning. Myristicine displays properties as an insecticide, acaricide (anti-worm), anti-inflammatory, analgesic, neurotoxic, antibacterial, anti-fungal, anticonvulsant and anti-diabetic agent. A related work deals with anti-inflammatory properties related to the inhibition of NO, cytokines, chemokines, and growth factors in dsRNA-stimulated macrophages via the calcium pathway. Nutmeg oil alleviates chronic inflammatory pain through inhibition of COX-2 expression in rat models. A study dealing with the comparison of natural myristicine as an effective insecticide against house fly and oriental cockroach was reported. Two detailed reviews on *Myristica fragrans* and biological properties are reported.

**Figure 6: Myristicine.**

**Sesamin**

Sesamin (Fig. 7), a phenolic ether is isolated from sesame oil.

**Figure 7: Sesamin.**

It exhibits antioxidant and anti-inflammatory properties. The article deals with the effect of sesamin on a model of Parkinson’s disease. The effects consist of lower levels of malondialdehyde, a product of lipid peroxidation and ROS, improved superoxide dismutase activity, and apoptosis. Attenuation of OS took place. These findings are in accord with mode of action entailing ET-ROS-OS (see Introduction).

**Piperine**

In relation to other components of pepper, piperine (Fig. 8), a phenolic ether alkaloid, is responsible for the pungency of pepper and is also an insecticide. Evidence revealed increased generation of ROS in piperine-treated rectal cancer cells. The AO N-acetylcySTEINE decreased apoptosis in the treated cells, demonstrating that the induced cytotoxicity was mediated by ROS, at least in part. A study showed piperine effectively protected primary cultured arterial monocytes from oxidative damage in rabbit model. Cepharanthine and piperine act as antioxidants by inhibiting NF-kB and NLRP3 activation and halt the progression of diabetic nephropathy. An investigation reported plant extract from *Piper nigrum* significantly reduced the OS status and ameliorated the neurodegeneration characteristic of Alzheimer’s disease-induced rats. Piperine, an anti-inflammatory and antioxidant agent, provides neuroprotective action, making the drug a potential candidate for the treatment of neurodegenerative diseases such as Parkinson’s. A similar investigation showed amelioration of cypermethrin-induced oxidative damage in rat brain. A study demonstrated that piperine is an effective antitumor compound in vivo and in vitro studies, involving a breast cancer model. Piperine shows anti-inflammatory, antinociceptive, and antiarthritic effects in an arthritis induced animal model. Piperine attenuates acetaminophen-induced hepatotoxicity in mice, comparable to the standard drug silymarin. Several reviews highlight the therapeutic potential and biological role.

**Figure 8: Piperine**

**Allicin**

Allicin (Fig. 9), a thiosulfinate compound present in garlic, possesses a wide spectrum of bioactivity. It is generated from the precursor allium (s-allylcystine sulfoxide).

**Figure 9: Allicin**

It is different from many other spices, in not belonging to the phenolic or phenolic ether classes. Allium undergoes redox reaction with thiols present in glutathione (GSH) and proteins, which is believed to be a key element in the biological action. It exhibits activity against bacteria and fungi. In mammalian cancer cells, the compound can destroy the cells or inhibit proliferation. There is advantageous use for the cardiovascular system. Allium demonstrates widespread applications in medicine and agriculture. The majority of the effects appear to involve redox mechanisms. The enormous potential is evident; results clearly demonstrate that allium is the active anticancer agent in garlic. The antimicrobial effect is due to interaction with thiol.
There is detailed treatment of the antifungal properties of allium and its metabolites. The derivative allitridium demonstrated impressive activity against a wide range of fungi. Also, there is synergy with amphotericin B, an important antifungal agent. Glutathione, an antioxidant thiol, prevents damage to the cell. Activity is reported against bacteria, viruses and parasites. A common mode of action appears to exist. Garlic and diallyl trisulfides displayed high activity against cancer cells. The S-S- bonds appear to be necessary for activity. Supporting evidence is provided by the order of activity against bacteria: diallyl trisulfide > diallyl disulfide > diallyl monosulfide. The biological effectiveness of allilic is likely due to its reactivity with thiol groups of tumor proteins and amino acids, as is illustrated in Scheme 4.

Another report addresses the anti-inflammatory responses in addition to cancer chemoprevention. The mechanistic studies appear to be in accord with part of the ET-ROS-OS approach involving the unifying theme. There is scarce discussion of the details of the unifying redox reports, which are highly relevant. Mode of ROS-OS action occurs without ET. The peroxy radicals can serve as a source of other ROS. There is some discussion previously of oxidizing properties. Scheme 5 is closely analogous to that of related peroxides.

Scheme 5: Redox mechanism for disulfides

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