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Sesquiterpenes: The Potent Antioxidants-A Review

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Abstract

Sesquiterpenes (STs) are 15 carbon terpenoids and found to have significant phytomedicinal, phytotoxic and agrochemical potentials. They are found to be present in the essential/edible oils. However, various STs have 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 will be used as scientific data base for the researcher working in this field.

Keywords: sesquiterpenes, sesquiterpene lactones, antioxidant, plant species, crude extract and isolation, biologically active compounds

Introduction

Sesquiterpenes

Sesquiterpenes (STs) are 15 carbon terpenoids comprising of mainly two types that is 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 smaller molecular weight, they are important volatile organic parts especially the essential oils, which are of great medicinal potentials. Besides presence in essential oils forms, they are also major constituents of various medicinal and economically important plants (Merfort *et al.*, 2001).

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 and besides these there are some esters or lactone group linked sesquiterpenes. Almost 5000 sesquiterpenes lactones have been reported. Among them 60 to 65% have been reported to be present as an essential/edible oils (Schmidt, 2006; Frega, 2000).

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

Antioxidants

Antioxidants are classically defined as molecules present in lower concentrations than 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 (Bolwell and Wojtaszek, 1997; Foyer and Noctor, 2005; Harborne, 1993, Khan *et al.*, 2005, 2006, 2007; Hussain *et al.*, 2008). Thus, there is a delicate balance between the generation and destruction of oxidant agents, which may be beneficial or deleterious to the organism (Foyer and Noctor, 2005; Maffei et al, 2007; Novelli, 2005; Khan *et al.*, 2005, 2006, 2007; Hussain *et al.*, 2008). Oxidation products from lipids and cholesterol are thought to be a contributing factor to the cause of various diseases, including cancer, atherosclerosis and some age-related diseases (Asada, 1996; Scott, 1985; Chan, 1987; Andersson, 1996; Ho et al, 2003; Jatoi *et al.*, 2007; Chun *et al.*, 2007; Pandhair and Sekhon, 2006). Lipid oxidation in food affects its nutritional quality which results a rancid flavor; one of the main consequences. Also loss of vitamins, polyunsaturated fatty acids and other essential compounds can occur during the process (Andersson *et al.*, 1996; Eriksson, 1982; Anwar and Bhanger, 2003; Manzoor *et al.*, 2007; Chan, 1987; Pandhair and Sekhon, 2006; Khan *et al.*, 2008).

NADPH oxidase catalyses the reduction of molecular oxygen to superoxide 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•), 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 (Moonis *et al.*, 1992; Sforcin, 2007; Pandhair and Sekhon, 2006; Khan *et al.*, 2005, 2006, 2007, 2008; Hussain *et al.*, 2008).

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 (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, MAPKs, are modulated by ROS (Desikan *et al.*, 2001, 2005; Neill *et al.*, 2002, 2003; Pitzschke and Hirt, 2006). Oxidative stress, resulting from the generation of ROS, such as superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($HO^{\bullet}$), is a common phenomenon (Maffei *et al.*, 2006; 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 (Foyer and Noctor, 2005; Pandhair and Sekhon, 2006). 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 (Apel and Hirt, 2004; Asada, 2006; Hancock *et al.*, 2002; Khan *et al.*, 2008).

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 (Duthie and Crosier, 2000; Park *et al.*, 2002; Kim *et al.*, 2002; (Khan *et al.*, 2008). A large number of plants have been screened as a

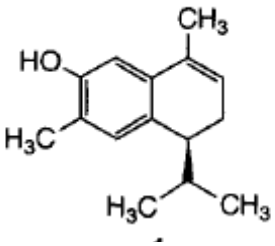
source of new additives for the food and pharmaceutical markets, which can provide a supplement to cope with oxidative stress (Shahidi, 1997; Park *et al.*, 2002; Kim *et al.*, 2002; Rosa *et al.*, 2007; Laloi *et al.*, 2004 ; Pandhair and Sekhon, 2006; Khan *et al.*, 2005, 2006, 2007, 2008; Hussain *et al.*, 2008).

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). GSH is the main intracellular antioxidant and plays an important role in these processes. GSH depletion leading to cell death, and GSH increase inhibiting cell proliferation (Menon *et al.*, 2003).

Antioxidant Sesquiterpenes from Plants

Various sesquiterpenes belonging to different sub-classes have been isolated from the plant species. Since we have excluded the sesquiterpenes reported from essential/edible oils, therefore, 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, 3-Napthol (**1**), p-cymene (**2**), and carvacrol (**3**) have been isolated from *Heterotheca inuloides* (Haraguchi *et al.*, 1997). 3-Napthol (**1**) exhibited potent DPPH radical scavenging activity. However, p-cymene (**2**), and carvacrol (**3**) showed no effect on 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical a concentration of 30 gg/mL. Sesquiterpenoids 1 showed potent antioxidative activity against linoleic acid autoxidation; almost 80% inhibition was observed at 10 gg/mL (Haraguchi *et al.*, 1997).



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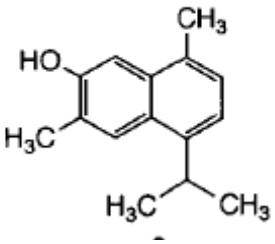

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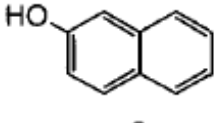

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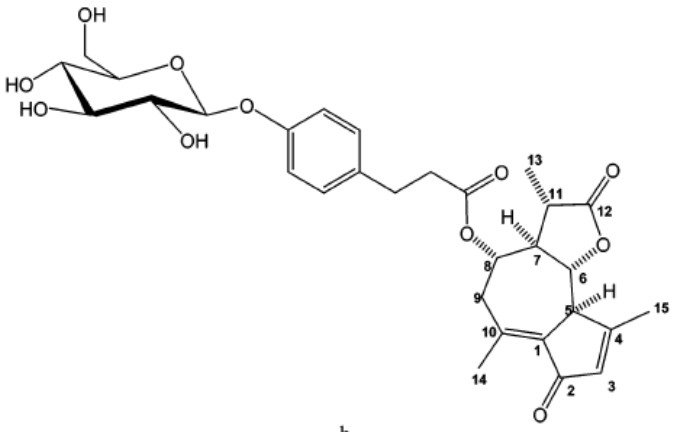
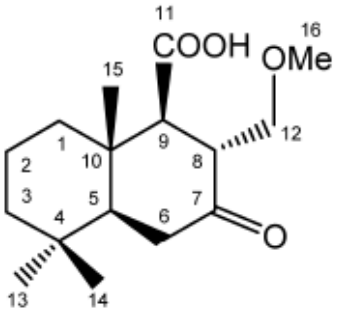
Feruloylpodospermic acids A and B and scorzonerin (**4**) were purified from the crude extract of the aerial parts of the Mongolian medicinal plant, *Scorzonera divaricata* (Tsevegsuren *et al.*, 2007). These were detected in the DPPH active fractions. To know the potential of compound against oxidative stress, naturally occurring antioxidant, chlorogenic acid was used 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 showed 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).



4[b]

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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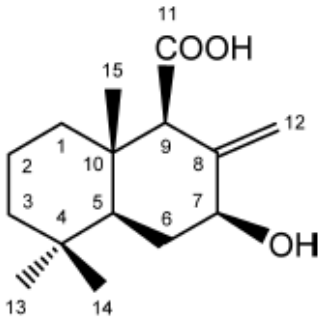
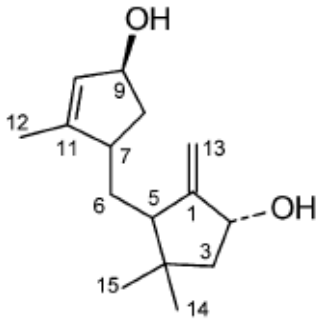


6

Sesquiterpenes like hirsutenols A, B and C (Yun *et al.*, 2002) sterins A, B and C were isolated from the culture broth of *Stereum hirsutum* (Yun *et al.*, 2002; Yun *et al.*, 2005) 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).



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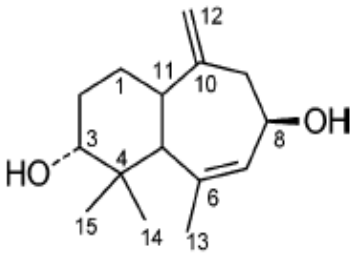

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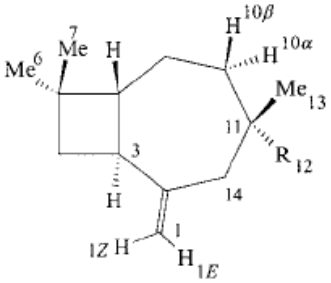
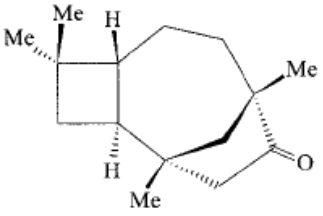
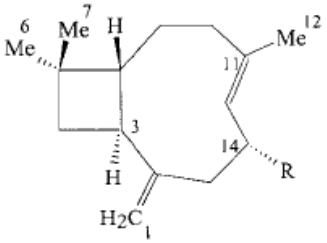
The antioxidant activities of the pure compounds [birkenal (**9**), birkenol (**10**), hushinone (**11**), and 6-hydroxycaryophyllene (**12**)] isolated in sufficient quantities from *Betula pubescens* ssp. *pubescens* and *B. pubescens* ssp. *czerepanovii* were assessed by measuring their ability to 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).



9 R = CHO (birkenal)
10 R = CH_2OH (birkenol)

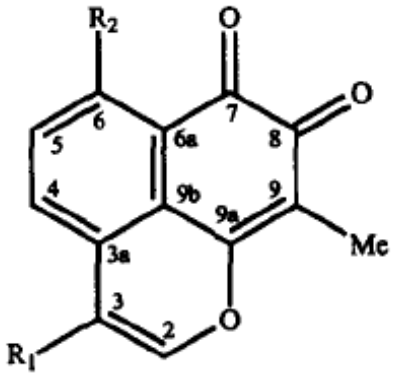


11 , hushinone



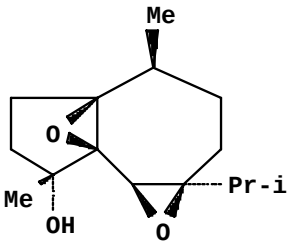
12 , R = OH (6-hydroxycaryophyllene)

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 sesquiterpene *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 the 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).



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

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 solution 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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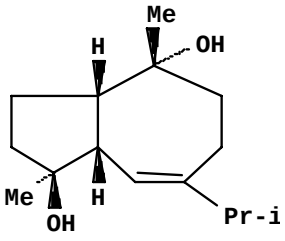

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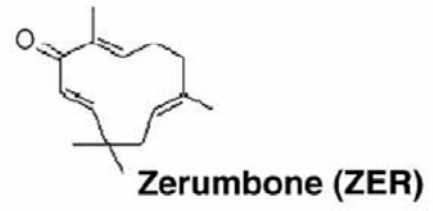
Zerumbone (ZER) (**18**), a sesquiterpene compound occurring in tropical ginger *Zingiber zerumbet* Smith (Nakamura *et al.*, 2004). ZER induced nuclear localization of the transcription factor Nrf2 that binds to antioxidant response element (ARE) of the phase II enzyme genes, suggesting that ZER is a potential activator of the Nrf2/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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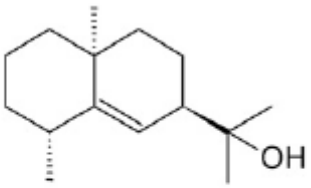
Arzanol, a pyrone-phloroglucinol etherodimer, and helipyrone, a dimeric pyrone [rosifoliol (**19**), 10-hydroxytremetone (**20**), acetoxytremetone (**21**) and acetoxyhydroxytremetone (**22**)], isolated from *Helichrysum italicum* subsp. *Microphyllum*. showed antioxidant activity (Rosa *et al.*, 2007). 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 ^{o}C) autoxidation of cholesterol, where arzanol showed significant antioxidant activity (Rosa *et al.*, 2007).



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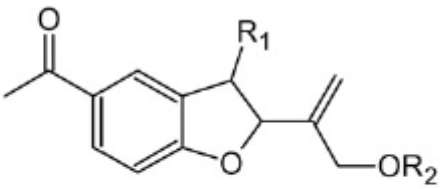

20 $R_1 = R_2 = H$
21 $R_1 = H$; $R_2 = Ac$
22 $R_1 = OAc$; $R_2 = H$

Polygodial (**23**) is a sesquiterpene, 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).

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 (Machida *et al.*, 1999; Harborne, 1993; Bolwell and Wojtaszek, 1997; Foyer and Noctor, 2005). 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).

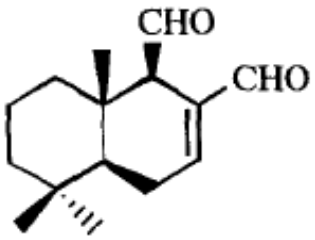

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Table 1. Sesquiterpenes with antioxidative potency isolated from plants

Chemical compounds	**Plant species**	**Family**	**Part(s) used**	**Methods**	**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*	-	Leaf extract	LC, VP, HPLC, NMR and spectroscopic techniques	Amakura *et al.*, 2002
Methylarzanol, Sesquiterpene Alcohol Rosifoliol	*H. italicum subsp. Microphyllum*	-	Leaves & flowers, Acetone extract	NMR, Spectroscopic techniques, DPPH	Rosa *et al.*, 2007
Parthenolide	*Tanacetum parthenium*	-	-	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 & 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*	-	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 & Kitanaka, 2005
1,2,3,4-Tetrahydro-la,28,7-trihydroxy-l-6-dimethyl-4P-isopropylnaphthalene-l-O-p-D-	Cotton seeds	-	Methanolic extract	NMR, DPPH	Zhang *et al.*, 1998

glucoside					
Ortho-naphthoquinones, Davidianones A, B and C	*Ulmus davidiana*	-	Methanolic extract	-	Kim *et al.*, 1996
Parthenolide, costunolide	*Magnolia grandiflora*	Compositae	Leaves	ARE	Umemura *et al.*, 2008
Parthenolide	*Tanacetum parthenium* Feverfew	-		HT22 cells	Herrera *et al.*, 2005

Conclusions 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 found to have significant antioxidant potentials. It has been found that most STs were 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 which containing STs have been used in traditional medicines for many centuries and continue to be utilized also in modern phytotherapy (Khan *et al.*, 2005, 2006, 2007, 2008; Hussain *et al.*, 2008). Therapeutic use of STs as pure chemicals, in spite of their broad utilization in form of plants or crude extracts, restricted to very few examples. This is due to the lack of establishment in the knowledge 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 relationships (QSAR), existed.

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