Review

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Sesquiterpenes: The Potent Antioxidants

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Abstract. Sesquiterpenes (STs) are 15 carbon terpenoids, having significant phytomedicinal, phytotoxic and agrochemical potentials. They are found to be present in the essential/edible oils and have also been reported from numerous plant species. In this review article, the antioxidant potentials of STs isolated from various plants have been presented. As the antioxidants prevent, protect or reduce the damaging/aging of the cell, therefore, they are of prime importance. This review will provide the literature on the antioxidative potency of STs probably for the first time, which could be used as scientific data base for the researchers working in this field.

Keywords: sesquiterpenes, sesquiterpene lactones, antioxidant, plant extracts, biologically active compounds

Sesquiterpenes. Sesquiterpenes (STs) are 15 carbon terpenoids comprising of mainly two types, oxygenated sesquiterpenes and hydrocarbon sesquiterpenes. The oxygenated forms occur bearing functional groups such as alcohols, ketones, aldehydes, acids or lactones in nature. Due to their small molecular weight, they are important volatile organic parts of especially the essential oils, which are of great medicinal potential. Besides their presence in essential oils, they are also major constituents of various medicinal and economically important plants (Merfort, 2002).

STs are one of the largest biogenetically homogenous groups of natural products known. More than 11,000 entries of sesquiterpenes have been reported so far. These sesquiterpenes have been divided into almost 24 different kinds (Schmidt, 2006). However, germacranolides, eudesmane, farnesane, elemane, guaiane, and chamigrane are well known besides some esters or lactone group-linked sesquiterpenes. Almost 5000 sesquiterpene lactones have been reported. Among them 60 to 65% have been reported to be present as essential/edible oils (Schmidt, 2006; Fraga, 2000).

Various STs have been found to be biologically active against cell proliferation, abnormal cell growth (cancer), inflammation, bearing antibacterial, antifungal, antispasmodic, cytotoxic, antimalarial, hepaprotective, insecticidal, allelopathic, enzyme inhibitory, antilipase effects as well as many other diseases and problems (Khan *et al.*, 2008; Liu *et al*., 2008; Macias *et al*., 2007; Pan *et al*., 2007; Miguel *et al.*, 2005; Ding *et al*., 2005; Rafi *et al*., 2005; Sharma *et al*., 2005; Yun *et al.*, 2002a,b; Guillen and Manzanos, 1999; Park and Kim, 1998; Nawrot, 1983). Besides that these STs have been reported to be active against the oxidative stress.

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Antioxidants. Antioxidants are classically defined as molecules present in concentrations lower than the biomolecules and may prevent, protect or reduce the extension of oxidative damage, such as glutation peroxidase, catalase and superoxide-dismutase. Other antioxidants, such as ascorbic acid (vitamin C) and tocopherol (vitamin E) are non-enzymatic antioxidants (Hussain *et al.*, 2008; Khan *et al.*, 2007, 2006, 2005; Foyer and Noctor, 2005; Bolwell and Wojtaszek, 1997; Harborne, 1993). Thus, there is a delicate balance between the generation and destruction of oxidants, which may be beneficial or deleterious to the organism (Hussain *et al.*, 2008; Khan *et al.*, 2007, 2006, 2005; Maffei *et al*., 2007; Foyer and Noctor, 2005; Novelli, 2005). Oxidation products from lipids and cholesterol are thought to be the contributing factor to the cause of various diseases, including cancer, atherosclerosis and some age-related diseases (Chun *et al.*, 2007; Jatoi *et al.*, 2007; Pandhair and Sekhon, 2006; Ho *et al*., 2003; Andersson *et al*., 1996; Chan, 1987; Scott, 1985). Lipid oxidation in food affects its nutritional quality which results in rancid flavour, one of the main consequences. Also loss of vitamins, polyunsaturated fatty acids and other essential compounds can occur during the process (Khan *et al.*, 2008; Manzoor *et al.*, 2007; Pandhair and Sekhon, 2006; Anwar and Bhanger, 2003; Andersson *et al.*, 1996; Chan, 1987; Eriksson, 1982).

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase catalyses the reduction of molecular oxygen to super-

oxide anion (O^{2-}) and the burst respiratory is paralleled by a higher consumption of oxygen (Krol *et al*., 1995). O^{2-} is the precursor of other reactive oxygen intermediates, including hydroxyl radical ($OH^{\bullet}$), hypochlorite (OCl^{-}) and hydrogen peroxide (H_2O_2). Oxidants produced by phagocytes may destroy important biomolecules as well as phagocyted microorganisms, and are also involved in the tissue injury associated with inflammatory diseases (Hussain *et al.*, 2008; Khan *et al.*, 2008, 2007, 2006, 2005; Sforcin, 2007; Pandhair and Sekhon, 2006; Moonis *et al.*, 1992).

Mitochondria are important intracellular sources of reactive oxygen species (ROS). During the oxidative phosphorylation process, mitochondria reduce O_2 to H_2O *via* the respiratory chain. ROS are continuously produced by plants under different stress conditions and in different cellular compartments (Navrot *et al*., 2007; Foyer and Noctor, 2003). Both the chemical identity of a given ROS and the intracellular site of its production seem to affect the specificity of its biological activity, further increasing the complexity of ROS signalling within plants (Laloi *et al.*, 2004). In several systems, various signalling pathways, particularly those involving, mitogen-activated protein kinase (MAPK)s, are modulated by ROS (Pitzschke and Hirt, 2006; Neill *et al.*, 2002; Desikan *et al.*, 2001).

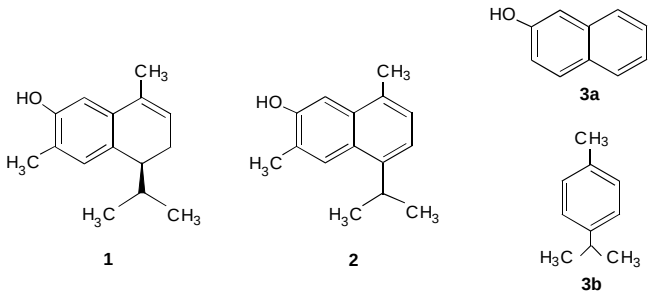
Oxidative stress, resulting from the generation of ROS, such as superoxide (O^{2-}) hydrogen peroxide (H_2O_2) and hydroxyl radicals ($HO^{\bullet}$), is a common phenomenon (Maffei *et al.*, 2007). In absence of stress and under physiological conditions, the level of ROS is maintained low by the activity of antioxidative systems, which include secondary plant metabolites and scavenging enzymes (Pandhair and Sekhon, 2006; Foyer and Noctor, 2005). Both biotic and abiotic factors induce changes in the ROS equilibrium and trigger cascades of signals eventually leading to increased ROS production and/or decreased antioxidant and scavenging activities (Khan *et al.*, 2008; Asada, 2006; Apel and Hirt, 2004; Hancock *et al.*, 2002).

Antioxidants are commonly used to increase the shelf life of lipids and lipid-containing products. Many *in vitro* studies indicate that phenolic compounds like flavonoids, coumarines, phenolic acid, lignans, hydroxycinnamates and stilbenes can have substantial antioxidant activity (Khan *et al.*, 2008; Kim *et al.*, 2002; Duthie and Crosier, 2000; Park *et al.*, 2000). A large number of plants have been screened as a source of new additives for the food and pharmaceutical markets, which can provide a supplement to cope with oxidative stress (Hussain *et al.*, 2008; Khan *et al.*, 2008, 2007, 2006, 2005; Rosa *et al.*, 2007; Pandhair and Sekhon, 2006; Laloi *et al.*, 2004; Kim *et al.*, 2002; Park *et al.*, 2000; Shahidi, 1997).

The redox state of the cell has been shown to be involved in cell cycle regulation and cell death/survival (Dong-Yun *et al.*, 2003). Glutathione (GSH) is the main intracellular antioxidant and plays an important role in these processes. GSH depletion leads to cell death, and increase in GSH inhibits cell proliferation (Menon *et al.*, 2003).

Antioxidant sesquiterpenes from plants. Various sesquiterpenes belonging to different sub-classes have been isolated from different plant species. Since we have excluded the sesquiterpenes reported from essential/edible oils, therefore, information relating to only the isolated compounds have been compiled and presented here for future research. Details of sesquiterpenes reported from various plant species is given in Table 1.

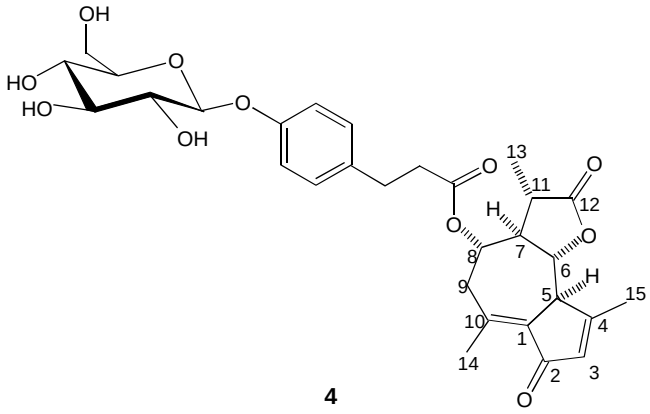
Sesquiterpenoids **1** (7-hydroxy-3,4-dihydrocadalin) and **2** (7-hydroxycadalin) have been isolated from *Heterotheca inuloides* (Haraguchi *et al.*, 1997), which showed potent 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity and almost 80% inhibition was observed at 10 µg/ml concentration. Structurally these sesquiterpenes, especially compound **2**, contain β-napthol (**3a**) and *p*-cymene (**3b**) moieties. These structurally related compounds **3a** and **b** showed almost no effect on linoleic acid autoxidation up to a concentration of 30 µg/ml (Haraguchi *et al.*, 1997).



Feruloylpodospermic acids A and B, scorzoneric acid and scorzonerin (**4**) were purified from the crude extract of the aerial parts of the Mongolian medicinal plants, *Scorzonera divaricata* and *S. pseudodivaricata* (Tsevegsuren *et al.*, 2007). These were detected in the DPPH active fractions. The potential of compound against oxidative stress, was determined using naturally occurring antioxidant, chlorogenic acid as control. Feruloylpodospermic acids A and B gave IC_{50} values of 36.36 and 34.24 μmol/ml, respectively, while chlorogenic acid had an IC_{50} value of 67.92 μmol/ml. However, the sesquiterpene, scorzonerin (**4**) did not show higher values compared to others. Scorzonerin (**4**) is a matricarin-based sesquiterpene lactone that carries an esterified dihydrocoumaric acid moiety, which in turn is glycosidically bound to glucose (Tsevegsuren *et al.*, 2007).

Table 1. Sesquiterpenes with antioxidative potency isolated from plants

Compound	Plant	Family	Part(s) used	Method	Reference
Apigenin-8-crhamnopyranoside carissone-11-acetoxy-4a-methoxyeudesmane	*Allophylus laevigatus*	Sapindaceae	Fruit, methanolic extract	For antioxidant analysis, Hidalgo 1994 method and for isolation spectroscopic techniques (NMR, CI-MS)	David *et al.*, 2004
5-Hydroxy-6,9-epoxyguaiane (not analysed for AO)	*Phyllanthus oxyphyllus* Miq	Euphorbiaceae	Roots, dichloromethane extract	DPPH assay, normal isolation	Sutthivaiyakit *et al.*, 2003
Globulol, sesquiterpene alcohol	*Euclyptus*	Myrtaceae	Leaf extract	LC, VP, HPLC, NMR and spectroscopic techniques	Amakura *et al.*, 2002
Methylarzanol, sesquiterpene alcohol rosifoliol	*Helichrysum italicum* ssp. *microphyllum*	Asteraceae	Leaves and flowers, acetone extract	NMR, spectroscopic techniques, DPPH	Rosa *et al.*, 2007
Parthenolide	*Tanacetum parthenium*	Asteraceae	-	Electromobility shift assay (EMSA)	Herrera *et al.*, 2005
Zerumbone	*Zingiber zerumbet* Smith	Zingiberaceae	Rhizome of plant	DPPH	Nakamura *et al.*, 2004
7-Hydroxy-3,4-dihydrocadalin and 7-hydroxycadalin	*Heterotheca inuloides*	Asteraceae	Dried flowers	NMR, spectroscopic techniques, DPPH	Haraguchi *et al.*, 1997
Scorzoneric acid and scorzonerin	*Scorzonera diwaricata*, & *S. pseudodiwaricata*	Asteraceae	Aerial parts, methanolic extract	HPLC DAD, LC-MS, NMR, spectroscopic techniques, DPPH	Tsevegsuren *et al.*, 2007
Hirsutenols D, E and F	*Stereum hirsutum*	Stereaceae	Fermentation broth	HPLC, NMR, DPPH	Yoo *et al.*, 2006
Methoxylaricinolic acid	*Stereum ostrea*	Stereaceae	Fruiting bodies	NMR, DPPH	Kim *et al.*, 2006
Godotol A and B	*Pluchea arabica*	Compositae	-	NMR, DPPH	Fatope *et al.*, 2004
Hushinone	*Betula pubescens* ssp. *pubescens*	Betulaceae	Air dried buds	TLC, GC-MS, NMR, DPPH	Klika *et al.*, 2004
Cacalol	*Calcalia delphinifolia*, Sleb et Zucc.	-	Freez dried	NMR, DPPH	Shindo *et al.*, 2004
Fukanefurochromone A, B, C, D, E and F	*Ferula fukanensis*	Umbelliferae	80% Methanol	NMR, HRMS,	Motai and Kitanaka, 2005
1,2,3,4-Tetrahydro-la,28, 7-trihydroxy-l-6-dimethyl-4P-isopropylnaphthalene-l-O-p-D-glucoside	Cotton seeds (*Gossypium hirsutum*)	Malvaceae	Methanolic extract	NMR, DPPH	Zhang *et al.*, 1998
Ortho-naphthoquinones, davidianones A, B and C	*Ulmus davidiana*	Ulmaceae	Methanolic extract	-	Kim *et al.*, 1996
Parthenolide, costunolide	*Magnolia grandiflora*	Magnoliaceae	Leaves	ARE	Umemura *et al.*, 2008
Parthenolide	*Tanacetum parthenium* Feverfew	Asteraceae		HT22 cells	Herrera *et al.*, 2005



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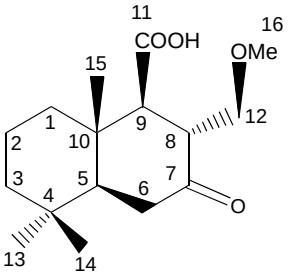
A bioassay guided separation from the methanolic extract of the fruiting bodies of *Stereum ostrea* led to the exploration of a new sesquiterpene, methoxylaricinolic acid (**5**), along with the known compound, laricinolic acid (**6**). In a panel for antioxidant effect, however, these compounds exhibited marginal inhibitory activity with an IC_{50} of 50 mg/ml (vitamin E, 1 mg/ml) against lipid peroxidation in rat liver microsomes evaluated by the thiobarbituric acid method (Kim *et al.*, 2006).



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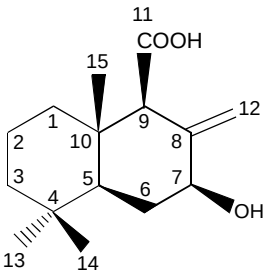

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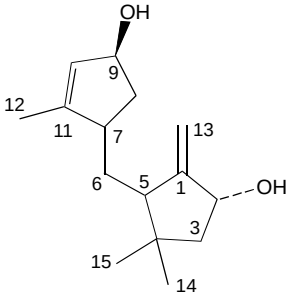
Sesquiterpenes like hirsutenols A, B and C (Yun *et al.*, 2002a), D, E and F (Yoo *et al*., 2006); and sterins A, B (Yun *et al*., 2002b) and C (Yoo *et al*., 2005) were isolated from the culture broth of *Stereum hirsutum* and were found to be good antioxidants. Two new sesquiterpenes, godotol A (**7**) and godotol B (**8**), were isolated from *Pluchea arabica* (Fatope *et al.*, 2004). DPPH free radical scavenging activity tests were performed on extracts and compounds **7** and **8**. These compounds lack antioxidant activity, inhibiting DPPH radicals at less than 10%, with BST, LC_{50} value of 290 µg/ml for **7** and 540 µg/ml for **8**, respectively (Fatope *et al.*, 2004).

The antioxidant activities of the pure compounds [birkenal (**9**), birkenol (**10**), hushinone (**11**), and 6-hydroxycaryophyllene (**12**)] isolated in sufficient quantities from *Betula pubescens* ssp. *pubescens* and *B. pubescens* ssp. *czerepanovii* were assessed by measuring their ability to scavenge DPPH radicals (Klika *et al.*, 2004). The test was performed on the samples at concentrations of 0.5 and 1.0 mg/ml, but significant scavenging of the radicals was not realized (the percentage of radicals scavenged varied between 1.5 and 2% and was basically independent of concentration). In contrast, the percentage of radicals scavenged by the reference compound, pyrogallol was 92% (Klika *et al.*, 2004). This test is normally considered to be a good preliminary screening test for evaluating the potential antioxidant properties of new compounds (Klika *et al.*, 2004).



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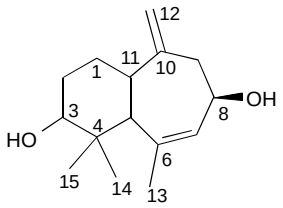

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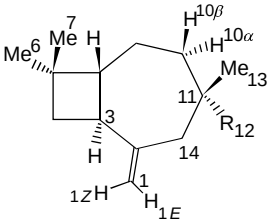
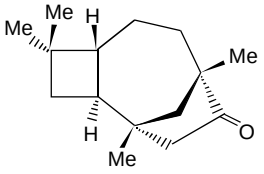
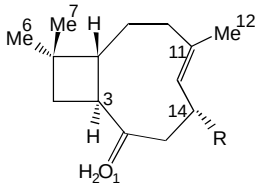


9 R = CHO (birkenal)
10 R = CH OH (birkenol)
$_2$



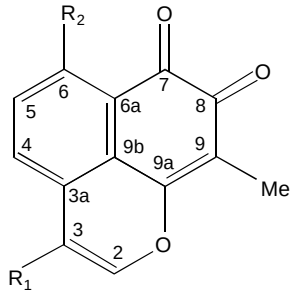
11 Hushinone



12 R = OH (6-hydroxycaryophyllene)

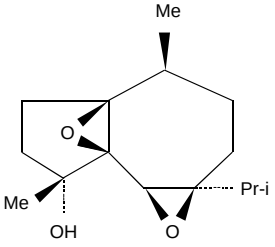
The sesquiterpene, cacalol was isolated from *Cacalia delphiniifolia* and characterized by MS and NMR spectroscopy. Cacalol showed potent antioxidant activities of IC_{50} of 40 nM (Shindo *et al.*, 2004). Three new sesquiterpenes *ortho*naphthoquinones, davidianones A (**13**), B (**14**) and C (**15**), together with four known compounds, namely, mansonones E, F, H and I, were isolated from the 80% aqueous methanolic extract of root bark of *Ulmus davidiana* (Kim *et al.*, 1996). The

antioxidative activities of compounds were evaluated by a thiobarbituric acid method using rat liver microsomes. The result shows that compounds **13** and **15** were active. The IC_{50} values of compound **13**, **14**, and **15** were 0.12, 6.90 and 0.80 µg/ml, respectively, compared with α- tocopherol (IC_{50} 0.10 µg/ml) (Kim *et al.*, 1996).



13 $R_1 = CH_2OH$; $R_2 = Me$
14 $R_1 = Me$; $R_2 = COOMe$
15 $R_1 = Me$; $R_2 = CH(OMe)_2$

Two new sesquiterpenes, 1S*, 4R*, 5S*, 6R*, 7S*, 10S*-1(5), 6(7)-diepoxy-4-guaiol (**16**) and 1S*, 4S*, 5S*, 10R*-4,10-guaianediol (**17**) have been isolated from the ethyl acetate soluble portion of the soft coral *Sinularia* sp. and their stereostructures were determined by spectroscopic methods and X-rays single crystal analysis. Both compounds showed antioxidant and cytotoxic activities (Zhang *et al.*, 2006).



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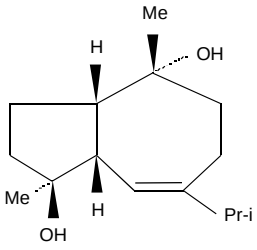

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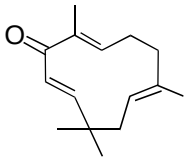
Zerumbone (ZER) (**18**), is a sesquiterpene occurring in tropical ginger *Zingiber zerumbet* Smith (Nakamura *et al.*, 2004). ZER induced nuclear localization of the transcription factor Nrf_2 that binds to antioxidant response element (ARE) of the phase II enzyme genes, suggesting that ZER is a potential activator of the Nrf_2/ARE-dependent detoxification pathway. In order to protect against excessive ROS, aerobic organisms have developed a number of cellular defences composed of non-enzymatic and enzymatic components. The results preliminarily confirmed that ZER did not show any scavenging effect against the stable free radical DPPH (Nakamura *et al.*, 2004).



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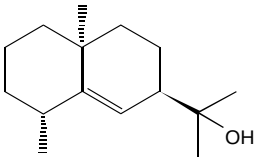
Arzanol, a pyrone-phloroglucinol etherodimer and helipyrone, a dimeric pyrone [rosifoliol (**19**), 10-hydroxytremetone (**20**), acetoxytremetone (**21**) and acetoxyhydroxytremetone (**22**)], isolated from *Helichrysum italicum* ssp. *microphyllum*, showed antioxidant activity (Rosa *et al.*, 2007). They could protect linoleic acid against free radical attack in assays of autoxidation and EDTA-mediated oxidation. Methylarzanol, as well as the sesquiterpene alcohol rosifoliol, showed a decreased, but still significant, protective effect against linoleic acid oxidation. Arzanol and helipyrone were also tested in an assay of thermal (140 °C) autoxidation of cholesterol, where arzanol showed significant antioxidant activity (Rosa *et al.*, 2007).



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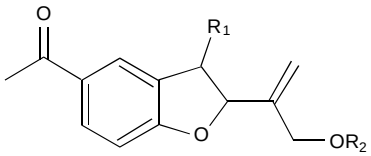
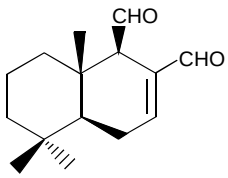


20 $R_1 = R_2 = H$
21 $R_1 = H$; $R_2 = Ac$
22 $R_1 = OAc$; $R_2 = H$

Polygodial (**23**) is a sesquiterpene, which exhibits a strong affinity for sulfhydryl groups with which it interacts by the Michael-type reaction; it can thus inactivate alcohol dehydrogenase, a typical thiol enzyme and thereby interfere with an enzymatic reaction essential for plasma membrane function. On the other hand, the widespread disruptive effects of polygodial against mitochondria and some other organelles prompted us to consider the involvement in its yeastcidal activity of a chemical reaction which can directly attack the phospholipid bilayers (Machida *et al.*, 1999).



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ROS including hydrogen peroxide, superoxide anions, and hydroxyl radicals, are highly toxic oxidants. These oxidants cause lipid peroxidation and can induce disruption of plasma membrane phospholipid bilayers, when overproduced or not suitably eliminated. Mitochondria are equipped with Mn-superoxide dismutase and a redox cycle involving GSH and GSH peroxidase (Foyer and Noctor, 2005; Machida *et al.*, 1999; Bolwell and Wojtaszek, 1997; Harborne, 1993). In the

mitochondrial matrix which lacks catalyse, GSH is the only defence available to cope with the potential toxic effects of hydrogen peroxide, produced endogenously in the electron transport chain. Mammalian cells with markedly depleted mitochondrial GSH were more sensitive to oxidative stress imposed by mitochondrial generation of ROS than those lacking cytosolic GSH. The effects of polygodial on the glutathione content and ROS generation of the yeast cells (*Saccharomyces cerevisiae*) were further examined in the isolated mitochondrial suspension (Machida *et al.*, 1999).

Conclusion and Recommendations. The present review attempts to summarize the outline of the existing knowledge of STs with special emphasis on their antioxidant activities. In conclusion, STs isolated from various plant species have significant antioxidant potentials and most of them are isolated from the plant family, Compositae, which is among the largest and ecologically most diverse plant families. Although there are several reports available on the STs bioactivities, however, only very few systematic studies on structure-activity relationships have been carried out. Detailed studies of this kind, however, would be highly desirable with respect to several aspects of medicinal/pharmaceutical, agrochemical and ecological interest, as most of the plant species, containing STs, have been used in traditional medicines for many centuries and continue to be utilized also in modern phytotherapy (Hussain *et al.*, 2008; Khan *et al.*, 2008, 2007, 2006, 2005). Therapeutic use of STs as pure chemicals, in spite of their broad utilization in the form of plant or crude extracts is restricted to very few examples. This is due to the lack of knowledge about establishment of structural relationship and its requirements for selectivity to a desired biological activity. It may, however, be conceived, that STs could play a valuable role as starting point for developing new therapeutic agents, if more information, especially in the form of quantative structure-activity relationship (QSAR), existed.

References

Amakura, Y., Umino, Y., Tsuji, S., Ito, H., Hatano, T., Yoshida, T., Tonogai, Y. 2002. Constituents and their antioxidative effects in eucalyptus leaf extract used as a natural food additive. *Food Chem.* **77:** 47-56.

Andersson, C.M., Hallberg, A., Hogberg, T. 1996. Advances in the development of pharmaceutical antioxidants. In: *Advances in Drug Research*, B. Testa and U. A. Meyer (eds.), vol. **28,** 65 p., Academic Press, New York, USA.

Anwar, F., Bhanger, M.I. 2003. Analytical characterization of *Moringa oleifera* seed oil grown in temperate regions of Pakistan. *J. Agric. Food Chem.* **51:** 6558-6563.

Apel, K., Hirt, H. 2004. Reactive oxygen species: metabolism, oxidative stress, and signal transduction. *Annu. Rev. Plant Biol.* **55:** 373-399.

Asada, K. 2006. Production and scavenging of reactive oxygen species in chloroplasts and their functions. *Plant Physiol.* **141:** 391-396.

Bolwell, G.P., Wojtaszek, P. 1997. Mechanisms for the generation of reactive oxygen species in plant defence-a broad perspective. *Physiol. Mol. Plant Pathol.* **51:** 347-366.

Chan, H.W.S. 1987. The mechanism of autoxidation. In: *Autoxidation of Unsaturated Lipids*, H. W. -S. Chan (ed.), pp. 1-16, Academic Press, London, UK.

Chun, J.K., Seo, D.W., Ahn, S.H., Park, J.H., You, J.S., Lee, C.H., Lee, J.C., Kim, Y.K., Han, J.W. 2007. Suppression of the NF-kappaB signalling pathway by ergolide, sesquiterpene lactone, in HeLa cells. *J. Pharm. Pharmacol.* **59:** 561-566.

David, J.P., Santos, I.D.dos, David, J.M. 2004. A new sesquiterpene from the fruits of *Allophylus laevigatus*. *Fitoterapia* **75:** 795-798.

Desikan, R., Mackerness, A.H.S., Hancock, J.T., Neill, S.J. 2001. Regulation of the arabidopsis transcriptome by oxidative stress. *Plant Physiol.* **127:** 159-172.

Ding, H., Li, G., Feng, J., Zhang, X. 2005. Antifungi active comopunds from *Inula britannica*. *J. Northwest, Tech. Univ. Agric. Forest*. **33:** 03.

Dong-Yun, S., Yu-Ru, D., Shan-Lin, L., Ya-Dong, Z., Lian, W. 2003. Redox stress regulates cell proliferation and apoptosis of human hepatoma through AKT protein phosphorylation. *FEBS Lett.* **542:** 60-64.

Duthie, G., Crosier, A. 2000. Plant-derived phenolic antioxidants. *Opin. Clin. Nutr. Metab. Care* **3:** 447-451.

Eriksson, C.E. 1982. Lipid oxidation catalysts and inhibitors in raw materials and processed foods. *Food Chem.* **9:** 3-19.

Fatope, M.O., Nair, R.S., Marwah, R.G., Al-Nadhiri, H.H.S. 2004. New sesquiterpenes from *Pluchea arabica*. *J. Nat. Prod.* **67:** 1925-1928.

Foyer, C.H., Noctor, G. 2005. Oxidant and antioxidant signalling in plants: a re-evaluation of the concept of oxidative stress in a physiological context. *Plant Cell Environ.* **28:** 1056-1071.

Foyer, C.H., Noctor, G. 2003. Redox sensing and signalling associated with reactive oxygen in chloroplasts, peroxisomes and mitochondria. *Physiol. Plant*. **119:** 355-364.

Fraga, B.M. 2000. Natural sesquiterpenoids. *Nat. Prod. Rep.* **17:** 483-504.

Guillen, M.D., Manzanos, M.J. 1999. Extractable components of the aerial parts of *Salvia lavandulifolia* and composition of the liquid smoke flavoring obtained from them. *J. Agric. Food Chem.* **47:** 3016-3027.

Hancock, J.T., Desikan, R., Clarke, A., Hurst, R.D., Neill, S.J. 2002. Cell signalling following plant/pathogen interactions

involves the generation of reactive oxygen and reactive nitrogen species. *Plant Physiol. Biochem.* **40:** 611-617.

Haraguchi, H., Ishikawa H., Sanchez, Y., Ogura, T., Kubo, Y., Kubo, I. 1997. Antioxidative constituents in *Heterotheca inuloides*. *Bioorg. Med. Chem.* **5:** 865-871.

Harborne, J.B. 1993. Biochemistry of plant pollination. In: *Introduction to Ecological Biochemistry*, pp. 36-70, 4th edition, Academic Press, London, UK.

Herrera, F., Martin, V., Rodriguez-Blanco, J., Garcia-Santos, G., Antolin, I., Rodriguez, C. 2005. Intracellular redox state regulation by parthenolide. *Biochem. Biophys. Res. Commun.* **332:** 321-325.

Ho, C.T., Rafi, M., Dipaola, R.S., Ghai, G., Rosen, R.T., Bai, N. 2003. Inducing Cell Apoptosis and Treating Cancer Using 1-O-acetylbritannilactone or 1,6-O,O-Diacetylbritannilactone, US Patent No. 6,627,623, 30th September, 2003.

Hussain, I., Khan, H., Khan, M.A. 2008. Screening of antioxidant activities of selected medicinal plants for their antioxidants potentials using 2,2-diphenyl picryl hydrazyl radical assay. *J. Chem. Soc. Pak.* (Submitted).

Jatoi, S.A., Kikuchi, A., Gilani, S.A., Watanabe, K.N. 2007. Phytochemical, pharmacological and ethnobotanical studies in Mango Ginger (*Curcuma amada* Roxb.; Zingiberaceae). *Phytother. Res.* **21:** 507-516.

Khan, T., Ahmad, M., Khan, H., Khan, M.A. 2005. Biological activities of aerial parts of *Paeonia emodi* Wall. *Afr. J. Biotechnol.* **4:** 1313-1316.

Khan, T., Ahmad, M., Khan, R., Khan, H., Ejaz, A., Choudhary, M.I. 2006. Evaluation of phytomedicinal potentials of selected plants of Pakistan. *American Laboratory* **38:** 20-22.

Khan, T., Ahmad, M., Khan, R., Khan, H., Choudhary, M.I. 2007. Phytotoxic and insecticidal activities of medicinal plants of Pakistan, *Trichodesma indicum, Aconitum laeve* and *Sauromatum guttatum*. *J. Chem. Soc. Pak.* **29:** 260-264.

Khan, A.L., Gilani, S.A., Fujii, Y., Watanabe, K.N. 2008. Monograph on *Inula britannica* L. Mimatsu Corporation, Tokyo-Japan.

Kim, Y.H., Yun, B.S., Ryoo, I.J., Kim, J.P., Koshino, H. 2006. Methoxylaricinolic acid, a new sesquiterpene from the fruiting bodies of *Stereum ostrea*. *J. Antibiot.* **59:** 432-434.

Kim, S.R., Park, M.J., Lee, M.K., Sung, S.H., Park, E.J., Kim, J., Kim, S.Y., Oh, T.H., Markelonis, G.J., Kim, Y.C. 2002. Flavonoids of *Inula britannica* protect cultured cortical cells from necrotic cell death induced by glutamate. *Free Rad. Biol. Med.* **32:** 596-604.

Kim, J.P., Kim, W.G., Koshino, H., Jung, J., Yoo, I.D. 1996. Sesquiterpene *o*-naphthoquinones from the root bark of *Ulmus davidiana*. *Phytochemistry* **43:** 425-430.

Klika, K.D., Demirci, B., Salminen, J.P., Ovcharenko, V.V., Vuorela, S., Baser, K.H.C., Pihlaja, K. 2004. New, sesquiterpenoid-type bicyclic compounds from the buds of *Betula pubescens*-ring-contracted products of β-caryophyllene? *Eur. J. Org. Chem.* 2627-2635.

Krol, W., Czuba, Z.P., Threadgill, M.D., Cunningham, B.D.M., Shani, J. 1995. Modulation of luminol-dependent chemiluminescence of murine macrophages by flavone and its synthetic derivatives. *Arzneim.-Forsch./Drug Res.* **45:** 815-818.

Laloi, C., Apel, K., Danon, A. 2004. Reactive oxygen signalling: the latest news. *Curr. Opin. Plant Biol.* **7:** 323-328.

Liu, B., Han, M., Wen, J.K. 2008. Acetylbritannilactone inhibits neointimal hyperplasia after balloon injury of rat artery by suppressing NF-kB activation. *J. Pharmacol. Exp. Ther.* **324:** 292-298.

Machida, K., Tanaka, T., Taniguchi, M. 1999. Depletion of glutathione as a cause of the promotive effects of polygodial, a sesquiterpene on the production of reactive oxygen species in *Saccharomyces cerevisiae*. *J. Biosci. Bioeng.* **88:** 526-530.

Macias, F.A., Galindo, J.L., Galindo, J.C. 2007. Evolution and current status of ecological phytochemistry. *Phytochemistry* **68:** 2917-2936.

Maffei, M.E., Mithofer, A., Boland, W. 2007. Insects feeding on plants: Rapid signals and responses preceding the induction of phytochemical release. *Phytochemistry* **68:** 2946-2959.

Manzoor, M., Anwar, F., Iqbal, T., Bhanger, M.I. 2007. Physico-chemical characterization of *Moringa concanensis* seeds and seed oil. *J. Am. Oil Chem. Soc.* **84:** 413-419.

Menon, S.G., Sarsour, E.H., Spitz, D.R., Higashikubo, R., Sturm, M., Zhang, H., Goswami, P.C. 2003. Redox regulation of the G1 to S-phase transition in the mouse embryo fibroblast cell cycle. *Cancer Res.* **63:** 2109-2117.

Merfort, I. 2002. Review of the analytical techniques of sesquiterpenes and sesquiterpene lactones. *J. Chromatogr. A* **967:** 115-130.

Miguel, M.G., Falcato-Simoes, M., Figueiredo, A.C., Barroso, J.M.G., Pedro, L.G., Carvalho, L.M. 2005. Evaluation of the antioxidant activity of *Thymbra capitata, Thymus mastichina* and *Thymus camphoratus* essential oils. *J. Food Lipids* **12:** 181-197.

Moonis, M., Ahmad, I., Bachhawat, B.K. 1992. Macrophage in host defence, an overview. *Indian J. Biochem. Biophys.* **29:** 115-122.

Motai, T., Kitanaka, S. 2005. Sesquiterpene chromones from *Ferula fukanensis* and their nitric oxide production inhibitory effects. *J. Nat. Prod.* **68:** 1732-1735.

Nakamura, Y., Yoshida, C., Murakami, A., Ohigashi, H., Osawa, T., Uchida, K. 2004. Zerumbone, a tropical ginger sesqui-

terpene, activates phase II drug metabolizing enzymes. *FEBS Lett.* **572:** 245-250.

Navrot, N., Rouhier, N., Gelhaye, E., Jacquot, J.P. 2007. Reactive oxygen species generation and antioxidant systems in plant mitochondria. *Physiol. Plant.* **129:** 185-195.

Nawrot, J. 1983. Principles for grain weevil (*Sitophilus granarius* L.) (Coleoptera: Curculionidae) control with use of natural chemical compounds affecting the behavior of beetles. *Prace Naukowe Instytutu Ochrony Roslin* **24:** 173-197.

Neill, S.J., Desikan, R., Clarke, A., Hurst, R.D., Hancock, J.T. 2002. Hydrogen peroxide and nitric oxide as signalling molecules in plants. *J. Exp. Bot.* **53:** 1237-247.

Novelli, E.L.B. 2005. Nutricao e vida Savdavel-Estresse Oxidativo e Metabolismo Energetico, Ribeir'ao Preto, sp: 288 p., Tecmedd, (in Portugese).

Pan, M.H., Chiou, Y., Cheng, A.C., Bai, N., Lo, C.Y., Tan, D., Ho, C.T. 2007. Involvement of MAPK, Bcl-2 family, cytochromec, and caspases in induction of apoptosis by 1,6-O,O-diacetylbritannilactone in human leukemia cells. *Mol. Nut. Food Res.* **51:** 229-238.

Pandhair, V., Sekhon, B.S. 2006. Reactive oxygen species and antioxidants in plants: an overview. *J. Plant Biochem. Biotechnol.* **15:** 71-78.

Park, E.J., Kim, J. 1998. Cytotoxic sesquiterpene lactones from *Inula britannica*. *Planta Med.* **64:** 752-754.

Park, E.J., Kim, Y., Kim, J. 2000. Acylated flavonol glycosides from the flower of *Inula britannica*. *J. Nat. Prod.* **63:** 34-36.

Pitzschke, A., Hirt, H. 2006. Mitogen-activated protein kinases and reactive oxygen species signalling in plants. *Plant Physiol.* **141:** 351-356.

Rafi, M.M., Bai, N.S., HO, C.T., Rosen, R.T., White, E., Perez, D., DiPaola, R.S. 2005. A sesquiterpenelactone from *Inula britannica* induces anti-tumor effects dependent on Bcl-2 phosphorylation. *Anticancer Res.* **25:** 313-318.

Rosa, A., Deiana, M., Atzeri, A., Corona, G., Incani, A., Melis, M.P., Appendino, G., Dessi, M.A. 2007. Evaluation of the antioxidant and cytotoxic activity of arzanol, a prenylated α-pyrone-phloroglucinol etherodimer from *Helichrysum italicum* subsp. *Microphyllum*. *Chemico-Biol. Interact.* **165:** 117-126.

Schmidt, T.J. 2006. Structure-activity relationships of sesquiterpene lactones. In: *Stud. Nat. Prod. Chem*., Atta-ur-Rahman (ed.), vol. **33,** pp. 309-392, Elsevier, B. V., USA.

Scott, G. 1985. Antioxidants *in vitro* and *in vivo. Chem. Britain* **21:** 648-653.

Sforcin, J.M. 2007. Propolis and the immune system: a review. *J. Ethnopharmacol.* **113:** 1-14.

Shahidi, F. 1997. Natural Antioxidant: an overview. In: *Natural Antioxidants Chemistry, Health Effects and Applications*, F. Shahidi (ed.), pp. 1-11, AOCS Press, Champaign, Illinoise, USA.

Sharma, N., Sharma, V.K., Seo, S.Y. 2005. Screening of some medicinal plants for anti-lipase activity. *J. Ethnopharmacol.* **97:** 453-456.

Shindo, K., Kimura, M., Iga, M. 2004. Potent antioxidative activity of cacalol, a sesquiterpene contained in *Cacalia delphiniifolia* Sleb et Zucc. *Biosci. Biotechnol. Biochem.* **68:** 1393-1394.

Sutthivaiyakit, S., Nakorn, N.N., Kraus, W., Sutthivaiyakit, P. 2003. A novel 29-nor-3,4-seco-friedelane triterpene and a new guaiane sesquiterpene from the roots of *Phyllanthus oxyphyllus*. *Tetrahedron* **59:** 9991-9995.

Tsevegsuren, N., Edrada, R., Lin, W., Ebel, R., Torre, C., Ortlepp, S., Wray, V., Proksch, P. 2007. Biologically active natural products from Mongolian medicinal plants *Scorzonera divaricata* and *Scorzonera pseudodi*-varicata. *J. Nat. Prod.* **70:** 962-967.

Umemura, K., Itoh, T., Hamada, N., Fujita, Y., Akao, Y., Nozawa, Y., Matsuura, N., Iinuma, M., Ito, M. 2008. Preconditioning by sesquiterpene lactone enhances H_2O_2-induced Nrf2/ARE activation. *Biochem. Biophys. Res. Commun.* **368:** 948-954.

Yoo, N.H., Kim, J.P., Yun, B.S., Ryoo, I.J., Lee, I.K., Yoon, E.S., Koshino, H., Yoo, I.D. 2006. Hirsutenols D, E and F, new sesquiterpenes from the culture broth of *Stereum hirsutum*. *J. Antibiot.* **59:** 110-113.

Yoo, N.H., Yoo, I.D., Kim, J.W., Yun, B.S., Ryou, I J., Yoor, E.S., Chinh, N.T., Kim, J.P. 2005. Sterin C, a new antioxidant from the mycelial culture of the mushroom *Stereum hirsutum*. *Agric. Chem. Biotech*. **48:** 38-41.

Yun, B.S., Lee, I.K., Cho, Y., Cho, S.M., Yoo, I.D. 2002a. New tricyclic sesquiterpenes from the fermentation broth of *Stereum hirsutum*. *J. Nat. Prod.* **65:** 786-788.

Yun, B.S., Cho, Y.R., Lee, I.K., Cho, S.M., Lee, T.H., Yoo, I.D. 2002b. Sterins A and B, new antioxidative compounds from *Stereum hirsutum*. *J. Antibiot.* **55:** 208-210.

Zhang, G.W., Ma, X.Q., Su, J.Y., Zhang, K., Kurihara, H., Yao, X.S., Zheng, L.M., 2006. Two new bioactive sesquiterpenes from the soft coral *Sinularia* sp. *Nat. Prod. Res.* **20:** 659-664.

Zhang, H.L., Nagatsu, A., Okuyama, H., Mizukami, H., Sakakibara, J. 1998. Sesquiterpene glycosides from cotton oil cake. *Phytochemistry* **48:** 665-668.