Send Orders of Reprints at reprints@benthamscience.net

 Current Medicinal Chemistry, **2013**, *20*, **984-1004**

Chinese Medicinal Herbs as Source of Antioxidant Compounds – Where Tradition Meets the Future

A. Matkowski*, W. Jamiołkowska-Kozlowska and I. Nawrot

Department of Pharmaceutical Biology and Botany, Medical University in Wroclaw, ul. Borowska 211, PL-50556 Wroclaw, Poland

Abstract: Medicinal plants are an essential part of Traditional Chinese Medicine (TCM), an ancient complex therapy considered today as one of the most complete complementary medicine system. Chinese Herbal Medicines (CHM) listings included in Chinese Materia Medica cover more than 1500 plants and a great number of composite preparations. Recently, several TCM herbs have been included into European Pharmacopoeia and many more are on the waiting list. The efficiency of TCM is based on the reinforcing of an organism's natural healing power and the ability to restore the energy homoeostasis. A likely mechanism of at least some of the activities is interacting with redox balance and prevention of oxidative stress. During the past two decades, hundreds of crude herbs, extracts, and isolated compounds have been screened for their antioxidant properties *in vitro* and *in vivo*. Consequently, some of traditional Chinese herbs can be regarded as source of very efficient antioxidant compounds, and this activity could explain some of their therapeutic and preventive usefulness. In this review, we outline the recent achievements in the worldwide quest for more efficient antioxidants, with Chinese medicinal and food plants in the central point. Various classes of antioxidant compounds will be mentioned, such as polyphenols or terpenoids that can act either as direct reactive oxygen species scavengers, transition metal reducers and chelators, or as chain breaking antioxidants. Some methodological considerations will be also discussed, with emphasis on the potential importance of the results obtained with antioxidant assays for human health and disease prevention. In this context, several examples of selected, most promising Chinese medicinal plants will be also presented in more detail.

Keywords: Antioxidant, Chinese herbal medicines, flavonoids, free radical, phytotherapy, polyphenols.

INTRODUCTION

Oxidative stress is associated with pathogenesis and progression of many diseases such as: diabetes, atherosclerosis, chronic inflammations, neurodegenerative disorders, and cancer, as well as aging of living organisms [1]. The direct consequence of excessive reactive oxygen species (ROS) incidence is the oxidative damage of vital biomolecules such as nucleic acids, membrane lipids and proteins.

The TCM philosophy of restoring the dysregulated body functions and increasing resistance to the detrimental conditions may involve the redox homoeostasis as one of the therapeutic objectives. Therefore, well known health benefits of some Chinese herbal medicines are likely to be influenced by their antioxidant properties Fig. (**1**).

To date, thousands of papers report antioxidant activity of extracts or isolated compounds from CHM, often as one of several studied pharmacological activities. Alternatively, selected herbal drugs were screened for antioxidant properties using quick *in vitro* assays as in the paper by Cai *et al.* [2] who tested 112 plants with TEAC antiradical assay, that was followed by another publication where the same authors have studied isolated compounds - various polyphenol and quinones and correlated some structural features to their antiradical activity [3]. However, using only antioxidant tests based on a single mechanism is not sufficient for reliable evaluation of a potentially useful substance [4]. In many papers, one can notice an attitude to enthusiastically proclaim a discovery of a powerful antioxidant, with "huge" potential in oxidative stress prevention and therapy, without a real support in the results actually obtained.

Moreover, the methodology used in the published work differs to a large extent, rendering the results difficult to compare. In many cases the results are contradictory, so the careful interpretation is necessary before declaring that a herb or a compound is, or is not a potent antioxidant. In this review, we have referred only to those plants, that have been verified in several studies and/or the experiments and included appropriate reference compound (such as Trolox, a pure polyphenol, ascorbic acid, BHT etc). Also, we have not included examples that did not exhibit reasonably high antioxidant potency even if the publication claimed the antioxidant properties of the tested sample. More specifically, if for example the EC_{50} in the DPPH (at 100 μM) assay is around 1 mg/mL, or the scavenging percent after a long incubation is 50%, the compound could not be reliably called a potent free radical scavenger. On the other hand, there are numerous *in vivo* studies associated with oxidative stress, for example in diabetes or inflammation where no actual antioxidant effect could be proved. The examples of the numerous CHM where antioxidant activity was verified experimentally are given in (Tables **1** and **2**), grouped after indication of the traditional descriptive pharmacological category of Chinese Materia Medica [5, 6]. Quite unexpectedly, the relationships between TCM-based description of herbs and their pharmacological properties have been rarely considered as a valid rationale for a study. One of the few papers was published by Ou *et al.* in 2003 [7], where anti-ROS activity using ORAC (oxygen radical scavenging antioxidant capacity) was compared between extracts from yin or yang tonifying herbs. The results suggested that yin-associated herbs are in average much stronger radical scavengers than yang ones. This simple rule seemed not to be confirmed by other studies like that by Wong *et al.* [8] using FRAP (ferric ions reducing) method, who suggested just an opposite correlations, but they had selected different herbs from both categories. Szeto and Benzie [9] who had tested the antigenotoxic properties of the same herbs as Ou *et al.* [7] did not observed any correlations. Then again, in the screening study of 45 herbs by Liao *et al.* [10], a correlation has been found to the formal flavor (taste) characteristic of the herbs. In this study, bitter and sour herbs (*Spatholobi caulis* – Ji xue teng, *Sanguisorbae radix* – Di yu, *Agrimoniae pilosae herba* – Xian he cao, *Salviae miltiorrhizae radix* – Dan shen, *Artemisiae anomalae herba* – Liu ji nu, and *Nelumbinis folium* – He ye, had the highest ORAC value, while the sweet and pungent tended to be less active (for example *Angelicae sinensis radix* -Dang gui, *Jujubae fructus* – Da zao). However, there were also many exceptions from this tendency, such as a bitter and sour *Cyathulae radix* – Chuan niu xi, that was the second weakest of all herbs. This situation perfectly illustrates the necessity of performing several complementing assays based on various mechanisms.

*Address correspondence to this author at the Department of Pharmaceutical Biology and Botany, Medical University in Wroclaw, ul. Borowska 211, PL-50556 Wroclaw, Poland; Tel: +48713482942; E-mail: pharmaceutical.biology@wp.eu

1875-533X/13 $58.00+.00

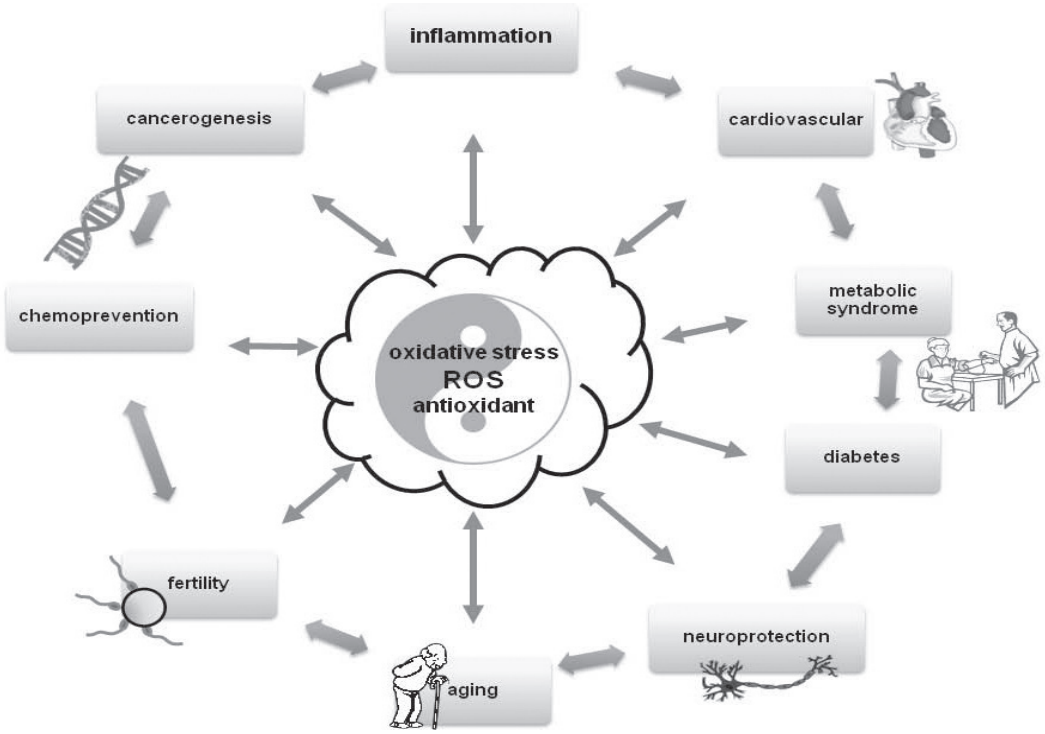

Fig. (1). Schematic representation of interactions between antioxidants and oxidative stress related disorders.

Table 1. Selected Examples of Traditional Chinese Herbs with Significant Antioxidant Potential Confirmed in Experimental Studies Grouped in Categories (Last Column) According to Chinese Materia Medica Classification*. Categories I to VIII. *See Footnote for Categories Description, (No Herbs in Categories II and V)

Plant Species	Part Used	Drug Name - Latin	Drug Name – Chinese Transcription	Antioxidant Constituents	Antioxidant Testing Methods	Reference	Cat. No.
Arctium lappa	Root	Arctii fructus	Niu bang zi	Arctigenin, quercetin, chlorogenic acid, caffeic acid, caffeoylquinic acid	DPPH, *in vitro* human cell lines K562, MCF-7, 786-0	[141]	I
Chrysanthemum morifolium	Flower	Chrysanthemi flos	Ju hua	Quercetin, apigenin, luteolin, hesperetin, diosmetin and flavonoid glycosides	DPPH, ABTS, ferrous ion chelating	[142]	
Elsholtzia splendens	Herb	Moslae herba	Xiang ru	Flavonoids	DPPH, β-carotene bleaching assay	[143]	
Mentha haplocalyx	Herb	Menthae herba	Bo he	Polyphenolic acids (lithospermic acid B)	DPPH, Iron reducing, Iron chelation, phospholipid peroxidation, ORAC.	[11, 16]	
Perilla frutescens	Leaf	Perillae folium	Zi su ye	Cinnamic acid derivatives, flavone glycosides, anthocyanins	TEAC, FRAP	[1, 2]	
Pueraria lobata, Pueraria sp	Root or flower	Puerariae radix, Puerariae flos	Ge gen	Isoflavonoids (puerarin, tectoridin, tectorigenin)	ROS scavenging activity, DPPH, lipid peroxidation, *in vivo* rats	[31, 144]	
Rheum officinale, R. palmatum	Rhizome and root	Rhei rhizoma et radix	Da huang	Tannins, flavanols, stilbenes (rhaponticin)	Chemiluminescence assays	[145]	III
Artemisia annua	Herb	Artemisiae annuae herba	Qing hao	Catechin, gentisic acid, sinapic acid, flavonols	DPPH	[146, 147]	IV
Buddleja officinalis	Flower	Buddlejae flos	Mi meng hua	Phenylethanoid glycosides (acteoside, echinacoside)	TEAC, FRAP, peroxynitrite scavenging	[148, 149]	
Camellia sinensis	Leaf	Camelliae sinensis folium	Cha ye	Epigallocatechin-3-gallate, caffeic acid, quinic acid, feruloylquinic acid	Various antioxidant assays	[150]	

(Table 1). contd….

Plant Species	Part Used	Drug Name - Latin	Drug Name – Chinese Transcription	Antioxidant Constituents	Antioxidant Testing Methods	Reference	Cat. No.
Coptis chinensis	Rhizome	Coptidis rhizoma	Huang lian	Isoquinoline alkaloids (berberine, coptisine)	DPPH, ABTS, superoxide anion radical and hydrogen peroxide scavenging	[74, 75]	
Forsythia suspensa	Fruit	Forsythiae fructus	Lian qiao	Phenylethanoid glycosides	Various assays	[1, 2]	
Fraxinus rhynchophylla	Bark	Fraxini cortex	Qin pi	Hydroxycoumarins (esculetin, fraxetin)	FRAP, TEAC	[1-3]	
Iris domestica	Rhizome	Belamcandae rhizoma	She gan	Isoflavonoids (irigenin, tectorigenin and glycosides), mangiferin, stilbenes (resveratrol, isorhapontigenin)	Many *in vitro* assays, oxidative mutagenesis Salmonella test	[36]	
Lithospermum erythrorhizon	Root	Lithospermi radix	Zi cao gen	Rosmarinic acid, shikonin	TEAC	[2]	
Lonicera japonica	Flower	Lonicerae flos	Jin yin hua	Flavones, flavonols, and glycosides, caffeoylquinic acids (chlorogenic acid)	FRAP, TEAC, DPPH	[1, 2, 25]	
Lycium barbarum	Fruit	Lycii fructus	Gou qi zi	Anthocyanins, carotenoids, ascorbic acid	Various assays *in vitro* and *in vivo*	[67]	
Nelumbo nucifera	Leaves	Nelumbinis folium	He ye	Flavonoids, tannins,	TBA, DPPH, ABTS, reducing power assay, erythrocyte hemolysis, lipid peroxidation	[1, 2]	
Oldenlandia diffusa	Herb	Heyotidis diffusae herba	Bai hua she she cao	Iridoid glycosides (scadoside, geniposidic acid)	LDL-oxidation	[151]	
Paeonia suffruticosa	Root bark	Moutan cortex	Mu dan pi	Paeonol, paeonoside, paeoniflorin	Various *in vitro* tests, ORAC	[152]	
Phellodendron amurense, Phellodendron chinense	Bark	Phellodendri cortex	Huang bai	Berberine, quercetin, kaempferol	DPPH	[153]	
Picrorhiza scrophulariifolia, Picrorhiza kurroa	Rhizoma	Picrorhizae rhizoma	Hu huang lian	Apocynin, androsin, picroside I, II, III	DPPH, FRAP, TBA	[154]	
Persicaria bistorta	Rhizoma	Bistortae rhizoma	Zu shen	Taxifolin, quercetin, kaempferol, luteolin, isorhamnetin, rhamnetin, tannins	Ischemia/reperfusion injury in the rat retina	[155]	
Prunella vulgaris	Inflorescence	Prunellae spica	Xia ku cao	Caffeic acid, rosmarinic acid, rutin, quercetin	Many *in vitro* and *in vivo* assays	[156]	
Rabdosia rubescens	Herb	Rabdosiae herba	Dong ling	Rosmarinic acid, oridonin	Oxidative DNA damage in blood cells	[157]	
Rehmannia glutinosa	Root	Rehmanniae radix praeparata	Shu di huang	Acteoside	UV-induced apoptosis in U937 cells, antioxidant enzymes activity, ORAC	[158, 159]	
Scrophularia ningpoensis	Root	Scrophulariae radix	Xuan shen	Iridoid glycosides (harpagoside, harpagide), phenylpropanoid glycosides(angoroside C, acteoside)	DNA adducts repair, ORAC	[10, 160]	
Scutellaria baicalensis	Root	Scutellariae radix	Huang qin	Bicalein, baicalin, wogonin, wogonoside, scutellarein	Many *in vitro* and *in vivo* assays	[75, 78]	
Scutellaria barbata	Herb	Scutellariae herba	Ban zhi lian	Wogonin, apigenin, luteolin, tetrahydroxyflavone	ORAC	[2, 75]	
Solidago virgaurea	Herb	Solidaginis herba	Liu zhi huang	Quercetin, caffeic acid, chlorogenic acid, saponin, triterpenoid glycosides of polygalacic acid	DPPH	[161]	
Sophora flavescens	Root	Sophorae flavescentis radix	Ku shen	Prenylated chalcones (kuraridin, kuraridinol), prenylated flavonol (kushenol C), prenylated flavanones(sophoraflavanone G, kurarinone)	DPPH, ABTS, peroxynitrite and total ROS assays	[28]	

(Table 1). contd….

Plant Species	Part Used	Drug Name - Latin	Drug Name – Chinese Transcription	Antioxidant Constituents	Antioxidant Testing Methods	Reference	Cat. No.
Viola yedoensis	Herb	Violae herba	Zi hua di ding	Flavonols	FRAP, TEAC	[1]	
Magnolia officinalis, M. obovata, M. hypoleuca.	Bark	Magnoliae cortex	Hou po	Lignans (obovatol, honokiol, magnolol etc)	ROS generation in cell lysate, DPPH,	[50]	VI
Pogostemon cablin	Herb	Agastachis herba	Huo xiang	Essential oils	DPPH, lipid peroxidation, carotene bleaching	[162]	
Artemisia capillaris/A. scoparia	Herb	Artemisiae scopariae herba	Yin chen hao	Cappilarisin, esculetin,	Various assays	[146]	VII
Polygonum aviculare	Herb	Polygoni avicularis herba	Bian xu	Avicularin, taxifolin, quercetin, kaempferol, luteolin, isorhamnetin, rhamnetin	Many *in vitro* tests	[163]	
Morus alba		Mori ramulus	Sang zhi	Flavonols (kaempferol and quercetin glycosides)	ORAC	[164, 165]	VIII
Photinia serrulata	Leaf	Photiniae folium	Shi nan (ye)	Essential oils (10-epi-γ-eudesmol, pinene, sabinene, α-humulene, α-thujene)	DPPH	[166]	
Trypterygium wilfordii	Root	Tripterygii radix	Lei gong teng	Phenolic terpenes (triptophenolide)	TEAC, FRAP	[167]	
Xanthium sibiricum	Fruit	Xanthii fructus	Cang er zi	β-sitostenone, β-sitosterol, scopoletin	TEAC	[2]	

*Chinese Materia Medica functional categories [16,17]: I-herbs that release the exterior: warming and cooling acrid herbs; III-herbs that purge and drain; IV-herbs that cool heat; VI-aromatic herbs that transform dampness; VII-herbs that drain and transform dampness; VIII-herbs that dispel wind dampness; IX-herbs that warm the interior and expel cold; X – spirit calming herbs; XI – Qi regulating herbs; XII-herbs that regulate the blood; XIII-herbs that transform phlegm and stop coughing; XIV-herbs that promote digestion; XV-tonifying herbs; XVI-herbs that stabilize and bind; XVII-herbs that expel parasites…

It also has to be borne in mind, that in a routine TCM practice, single herbs are rarely prescribed. Usually, a mix of several herbs is composed for the patient or a compound patent medicine is prescribed. The multi-component CHMs are more complicated to study and interpret, but some of them have been investigated, also for antioxidant properties. The composite formulations will not be fully covered in detail by the present review. Nevertheless, most of them contain plants that will be mentioned as individual herbs. A few examples of such preparations are cited below.

Dan zhi xiao yao wan, consisting of: Moutan (Paeoniae suffruticosae) cortex, Paeoniae radix, Gardeniae fructus, Menthae haplocalycis herba, Bupleuri radix, Atractylodis macrocephalae rhizoma, Glycyrrhizae radix, Angelicae sinensis radix, Poria cocos, Zingiberis rhizoma) was studied as the whole formulation and individual herbs [11]. The order of anti-ROS activity by ORAC test of the single herbs was: Mentha haplocalyx > Glycyrrhiza uralensis > Gardenia jasminoides > Paeonia suffruticosa and the authors suggest rather additive contribution than synergistic effect of each component.

A synergistic effect between the constituents was in turn suggested for Sheng mai san [12], a cardiac tonic and Qi enhancer comprised of *Panax ginseng, Ophiopogon japonicus* and *Schisandra chinensis*. The complete formula had higher *in vitro* anti-radical and *in vivo* antioxidant enzyme expression-inducing activity than was predicted from simple sum of the three herbs.

In Qi zhu tang, the formula of *Astragali radix* (Huang qi), *Atractylodis macrocephalae rhizoma* (Bai zhu), *Notoginseng radix* (San qi) and Poria (Fu ling), some incomplete combinations were highly active *in vitro*, but only a complete formula was fully active both *in vitro* and *in vivo*. Interestingly, the individually pro-oxidant Poria, when added to the remaining herbs enhanced the total antioxidant potency of the drug [13].

A variety of phytochemical and pharmacological approaches are used for extraction, isolation and antioxidant activity evaluation in Chinese medicinal plants and have been recently reviewed by Li *et al.* [1].

Therefore, in this review, we will focus on the major phytochemical classes such as various polyphenols or terpenoids, providing well documented examples of their activity and occurrence in CHM. Selected examples of plant species and crude drugs exhibiting antioxidant properties in various assay methods were listed in (Tables **1** and **2**), as a result of comprehensive literature survey using NHL Pub Med, Elsevier Scopus, ISI Web of Science and CAS SciFinder databases with following search terms: "antioxidant", "Chinese medicine", "plant".

Typical structures representing compounds from the major phytochemical classes are shown in Fig. (**2**). through 10.

POLYPHENOLS

Their versatile but usually rather mild activities suit well to the principles of TCM in terms of limited side effects, flexible dosage, and the modulating effect rather than strong influence on physiological processes. The importance of plant polyphenols as antioxidants, their distribution and diversity has been reviewed in numerous publications (e.g.[4, 14]).

Simple Phenolic Acids, Depsides, Phenol Glycosides and Coumarins

This versatile category embraces small polyphenolic molecules derived from hydroxybenzoic or hydroxycinnamic acids as well as their glycosides and oligomers.

Hydroxyphenolic acids often occur in conjugated forms, such as gallotannins (gallic acid oligomeric glycosides), depsides (such as caffeic acid oligomers) or curcuminoids.

Oligomeric caffeic acids have superior antioxidant power due to the numerous hydroxyl groups substituting the aromatic rings. A dimer - rosmarinic acid determines antioxidant activity in CHMs from Lamiaceae (e.g. *Lycopus lucidus* – Ze lan) and Boraginaceae (*Lithospermum erythrorhizon* - Zi cao gen). Higher oligomers such as tri- and tetrameric lithospermic and salvianolic acids Fig. (**2**) are the main antioxidants in Dan shen (*Salviae miltiorrhizae radix*) and

Table 2. Selected Examples of Traditional Chinese Herbs with Significant Antioxidant Potential Confirmed in Experimental Studies Grouped in Categories (Last Column) According to Chinese Materia Medica Classification*. Categories IX to XVII

Plant Species	Part Used	Drug Name - Latin	Drug Name – Chinese Transcription	Antioxidant Constituents	Antioxidant Testing Methods	Reference	Cat. No.
Alpinia officinarum	Rhizome	Alpiniae officinari rhizoma	Gao liang jiang	Tannins, flavonoids, phenylpropanoids,	TEAC	[2]	IX
Cinnamomum cassia	Bark	Cassiae cortex	Gui zhi	Tannins	TEAC, FRAP	[1, 2]	
Zingiber officinale	Rhizoma	Zingiberis rhizoma recens	Sheng jiang	Gallic acid, cinnamic acid	*In vitro* on human breast carcinoma cells	[168]	
Albizia chinensis	Flower	Albiziae flos	He huan hua	Quercitrin	DPPH/Trolox	[169]	X
Citrus aurantia	Fruit,	Aurantii fructus, fructus immaturus	Zhi ke, Zhi shi	Flavanones (naringenin, naringin, hesperidin)	TEAC	[2]	XI
Rosa chinensis, R. rugosa	Flower (bud)	Rosae flos	Mei gui hua	Flavonols, tannins, anthocyanins		[170]	
Acacia catechu	Catechu	Catechu	Er cha	Tannins	Various antioxidant assays	[171]	XII
Agrimonia pilosa	Herb	Agrimoniae pilosae herba	Xian he cao	Quercetin, hyperoside, quercitrin, taxifoliol, luteolin glycosides, rutin, tannins,	DPPH, ABTS, lipid peroxidation	[172]	
Artemisia argyi	Leaf	Artemisiae argyi folium	Ai ye	Jaceosidin, polysaccharides,	Chemiluminescence, pyrogallol method, different *in vitro* tests	[173, 174]	
Carthamus tinctorius	Flower	Carthami flos	Hong hua	Chalcones (carthamin), gallic acid	DPPH, chelating power and lipid peroxidation	[175]	
Crocus sativus		Croci sigma	Fang hong hua	Carotenoids (crocin, crocetin)	DPPH	[62]	
Curcuma longa	Rhizoma	Curcumae longa rhizoma	Jiang huang	Curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin)	Various *in vitro* and *in vivo* assays	[20, 19]	
Lycopus lucidus	Herb	Lycopi lucidi herba	Ze lan	Rosmarinic acid, luteolin glucuronides	DPPH, nitric oxide scavenging, reducing power	[25]	
Panax notoginseng	Root	Notoginseng radix	San qi	Saponins (ginsenoside, notoginsenoside)	Many *in vitro* and *in vivo* tests	[58, 176, 177]	
Reynoutria japonica	Rhizome	Polygoni cuspidati rhizoma	Hu zhang	Stilbenes (polydatin, resveratrol), tannins, flavanols (epicatechin)	Many *in vitro* and *in vivo* tests	[123, 128]	
Rubia cordifolia	Root	Rubiae radix	Qian cao gen	Hydroxyanthraquinones, gallic acid, tannins	Many *in vitro* and *in vivo* tests	[178, 179]	
Sanguisorba officinalis	Root	Sanguisorbae radix	Di yu	Tannins, flavanols, gallic acid	Many *in vitro* and *in vivo* assays, ORAC	[10, 180]	
Salvia miltiorrhiza (S. przewalskii, S. trijuga, S. yunnanensis).	Root	Salviae miltiorrhizae radix	Dan shen	Phenolic acids (danshensu oligomeric rosmarinic, lithospermic, and salvianolic acids), tanshinones	Many *in vitro* and *in vivo* assays	[13, 101, 104, 113, 181]	
Sophora japonica	Fructus	Sophorae fructus	Huai jiao	Genistein and its glycosides, sophoricoside and its glycosides, rutin and gallic acid-glucopyranoside	DPPH, ORAC	[182]	
Spatholobus suberectus	Steam and root	Spatholobi caulis et radix	Ji xue teng	Epicatechin,	Several hydrogen peroxide luminescent assays, Protection against oxidative damage *in vitro* on PC12 cells	[183]	

(Table 1) contd….

Plant Species	Part Used	Drug Name - Latin	Drug Name – Chinese Transcription	Antioxidant Constituents	Antioxidant Testing Methods	Reference	Cat. No.
Verbena officinalis	Herb	Verbenae herba	Ma bian cao	Iridoids (hastatoside, verbenalin, aucubin), verbascoside, verbenalin, phenylpropanoids, flavonoids, luteolin, terpenoids	DPPH, ABTS	[184]	
Platycodon grandiflorum	Root	Platycodonis radix	Jie geng	Triterpenoid saponins	Lipid peroxidation, DHHP, ABTS, FRAP	[56, 185]	XIII
Crataegus pinnatifida	Fruit	Crataegi fructus	Shan zha	Flavonoid(vitexin-4''-O-glucoside, rutin, quercetin), tannin, gallic acid, 4-aminobenzoic acid	TEAC, FRAP	[1, 2]	XIV
Astragalus mongholicus/ (A. membranaceus)	Root	Astragali radix / Astragali mongholici radix	Huang qi	Isoflavonoids, triterpene glycosides, polysaccharides	DPPH, ABTS, FRAC, TOSC	[186]	XV
Cistanche deserticola	Herb	Cistanchis herba	Rou cong rong	Phenylethanoids	Free radical scavenging	[18]	
Codonopsis pilosula	Root	Codonopsis radix	Dang shen	Steroid glycosides, polysaccharides	Lipid peroxidation	[58]	
Drynaria fortunei	Rhizoma	Drynariae rhizoma	Gu sui bu	Flavan-3-ol and its glucosides, epicatechin, naringin	Several luminescence assays, Protection against oxidative damage *in vitro* on PC12 cells	[183]	
Epimedium brevicornu Epimedium sp.	Herb	Epimedii herba	Yin yang huo	Prenylflavonols (icariin, epimedin A, B)	Various assays	[26]	
Glycyrrhiza uralensis	Root	Glycyrrhizae radix	Gan cao	Flavanones, chalcones, isoflavones	DPPH, TEAC, FRAP, ORAC	[1, 2, 11, 70]	
Paeonia lactiflora	Root	Paeoniae lactiflorae radix	Bai shao	Paeoniflorin	*In vitro* tests on HUVECs endothelial cells, ORAC	[187]	
Psoralea corylifolia	Fruit	Psoraleae fructus	Bu gu zhi	Psoralen, isopsoralen, psoralidin, corylifol A, isoflavones (genistein, daidzein, prenyldaidzein)	Many *in vitro* assays	[188, 189]	
Cornus officinalis	Fruit	Corni fructus	Shan zhu yu	Iridoid glycoside (morroniside, loganin), cornusiin A, B, C, hydrolysable tannins	TEAC, FRAP	[1, 2]	XVI
Prunus mume	Fruit	Mume fructus	Wu mei	Chlorogenic acid	DPPH, ABTS, lipid peroxidation	[190]	
Rhus chinensis	Nut galls	Galla chinensis	Wu bei zi	Tannic acid	Various *in vitro* tests	[191]	
Rosa laevigata	Fruit	Rosae laevigatae fructus	Jin ying zi	Gallic acid, isostrictinin, catechin, ellagic acid	DPPH, hydroxyl radical and superoxide radical scavenging, ORAC	[192]	
Rubus chingii	Fructus	Rubi fructus	Fu pen zi	Vanillic acid, kaempferol, tiliroside	DPPH	[193]	
Terminalia chebula.	Myrobalan	Chebulae fructus	He zi	Saponins (ivorenosides A, B, C), tannins	DPPH, ABTS	[2, 194]	
Areca catechu	Seed, pericarp	Arecae pericarpium, Arecae semen	Da fu pi, Bing lang	Tannins, catechins	DPPH, TEAC, ABTS	[2]	XVII
Quisqualis indica	Fruit	Quisqualis fructus	Shi jun zi	Various polyphenols	Free radical scavenging activity	[195]	

*Chinese Materia Medica categories [16, 17]: I-herbs that release the exterior: warming and cooling acrid herbs; III-herbs that purge and drain; IV-herbs that cool heat; VI -aromatic herbs that transform dampness; VII-herbs that drain and transform dampness; VIII-herbs that dispel wind dampness; IX-herbs that warm the interior and expel cold; X – spirit calming herbs; XI – Qi regulating herbs; XII-herbs that regulate the blood; XIII-herbs that transform phlegm and stop coughing; XIV-herbs that promote digestion; XV-tonifying herbs; XVI-herbs that stabilize and bind; XVII-herbs that expel parasites.

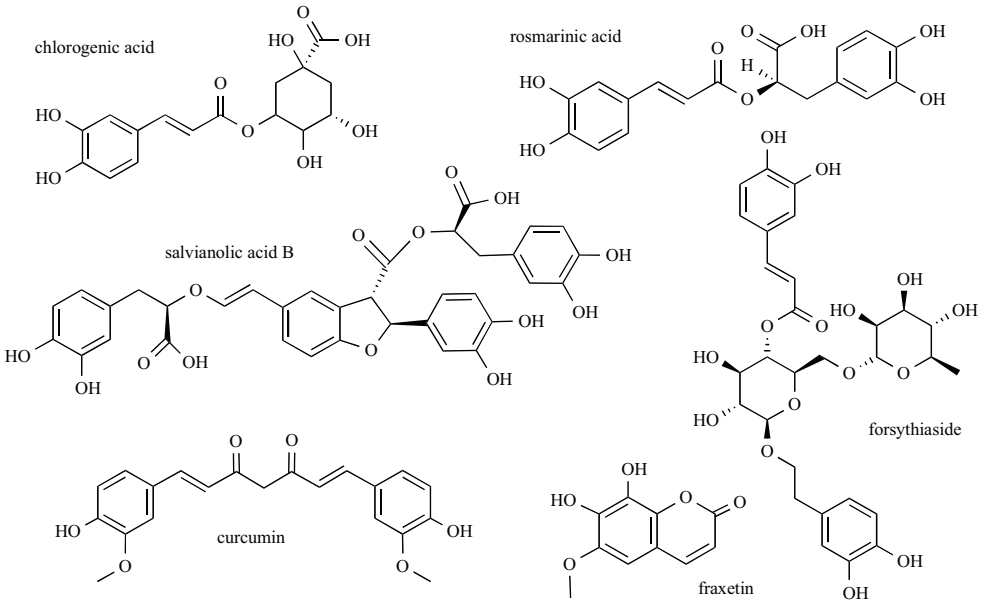

Fig. (2). Examples of structures of antioxidant phenolic compounds, derivatives of hydroxycinnamic acids: depsides, coumarin, curcuminoid, and phenylpropanoid glycoside.

their activity was confirmed by several studies using *in vitro* and *in vivo* approach, that have been reviewed recently by Wang [15]. These compounds have been also found in *Menthae haplocalycis herba* (Bo he) and their DPPH scavenging determined [16] showing the highest activity of lithospermic acid B and its salts, that reduced 50% of the free radical at concentrations below 20 μM.

Chlorogenic acid and related caffeoylquinic depsides were also main antioxidants in *Lonicerae flos* [17] as revealed by coupling HPLC chromatographic separation with post-column online estimation of DPPH scavenging. The EC_{50} were below 5 μg/ml for two dicaffeoylquinic acid isomers, while for chlorogenic acid – the predominant polyphenol the value was 7.76 μg/ml.

Coumarins are a common group of cyclic phenylpropanoid (*ortho*-coumaric acid) derivatives of specific structure. Hydroxylation of the coumarin skeleton is a prerequisite for antioxidant activity, like in esculetin (6,7 dihydroxycoumarin) and fraxetin (7,8 dihydroxy-6-methoxycoumarin, Fig. **2**) present along other coumarins in *Fraxinus rhynchophylla* bark (Qin pi). Esculin - the 6-glucoside of esculetin was over one order of magnitude weaker in ORAC test than the aglycone [3] because of blocking of one hydroxyl group by glycosylation.

Antioxidant phenylethanoid glycosides are contained for example in following CHM:

forsythiaside Fig. (**2**) in *Forsythiae fructus* (Lian qiao), acteoside and echinacoside in *Buddlejae flos* (Mi meng hua), acteoside, tubuloside B etc. in *Cistanchis herba* (Rou cong rong) [18], salidroside in *Rhodiolae rhizoma* (Hong jing tian) [1].

Curcuminoids

These dimeric ferulic acid derivatives Fig. (**2**) are found in the rhizomes of several medicinal plants from the genus Curcuma. In TCM, the well-known spice turmeric (*Curcuma longa*) is used under the name Jiang huang (*Curcumae longae rhizoma*) and other species like *C. phaeocaulis, C. zedoaria,* and *C. kwangsiensis* as E zhu. Both herbs are under the category "blood invigorating and stasis removing" and have bitter/pungent and warm character and are related to liver and spleen [5, 6]. Another TCM herb is obtained from the root tubers of various Curcuma species, known as *Curcumae radix* – Yu jin. Its formal taste is bitter and pungent, but contrary to the rhizomes, the temperature is cold.

Apart from the non-volatile polyphenolic curcuminoids, various turmeric species contain essential oils rich in pungent sesquiterpenes, similarly to all Zingiberaceae. The main constituent of turmeric is curcumin – diferuloylmethane, a lipophilic yellow substance that is also the main bioactive compound. The antioxidant activity of curcuminoids is determined by their polyphenolic character and has been studied both *in vitro* and *in vivo* and several review papers have been also published, recently [19, 20].

However, their low bioavailability is the main obstacle *in vivo*, that can be overcome by using nanotechnology (e.g. nanosomes, emulsions) [21]. Also, curcuminoids in some experimental conditions, such as presence of transition metal (Cu or Fe) ions may show pro-oxidant effects in oxygen radical reactions [22].

Flavonoids

It is the most common group of polyphenolic plants compounds, which are responsible for color pigmentation. In contrast to the group name, flavonoids are not just pigments and not always yellow. Their physiological function in plants and their pharmacological properties are diverse. Flavonoids frequently contribute to the therapeutic properties of medicinal herbs, as well as to the beneficial properties of foodstuffs. As ubiquitous components of plant tissues they are also important active principles of many Chinese herbal medicines. Flavonoids can constitute a considerable fraction of some CHM, such as Huang qin (*Scutellariae baicalensis radix*) which is described in detail in a separate section of this review. Flavonoids occur in plant cells mainly as glycosides that are more water-soluble than corresponding aglycons. Hence, flavonoid glycosides are more likely to be extracted in decoctions – the typical form of using TCM herbs. Some of the flavonoid classes such as flavonols and flavones are universally present in leaves and flowers, while others are present in variable amounts also in other plant organs – fruits, roots, wood, bark or seeds. In addition to the differences in the core structure of major classes of flavonoids: chalcones, flavones, flavonols, flavanones, anthocyanins, and isoflavonoids, there is great diversity of substitution patterns of the aromatic rings A and B Figs. (**3**-**6**). The typical substitution is hydroxy- and methoxy- group, but other modification such as prenylation or acylation can be found. Also, most of the aglycons can be glycosylated by a number of carbohydrates – both monomeric and oligomeric sugars (hexoses and pentoses) and sugar acids (such as

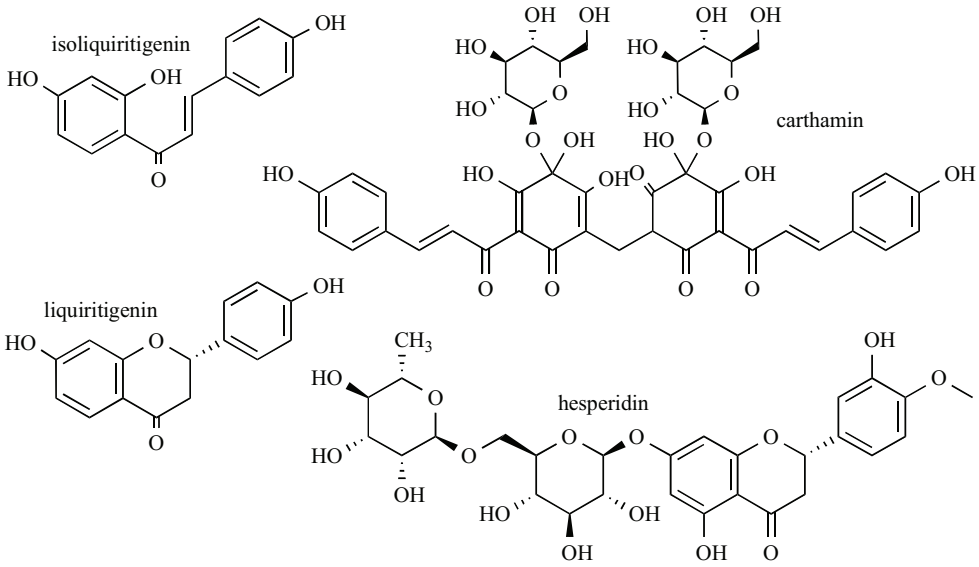

Fig. (3). Examples of structures of antioxidant flavanones and chalcones.

glucuronic acid in the important flavones from Huang qin – baicalin – Fig. **4** and wogonin). Similarly to other polyphenols, highly hydroxylated flavonoids have superior antioxidant activity [23].

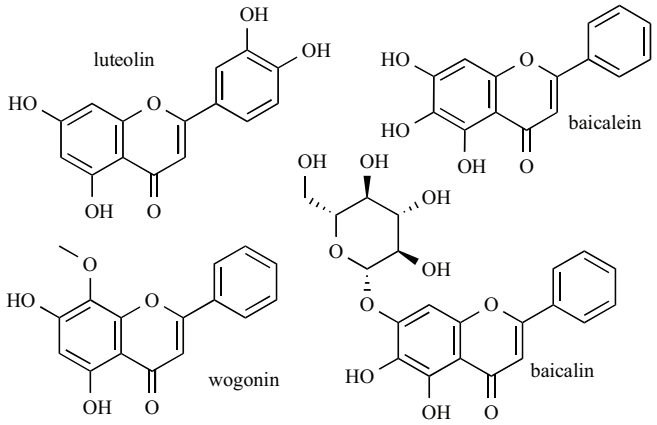

Fig. (4). Examples of structures of antioxidant flavones.

Chalcones have no heterocyclic ring. They are direct biosynthetic precursors of flavanones and are found together for example in *Glycyrrhizae uralensis radix* (Gan cao). The main chalcones in this herb are isoliquiritin and the aglycone isoliquiritigenin Fig. (**3**), while liquritin and liquiritigenin Fig. (**3**) are the respective flavanones. Another example of chalcone-containing Chinese herb is *Carthamus tinctorius* (*Carthami flos* – Hong hua) with a rare conjugated dichalcone – carthamin and several other chalcones [3]. Flavanones such as hesperidin Fig. (**3**), naringenin, naringin are major antioxidants in Citrus fruits and peel (called Zhi shi – *Aurantii fructus immaturus* – unripe bitter orange, Zhi ke – *Aurantii fructus* – ripe bitter orange, as well as Chen pi – *Citri reticulatae pericarpium*, Qing pi – *Citri reticulatae pericarpium viride* – mandarin peel ripe or green, respectively) [2].

Flavones, such as luteolin and its glycosides contribute to the antioxidant activity of *Lonicera japonica* (*flos* and *caulis*) [2, 3, 24] and *Lycopi lucidi herba* (Ze lan) [25] along with phenolic acid depsides (chlorogenic and rosmarinic, respectively). The free radical scavenging and transition metal reduction were tested with *in vitro* assays (DPPH, NO, hydroxyl radical and peroxynitrite scavenging, and phosphomolybdenum reduction). Free radical activity of *Lonicera japonica* extracts was ascribed to individual compounds by using on-line HPLC-DPPH biochromatography [17]. In this study, luteolin was the most active flavone (EC_{50} 5.78 μg/ml), while the glycosides were significantly weaker (EC_{50} above 7.5 μg/ml). Many other herbs also contain flavone glycosides and depending on the hydroxylation pattern and glycosylation, they typically have at least some antioxidant activity [2, 3].

Somehow unique are the flavones from the genus Scutellaria, most abundant in one of the principal CHMs – *Scutellaria baicalensis* (Huang qin). The unsubstituted B-ring and varied substitution of A-ring determine their relatively high lipophilicity and many pharmacological activities that are described in a separate section dedicated to this plant.

Flavonols are commonly found in aerial parts of land plants in form of a variety of glycosides, usually with quercetin, kaempferol or less frequently other structures, as aglycones. Their antioxidant properties are well established by numerous studies using *in vitro* chemical and cell-based assays, as well as *in vivo* studies. Chinese medicinal plants contain considerable amounts of flavonols that contribute to their antioxidant properties, for example: *Mori folium* (Sang ye) [2], *Sophorae flos* (Huai hua) [3], *Polygoni avicularis herba* (Bian xu) [2].

The prenylated flavonoids that have been studied for antioxidant properties are present in *Epimedii herba* (pinyin: Yin yang huo, the aerial parts from *Epimedium brevicornu, E. koreanum, E. pubescens, E. wushanense*, and other species), the drug used for treating sexual dysfunctions. They include icariin Fig. (**5**), epimedin A, B, C etc., brevicornin, breviflavones A and B and others. Chemically, they are 8-C-prenyl-4'-methoxyflavonols, O-glycosylated in positions 3 and/or 7. The sugars involved are usually: rhamnose, xylose, glucose [26].

Antioxidant properties of Epimedium prenylflavonols were demonstrated in direct *in vitro* chemical tests such as free radical scavenging (against DPPH, hydroxyl radical and superoxide radical anion), as well as in protecting liver microsomes and mitochondria from Fenton-reaction induced oxidative damage. Icariin protected cultured neuronal cells from hydrogen peroxide induced toxicity via inhibition of lactate dehydrogenase leakage, GSH depletion and DNA damage that would result in cell death. This neuroprotective effect, based on the inhibition of caspase-3 and p53 has been postulated to act through inhibiting of JNK/p38MAPK phosphorylation [26, 27]. Prenylated flavonoids are also present in *Sophorae flaven-*

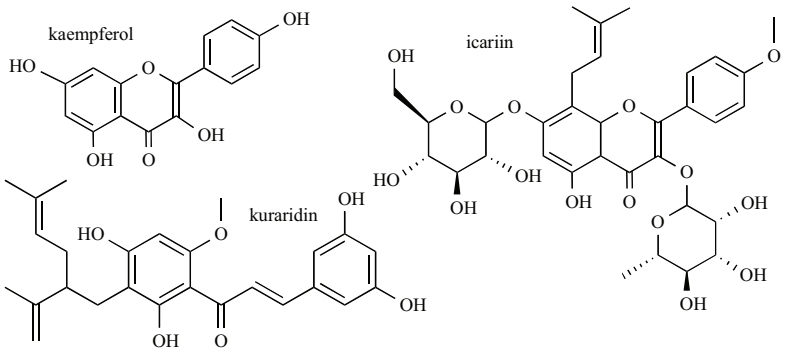

Fig. (5). Examples of structures of antioxidant flavonols, prenylflavonols and prenylchalcones.

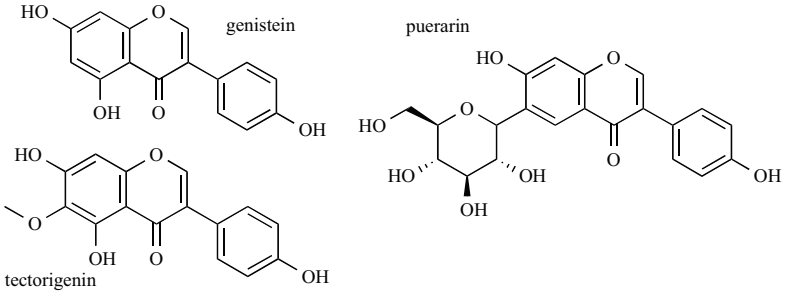

Fig. (6). Examples of structures of antioxidant isoflavonoids.

scentis radix (Ku shen) and their antioxidant activity confirmed by several *in vitro* assays (DPPH and ABTS free radical scavenging, peroxynitrite scavenging, and intracellular ROS generation induced by tert-butyl hydroperoxide). In Ku shen, the prenylated chalcones (kuraridin and kuraridinol), along with a minor prenylated flavonol, kushenol C (EC_{50} - 10.67, 14.08, 0.62, and 3.17 μg/ml in DPPH, ABTS, peroxynitrite, and total ROS scavenging assays, respectively) were the most active antioxidants, while the contribution of prenylated flavanones: sophoraflavanone G, kurarinone, kushenol E, leachianone G, kurarinol, sophoraflavanone G, and kurarinone to the total antioxidant properties of the tested extracts was lower [28].

Isoflavonoids

Isoflavonoids differ in their basic skeleton to all other flavonoids because the phenyl ring 'B' is connected with carbon atom number 3 of the benzopyran part of the molecule. During biosynthesis, the B-ring is moved from the C2 position in a series of reactions catalyzed by isoflavone synthase enzymatic complex. Isoflavonoids have been detected in several botanical families, but occur in larger quantities in Fabaceae and Iridaceae [29]. The first family is represented in the TCM by such important plants as soybean (*Glycine max*) that besides being used as staple food, provides the drugs - Da dou juan (young sprouts), dan dou chi (*Sojae semen praeparatum*), and kudzu vine - *Pueraria lobata* and *P. thunbergiana*.

Genistein - 5,7,4'-trihydroxyisoflavone Fig. (**6**) is one of the major dietary isoflavones, which has been intensively studied *in vitro* and *in vivo*, including clinical trials. As a result, a vast literature exist on this compound and other soybean isoflavonoids including hundreds of review papers (e.g. [30]). Antioxidant activity is only one of the numerous properties of the soybean isoflavones, so we will omit the detailed description of them.

Other example of Chinese traditional herbs from Fabaceae - the root of *P. lobata – Puerariae radix* known as Ge gen contains puerarin – a C-glucoside, and several other isoflavones. The *in vivo* antioxidant activity of Ge gen standardized extract containing puerarin was assessed by Bebrevska *et al.* [31] in streptozotocin-induced diabetic rats. The extract administered orally at the daily dose corresponding to 50 mg/kg of puerarin decreased the lipid peroxidation markers down to the negative control levels.

Pretreatment by puerarin at 10, 50 or 100 μM, protected pancreatic islets from oxidative injury by hydrogen peroxide, decreased intracellular ROS and dose-dependently stimulated activity of CAT (by more than 50%) and SOD (more than three-fold at 100μM) in the islet cells [32]. Among several isoflavonoids present in *Puerariae radix*, puerarin contributes most to the anti-radical activity of the drug, being the only compound that showed positive correlation with antioxidant potential of *Pueraria sp.* extracts tested by DPPH assay [33]. On the other hand, in the chemiluminescence assay, the crude extract exhibited more typical antioxidant activity than pure puerarin [34]. *Puerariae flos* – the flowers of *P. thunbergiana* or *P. lobata* (Ge hua) contain tectorigenin – a methoxylated isoflavone that has higher lipophilicity than genistein or puerarin, while it is still a potent antioxidant, able to inhibit lipid peroxidation caused by bromobenzene in rats by almost 60% at the dose of 10 mg/kg body weight [35].

Tectorigenin Fig. (**6**) is a typical example of the Iridaceae-type isoflavone that are usually highly hydroxylated and methoxylated. One of the most important herbs containing these compounds is *Belamcandae rhizoma* She gan – a rhizome from *Iris domestica*, previously known as *Belamcanda chinensis*). The major compounds are the isoflavone glycosides – tectoridin, iridin, iristectorin A, B, and their respective aglycones. The extracts and isoflavonoids from She gan can efficiently scavenge free radicals (in DPPH assay the lowest EC_{50} was 12.9 μg/ml for isoflavonoid aglycone fraction), reduce transition metals more efficiently than ascorbic acid, and inhibit lipid peroxidation by about 90% (both aglycone and glycoside fractions) [36]. Tectorigenin from *Belamcandae rhizoma* protected cultured hippocampal cells from oxidative injury induced by glutamate with EC50 of 62.25 μM [37]. Other antioxidant compounds isolated from this plant include stilbenes and xanthones, and are mentioned in the respective sections of this paper.

Tannins

Tannins are usually powerful antioxidants and free radical scavengers. This activity is due to a very high number of hydroxyl

groups substituting aromatic rings. Tannins are complex molecules built of polyphenolic units connected via estrification or condensation (to give C-C bonds). Their molecular mass is usually between 500-3000 Da. There are two major classes of tannins, differing in their chemical structures and properties. Typically, all tannins are defined by their ability to bind and precipitate proteins as a result of permanent cross linking with some protein aminoacids. Hydrolysable tannins are oligomeric hydroxybenzoic acids glycosides that can be hydrolyzed to the free polyphenolic units and sugars in acidic and alkaline solutions. The phenolic parts are build of gallic acid – gallotannins Fig. (**7**) or hexahydroxydiphenic acid (a depsidic form of gallic acid connected via C-C bond, that upon hydrolysis gives rise to a lactone form ellagic acid) - ellagitannins. Condensed tannins, a class closely related to flavonoids, are built of flavan-3-ol units such as catechin or epicatechin, or their derivatives Fig. (**7**). Condensed tannins also called oligomeric proanthocyanidins, are resistant to standard hydrolysis and count to the nature's strongest antioxidants. Mixed forms are also present in plants.

Both groups, being highly polar, are soluble in water, hence their presence in infusions and decoctions from herbs that contain them. Pharmacologically, one of the most pronounced properties of tannins is their astringency. Consequently, they exhibit anti-inflam matory, wound healing, antihaemorrhagic, antidiarrheal, and antimicrobial properties. Tannin-rich herbs are important in every traditional and folk medicine as well as in modern phytotherapy, and are included in all Pharmacopoeias. In the TCM, several herbs contain high levels of tannins that determine their activity [5, 6]. For example in the stop-bleeding category there are: Di yu – *Sanguisorbae radix*, Xian he cao – *Agrimoniae pilosae herba*, and in the "astringent herbs": Wu bei zi - *Galla chinensis* (*Rhus chinensis*), Shi liu pi - *Granati pericarpium*, He zi - *Chebulae fructus*. Two herbs from Polygonaceae – *Rhei rhizoma et radix* and *Polygoni cuspidati rhizoma* are also rich in a variety of tannins, accompanied by anthraquinones. This combination provides them with dual properties depending on the specific indication. For example Da huang can act as laxative (from anthraquinones) or antidiarrheal (from tannins). Among many CHMs screened for antioxidant activity, the tannin-rich herbs are usually the strongest. In the studies of Cai *et al.* [2] and Li [1], following herbs had high ABTS radical scavenging (with TEAC values from 2 to 17.6 mmol Trolox equivalents per 100g dw) and ferric reducing capacity: Er cha (*Acacia catechu*), Qin pi (*Fraxini cortex*), Wu bei zi (*Rhus chinensis*), He zi (*Chebulae fructus*), Shi liu pi (*Granati pericarpium*), Di yu (*Sanguisorbae radix*), and tea leaves (also rich in flavan-3-ols and other tannins).

Stilbenes

Basic structure of stilbene molecule consists of two aromatic rings connected with two-carbon unit. Their formation during biosynthesis by stilbene synthase is analogous to flavonoids but an additional decarboxylation takes place while folding the second ring attached to the phenylpropanoid backbone (e.g. *p*-coumaroyl moiety). As a result, a most widespread trihydroxystilbene is formed, known as resveratrol. The native *trans*-resveratrol gets reversibly isomerized to *cis*-form upon illumination. *Trans*-resveratrol is considered the actual bioactive form. Further modifications of hydroxylated stilbenes include additional hydroxy groups, their methylation, glycosylation, and dimerization. Hydroxystilbenes are typically abundant in Polygonaceae, but occur in many other taxa. *Polygoni cuspidati rhizoma* (Hu zhang) – the rhizomes of Japanese knotweed – *Reynoutria japonica* is believed to be the world's most abundant source of resveratrol and its glycoside – polydatin (*trans*-piceid, Fig. **8**). This remarkable plant will be described in more detail below. Resveratrol has a worldwide reputation as one of the most beneficial polyphenols possessing multiple therapeutic and preventive values, for example rejuvenating (acting through the ones very promising sirtuin function), antineoplastic, antiatherogenic, antihypertensive, and anti-inflammatory and many more. During the last decades, it has become one of the most (if not the first one) studied natural products with thousands of publications documenting miscellaneous activities. It has been also frequently reviewed from different viewpoints [38-41]. Its antioxidant activity, disregarding the origin from grapes (or wine), peanut skin, or Hu zhang, has been reported repeatedly both *in vitro* and *in vivo* [42, 43].

Other stilbenes, including polydatin have been also frequently studied, albeit less extensively [42]. In other CHMs, stilbenes are found in *Polygoni multiflori radix* (He shou wu) and the strongest free radical scavenging compound in DPPH assay was 2,3,5,4'-tetrahydroxystilbene with EC_{50} of 0.38 μM [44]. Stilbenes are also present in Da huang (*Rhei rhizoma*) – but in larger amount only in other than *Rheum officinale* or *R. palmatum* unofficial species that are sometimes found as adulterants [45]. Therefore, their contribution to the antioxidant activity of Da huang is insignificant.

On the other hand, some stilbenes – resveratrol, a dimer shegansu B, and isorhapontigenin are contributing to the antioxidant properties of an unrelated herb - She gan (*Belamcandae rhizoma*, from a monocot *Iris domestica*). Isorhapontigenin at concentrations below 100 μM can almost completely protect complex lipid molecules such as LDL as well as DNA from oxidative damage. The protective effect was studied in hepatic microsomes, neuronal mitochondria and synaptosomes and was higher than exerted by a reference antioxidant – vitamin E [46, 47]. It has also inhibitory effect on superoxide (33.8% inhibition at 100μM) and hydrogen peroxide (56.8% inhibition) production by activated rat neutrophils. The ability of this compound to directly scavenge oxygen free radicals (superoxide and hydroxyl) was confirmed by electron spin resonance study [46].

Xanthones

Xanthones are present in several distantly related botanical families e.g. in dicots Anacardiaceae, Clusiaceae, Gentianaceae, Polygalaceae, and monocots Asparagaceae, Iridaceae. Biosynthetically, they originate from general phenylpropanoid pathway, but the xanthone backbone formation is distinct from that of flavonoids or stilbenes and catalyzed by benzophenone synthase [48, 49]. One of the important herbs containing xanthone glycosides is *Belamcandae rhizoma* (She gan). The major compound from this group is mangiferin, 1,3,6,7-tetrahydroxyxanthone 7-C-glucoside Fig. (**8**). Mangiferin has been typically obtained from *Mangifera indica* – the mango tree, but is also mentioned as a bioactive marker of she-gan. The most of the published studies have used mangiferin from *M. indica*, though. In our studies, we have confirmed the free radical scavenging (by DPPH assay – EC_{50} = 7.0 μg/ml), transition metal reducing (in phosphomolybdenum assay), and oxidative mutagenesis inhibiting (56%inhibition) properties of mangiferin from She gan [50].

Lignans

Lignans are the group of plant polyphenols whose structure is determined by two β, β- linked cinnamic residues or their biogenetic equivalents. Further modifications, like oxysubstitution, with or without O-methylation yield more or less complex structures. Lignans are characteristic compounds for several CHMs, for example *Arctii fructus* (arctigenin, secoisolariciresinol), *Schisandrae fructus* (schisandrin A, B, etc), *Magnoliae cortex* (honokiol, magnolol, obovatol). The free radical scavenging activity of these compounds, tested *in vitro* was moderate [2, 3]. For example, in the DPPH assay, the lignans from magnolia bark had an EC_{50} value between 21.6 to 38.5 μg/ml [51].

Some constituents from this group are quite well absorbed after oral administration. According to Chen *et al.* [52] schisandrin A,

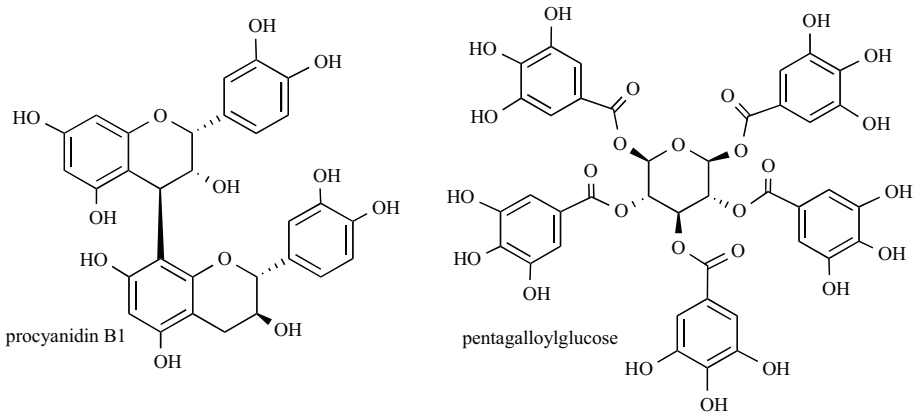

Fig. (7). Examples of structures of antioxidant tannins.

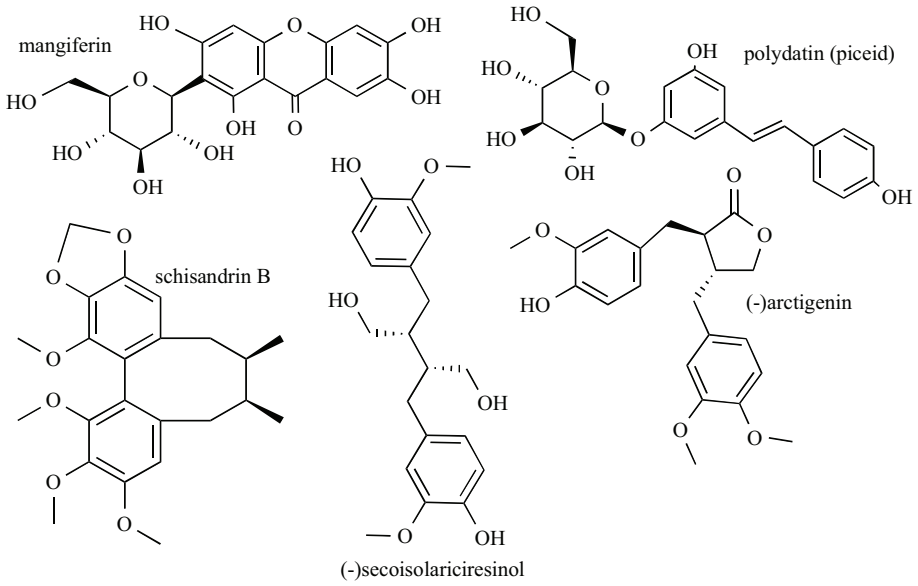

Fig. (8). Examples of structures of other antioxidant polyphenols: xanthone, stilbene, and lignans.

schisandrin B and schisandrol A are absorbed especially in duodenum but also in other segments of intestine and are detected in plasma 30 minutes after oral administration. That may be the reason why in comparative study of curcumin and schisandrin B against oxidant-induced cyto/hepato-injury caused by CCl_4, a better protection by schisandrin B was the case *in vivo* while *in vitro* curcumin was more active. The protective ability of schisandrin B is claimed to be associated with enhancing glutathione antioxidant response to low concentration of ROS, arising from CYP-catalyzed metabolism of schisandrin B [53]. Fruits of *Schisandra chinensis* have higher antioxidant capacity compared to pure schisandrin B suggesting additive role of active constituents and theirs mechanisms of action [54].

A few antioxidant lignans (forsythialan A and B) were also isolated as minor compounds from *Forsythia suspensa*, and tested for protection from peroxynitrite-induced oxidative stress in LLC-PK1 cells (porcine kidney cell line) measured by LDH leakage and cell viability. Forsythialan A at 50 μM was able to decrease both parameters almost to a control level [55].

ANTHRAQUINONES

Anthraquinones occur in several herbs from Polygonaceae – for example in *Rhei rhizoma* (Da huang) used in the TCM for gastric problems, and in *Polygoni cuspidati rhizoma* (described in detail in another section). Anthraquinones serve as laxative principle due to their irritating action towards colon. *In vitro*, anthraquinones such as emodin Fig. (**9**), chrysophanol, physcion, rhein, and their glycosides exhibit free radical scavenging and antioxidant activity, but in the abovementioned herbs, it's rather the abundant tannins, flavan-3-ols and stilbenes that determine their antioxidant properties [2, 3].

TERPENOIDS

Di- and Triterpenoids

Di- and triterpenoids are rarely regarded as potent antioxidants. However, some distinct compounds from these groups display antioxidant properties comparable to that of polyphenols. Even though, their activity depends on the presence of analogous structural attributes such hydroxyl group close to the conjugated double bonds. Sometimes, the activity is attributed to such diterpenoids as in *Tripterygium wilfordii* roots (Lei gong teng) – which is a potent anti arthritic drug. In the study of Cai *et al.* [2], Lei gong teng was the 11th strongest of 112 tested herbs in TEAC assay, but the contribution of terpenoids (triptophenolide etc) to this score remains uncertain.

Another group of potentially antioxidant diterpenoids are tanshinones from *Salvia miltiorrhiza*, which will be described in detail in a separate section below. The presence of other highly antioxidant abietane diterpenoids, similar to that from rosemary or sage

(rosmanol, carnosol etc) is likely in CHM from Lamiaceae, but no reliable data are available to date, that would confirm this presumption.

On the other hand, various triterpenoids have been studied for antioxidant potential in such plant as: *Platycodon grandiflorus* (Jie geng), *Codonopsis pilosula* (Dang shen), *Panax ginseng* (Ren shen), or *Astragalus mongholicus* (Huang qi). The triterpenoid or steroid saponins from abovementioned herbs (various platycosides, codonosides, tangshenosides, ginsenosides Fig. (**9**), astragalosides and related compounds) and some others of similar composition, exhibit free radical scavenging activity, but also ability to protect polyunsaturated lipids from peroxidation as well as to ameliorate oxidative stress in cell cultures and *in vivo* [55-62]. Even though, phenolic fractions are also present in these plants and most likely, they influence the total antioxidant capacity significantly.

Carotenoids

The lipophilic molecules of carotenoids are based on general model consisting 40-carbon structure build from isoprenoid units, which include a chromophoric system of conjugated double bonds. These bright colored pigments are present in every photosynthesizing cell protecting the photosystems from photoinduced damage. Their ability to quench singlet oxygen is an important aspect of this protection and makes them useful as preventive pharmacologically active compounds. Most of carotenoids are lipophilic species, but hydrocarbon carotenes are less polar than oxidized xanthophylls. Several medicinal plants contain also uncommon oxidized carotenoid glycosides that are water soluble. Crocin Fig. (**9**) and the aglycone crocetin (a carboxycarotenoid) are the most obvious examples that occur in the famous spice and medicinal substance – *Croci stigma* – saffron. Saffron has been used in phytotherapy of many regions since antiquity and is also important in TCM under the name Fang hong hua. Saffron hydrophilic carotenoids, that are also present in *Gardeniae fructus* (Zhi zi) have been tested for antioxidant properties *in vitro* and *in vivo*. There are differences in activity between the aglycone crocetin and crocin in various test systems – crocetin was 6 times more active in lipid peroxidation inhibition, while glycosides were superior in phosphomolybdenum reduction assay, that is performed in aqueous environment and in DPPH scavenging [63]. *In vivo*, extracts from *Croci stigma* decreased the LDL-oxidation susceptibility by more than 30%, when given to patients with coronary artery disease in the amount of 100 mg/day [64]. Similar results in terms of ameliorating oxidative, hyperlipidemia-associated lesions in tissues by crocin and crocetin from saffron and *Gardenia jasminoides* have been performed on various animals such as rabbits, rats or quails [65, 66]. The antioxidant properties of crocin are therefore essential for their antiatherogenic activity. In indomethacin treated mice, the anti-ulcerogenic activity based on antioxidant properties and elevation of GSH levels was similar to omeprazol [65, 66].

Antioxidant carotenoids and their fatty acids esters are also found in Chinese wolfberry fruits (*Lycium barbarum* or *L. chinense*. - Gou qi zi, also known as Goji berries) [67]. Consumption of fruit extract improves significantly the antioxidant status of human serum – the SOD and GPx activities increased by 8.4 and 9.9%, respectively, while MDA (lipid peroxidation marker) levels decreased by 8.7% [68]. The extensive literature confirms antioxidant properties of Gou qi zi *in vitro* and *in vivo*, but whether carotenoids contributes to this activity was not established [69].

OTHER COMPOUNDS

Polysaccharides, present in every plant cell wall, are rarely considered as pharmacologically relevant antioxidants. Their activities relate more to the immune responses, inflammatory processes and diabetes [70]. Nonetheless, there are numerous examples of antioxidant studies of polysaccharide fractions from Chinese medicinal mushrooms (e.g. *Ganoderma lucidum* [71], *Cordyceps sp*. [72], *Poria cocos* [70], and such herbs as: *Plantago asiatica* (seeds) [73], *Dendrobium fimbriatum* [74], or even in the polyphenol rich herbs like *Gardenia jasminoides, Salvia miltiorrhiza, Astragalus mongholicus*, *Scutellaria baicalensis* and many more [70]. This function of polysaccharides can be of some relevance because of the traditional way of herb ingestion is decoction in which the water soluble glycans are present.

Protoberberine Alkaloids

Huang lian - *Coptidis rhizoma* (from *Coptis chinensis*, Ranunculaceae) contains several isoquinoline alkaloids such as berberine Fig. (**10**) and its derivatives. Antioxidant activity of berberine and related alkaloids was established and its role in neuroprotective properties in Alzheimer disease has been suggested [75, 76]. Berberrubine and coptisine had the highest scavenging activity towards hydroxyl radical generated in Fenton reaction, and monitored by ESR. Iron chelating properties and direct quenching by hydroxyl group in C-9 position were proposed as main mechanisms of this activity [75]. In the other study, *in vitro* peroxynitrite scavenging and inhibition of ROS generation in rat kidney mitochondria was demonstrated where groenlandicine and jateorrhizine Fig. (**10**) were highly potent in the first assay (EC_{50} below 1 μM) while groenlandicine and coptisine Fig. (**10**) were the most active alkaloids in the ROS test (IC_{50} about 50 μM) [76].

SELECTED TRADITIONAL CHINESE MEDICINAL PLANTS THAT HAVE STRONG ANTIOXIDANT PROPERTIES

Scutellaria baicalensis (Scutellariae baicalensis radix - Huang Qin)

Scutellaria baicalensis Georgi. (family Lamiaceae) grows naturally in East Asia – Eastern Siberia, Mongolia, China, Korea and Japan.

Typically for the Lamiaceae, it has zygomorphic, blue-purple flowers blooming abundantly, hence the ornamental value of this plant. Thick, yellow roots are used for phytotherapeutic purposes. The crude drug name is *Scutellariae baicalensis radix* (Chinese name Huang qin). Rarely, other species are substituted for *S. baicalensis* – i.e. *S. amoena* (Nan Huang qin), *S. rehderiana* (Gan su Huang qin), and *S. visidula* (Nian mao Huang qin). According to the formal characteristic it has very pronounced bitter taste and cold temperature. Its organ relationship is Lung, Gall bladder and Stomach and direction of activity sinking. In the TCM pharmacological classification it is placed as "heat clearing and dampness-drying" herbs. The TCM indications relate to inflammatory processes in respiratory tract, jaundice and hepatitis, abdominal pains, and several others in combination in different herbs. Interestingly, one of the specific TCM indications is fetus calming, the activity that might be reflected by the BDZ receptor affinity of wogonin [5, 6].

The plant belongs to the most important CHMs, and has been increasingly used also in Western countries. Recently, Huang qin monograph has been included in European Pharmacopoeia.

Chemical Composition

Lipophilic flavones with unsubstituted B-ring constitute the major fraction reaching 20% of the root dry mass. The main compound is baicalin, a 7-O-glucuronide of baicalein (5,6,7-trihydroxy flavone), followed by wogonoside (wogonin-7-O-glucuronide) and oroxylin A (5,7-dihydroxy-6-methoxyflavone). Minor flavones include: norwogonin, skullcapflavones I and II, scutellarein, scutellarin, chrysin. Flavone (chrysin) C-glycosides, flavanones (dihydrobaicalein and dihydrochrysin) and chalcones are present, too.

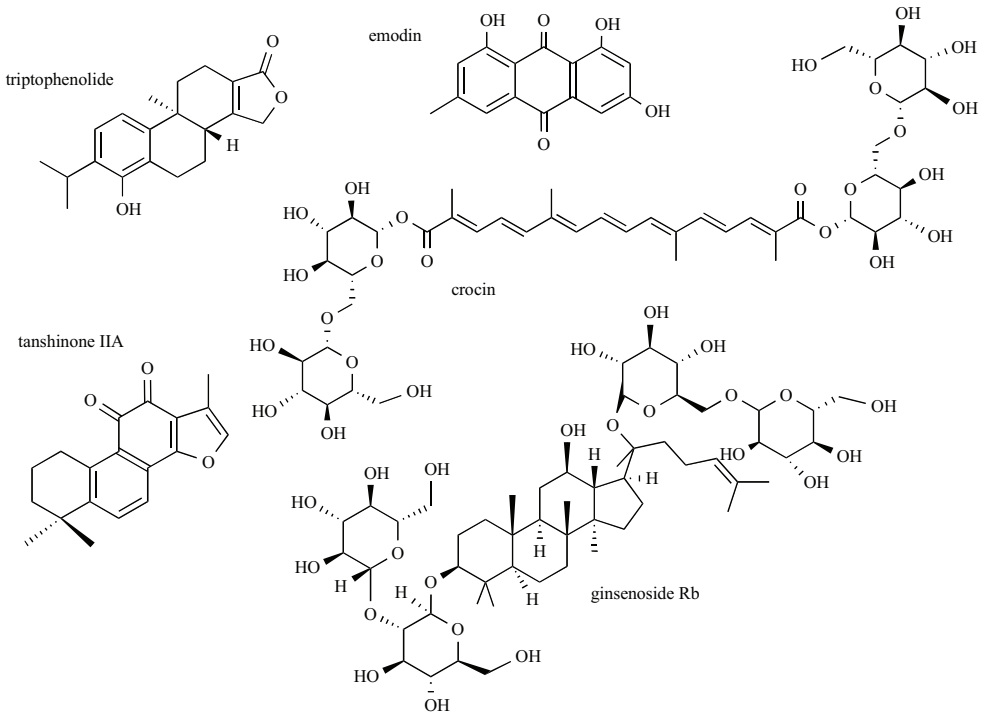

Fig. (9). Examples of structures of antioxidant terpenoids and an anthraquinone.

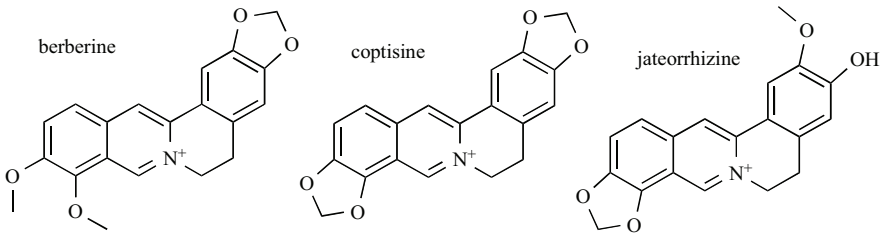

Fig. (10). Examples of structures of antioxidant isoquinoline alkaloids.

The minor fraction of neoclerodane diterpenoids – scutalbin I and II, scutecyprol B, jodrelin A and B, was also isolated. The phytochemistry and pharmacological properties of plants from the genus Scutellaria have been recently reviewed by Shang *et al.* [77] with *S. baicalensis* mentioned as the most thoroughly described medicinal Skullcap species.

Antioxidant Activity

The predominant flavones of Huang qi – baicalin, baicalein, wogonin, are also main antioxidant compounds Fig. (**4**). Various mechanisms are involved in antioxidant properties of the herb, i.e. direct free radical scavenging, iron chelation, ion reduction, as well as protection of biomolecules from oxidative damage.

Sequestration of iron by chelation can decrease its participation in ROS generating Fenton reaction. Baicalein can bind ferrous iron to hydroxyl groups in positions C-6 and C-7 in a stable complex baicalein$_2$-Fe^{2+}.The presence of 5,6,7-trixydroxy-pattern in A-ring is crucial for the high iron binding capacity, and enables a second type of binding where ferrous ion are in 1:1 proportion [78]. The binding of iron to baicalein is stronger in physiological conditions than to the reference iron(II) chelator ferrozine and similar to deferoxamine.

Baicalein, at 10μM can completely inhibit Fenton reaction induced lipid peroxidation due to the two complementary mechanisms – direct ROS scavenging and iron chelation. Baicalin has only limited chelating ability and only free radical scavenging results in partial protection of lipids [79].

Wozniak *et al.* [80] tested four major flavonoids for DPPH scavenging confirming high anti-radical activity of baicalein (EC_{50} 9 μg/mL), followed by baicalin while wogonoside and wogonin had very low or none activity, respectively. In most screening studies, *Scutellariae radix* or isolated baicalin/baicalein count to the most potent antioxidants [1, 2]. In the list of over 150 CHMs by Li *et al.* [1] tested for TEAC, Huang qin was the sixth strongest (184.3 μmol Trolox equivalents/g). In the study by Cai *et al.* [3] on isolated polyphenols from CHMs, baicalein was the strongest flavone (TE over 2.5 mmol), and second only to quercetin (a flavonol) among all non-tannin compounds. Wozniak *et al.* [81] observed differences in performances of the four major flavones in three antioxidant *in vitro* assays using distinct mechanisms i.e. DPPH scavenging, transition metal reduction (by phosphomolybdenum assay) and lipid peroxidation inhibition. While baicalein was highly active in all tests, in the reducing power baicalin was equally active (0.14 and 0.15 ascorbic acid equivalents, respectively), and the other two flavones were several times weaker. On the other hand, in the Fenton reaction-induced lipid peroxidation (LPO), both aglycones (baicalein and wogonin) were equally active and completely stopped peroxidation at concentrations over 125 μg/mL (IC_{50} 53 μg/mL), while baicalin inhibited LPO by 50%, and wogonoside had no activity. Interestingly, at the lower concentration (up to 10 μg/mL) pro-oxidant activity of baicalin was noticed.

Długosz *et al.* [82-84] studied effects of baicalin-rich fraction from Huang qin on oxidative stress markers in human erythrocytes and mitochondria. Baicalin at concentrations above 5 μg/mL, inhib-

ited (by more than 20%) ROS generation and lipid peroxidation in cells and isolated mitochondria exposed to *t*—BuOOH, Cr(III) and Cr(VI) or xylene. Baicalin also increased ferric reducing potential in human plasma taken from healthy subjects. However, the same authors have also reported pro-oxidant activity in lower (below 2 μg/ml) concentrations of baicalin fraction.

Apart from the above studies, numerous other reports confirm these findings by extensive *in vitro* testing using a variety of antioxidant assays, such as nitric oxide scavenging, lipid peroxidation, quenching of various ROS or model free radicals, metal chelation and reduction etc. In most of the studies, baicalein or baicalin were strongest [85-87] but other flavones such as wogonin in NO assay or oroxylin A in lipid peroxidation were superior as well [88].

A variety of cultured cells are protected from oxidative stress by *Scutellariae baicalensis radix* flavones [89]. For example, baicalein and the other flavones can scavenge intracellular ROS and inhibit membrane lipid, protein and DNA oxidative destruction, and lactate dehydrogenase leakage, induced by hydrogen peroxide treatment [85, 86, 89, 90]. These complex activities result in improved cell survival of cells pre-treated with 10 μM baicalein. Cytoprotective action of baicalin in endothelial cells can be also partially attributed to peroxynitrite scavenging complementing to the inhibition of endogenous iNOS and COX2 by downregulating NFκB [91]. Hepatoprotective properties, suggested by traditional use of Huang qin can be also attributed to antioxidant activity in liver cells. In hemin/nitrite/hydrogen peroxide – induced liver injury, the flavones: baicalein, baicalin, and wogonin (at 5 and 25 μM) reduced the level of lipid peroxidation and protein nitration dose dependently [92].

The flavone-rich extract protects cerebral-ischemic rats from deleterious effects related to ischemia/reperfusion stress. The model ischemic rats supplied orally with *Scutellariae baicalensis radix* extract had improved cognitive functions similar to the reference drug treated, but additionally their oxidative stress markers decreased [93]. In a single study, the pro-oxidant effect of baicalein was suggested as a mechanism for protection of cardiomyocytes against hypoxia/reoxygenation injury [94]. Baicalein-pretreated cells were more resistant to the reoxygenation injury monitored as LDH leak, than the cells treated during the onset of oxidative stress. The co-treatment with antioxidant substances or catalase abolished the protective effect of baicalein. The potential of Baikal skullcap flavones antioxidant properties in therapy of neurodegenerative disorders has been recently reviewed [95].

In conclusion, Huang qin flavones, particularly baicalein and baicalin are powerful antioxidants *in vitro* and *in vivo*, and this activity is likely to significantly contribute to the overall complex preventive and therapeutic value of this herb. Thus, its growing popularity and inclusion in Western countries pharmacopoeias such as PhEur is fully justified.

Salvia miltiorrhiza (Salviae miltiorrhizae Radix - Dan Shen)

Salvia miltiorrhiza Bunge, (Lamiaceae) is indigenous to East Asia (China, Japan, Korea, Mongolia) and is a perennial with thick, red colored roots that are used medicinally.

The official species can be substituted by other related *Salvia sp*., mainly *S. przewalskii, S. trijuga, S. yunnanensis.* According to the TCM classification [5, 6], danshen is bitter in taste and has pronounced cool temperature. It is strongly associated with Heart, Pericardium, and moderately with the Liver. Danshen belongs to the "Blood invigorating and stasis removing" herbs with "deep" action. The therapeutic TCM indications are mostly related with blood regulation:

1. Activates blood circulation and breaks up blood stasis – acts in cardiovascular and gynecological/menstruation disorders. It is also used in traumatic injuries and swelling. Its cooling action dispels heat from the Heart and blood resulting in spirit calming for treating insomnia. It is most often used in mixtures with other herbs, depending on the particular indication. Regarded as highly active, it should be used with cautions by patients with hypermenorrhea, hematuria, or hemoptysis. A number of animal and clinical studies have been performed in order to check the relevance to the actual disorders in clinical situations [96]. It has been used in following cardiovascular disorders: coronary artery disease; hypertension; arrhythmias; stroke; myocardial infarction; peripheral and pulmonary vascular disease; renal malfunctions and diabetes. The pharmacological properties of *Salvia miltiorrhiza* have been also recently reviewed in several papers [15, 97] and include antioxidant, anti-microbial, antiviral, anticancer, anti-inflammatory, anti-ischemia/reperfusion, anti-thrombotic, antihypertensive, anti-fibrosis. In 2013, Dan shen monograph has been included in European Pharmacopoeia.

Chemical Composition

Unlike Huang qin, *Salviae miltiorrhizae radix* contains two major groups of compound of distinct chemical structures and different physicochemical and pharmacological properties. One group are hydroxycinnamic acids derivatives, mainly in form of depsides from dimeric to tetrameric molecules that are built with caffeic and hydroxyphenyllactic acids blocks. Major compounds from this group are: salvianolic acids (A, B, and so on), lithospermic acid (A and B), and rosmarinic acid. A monomeric phenol carboxylic acid – danshensu and protocatechuic acid and aldehyde are also present in significant amount [98]. Due to the exceptionally high number of hydroxyl groups, the oligomeric depsides are superior antioxidants and exhibit a number of other pharmacological activities reviewed recently by Ho and Hong [99]. A lignan, (+)-1-hydroxypinoresinol-1-O-β-D-glucoside was also identified in Dan shen [100].

The other major group is quinoid diterpenoids called tanshinones. They have abietane basic structure, but differ in the detailed ring arrangement, stereochemistry and substitution pattern. They are usually brightly colored – red (from bright to burgundy – Chinese plant name meaning literally "red root" or "red ginseng"), yellow, and orange, rarely green or faintly colored. Not all compounds collectively included into tanshinones have the typical ortho-quinone tetracyclic structure. The most abundant are tanshinone IIA, cryptotanshinone, tanshinone I, with tens of minor compounds such as: miltirone (with no heterocyclic furan ring), oxomiltirone, methyltanshinoate, etc. For the full listing of compounds from both group compare any of the recent reviews or phytochemical analytic papers [15, 97, 98].

Antioxidant Activity

Both major classes have antioxidant properties but the actual activity results from the abundance of polyphenolic acids that are much stronger antioxidants with little contribution from tanshinones. Danshen extracts and both phytochemical classes have been studied for this activity *in vitro* using a variety of methods, such as direct free radical and ROS scavenging (DPPH, ABTS, superoxide anion radical, peroxynitrite, hydrogen peroxide) and reducing power towards metal ions such as ferrous iron. In DPPH scavenging [101] the tetrameric lithospermic acid B had highest efficacy (EC_{50} 3.87 μM), followed by trimeric lithospermic acid and dimeric rosmarinic acid. The lyophilized hydroalcoholic extract from Dan shen possessed strong ferric iron reducing power and high scavenging activities against free radicals including superoxide anion, hydroxyl and DPPH radicals (over 80%), but a weaker activity (up to 30%) in hydrogen peroxide assay and no ferrous ion chelating activity [102]. Two isolated compounds, danshensu and salvianolic acid B efficiently scavenged almost 100% of ABTS, DPPH, hydroxyl, and superoxide radicals, but were weaker than ascorbic acid in hydrogen peroxide reduction and iron chelating [103]. Salvianolic acid A,

tested along with salvianolic (lithospermic) acid B in DPPH and ABTS scavenging, had similar potencies, and IC_{50} of both oligomers were below 2 μg/mL [104]. The DPPH scavenging, ferric reducing and iron chelation efficiency was enhanced by preparing nanoparticles from the roots prior to extraction. Here, the extractability of salvianolic acid B was markedly increased and not of the tanshinones [105].

In the screening study of three *Salvia sp.* including two used as dan shen (*S. miltiorrhiza* and *S. przewalskii*) based on three complementary antioxidant tests, a correlation was noticed between antioxidant activity and polyphenol content but not to tanshinone presence [106]. Partitioning of the methanolic extract between different solvents, allowed to concentrate the DPPH and ABTS scavenging and ferric reducing activity in ethyl acetate fraction [107]. Ethyl acetate is a preferred solvent for phenolic acids extraction. In this study, hexane fraction was inactive, and it is known to contain mainly tanshinones.

The above mentioned lignan, (+)-1-hydroxypinoresinol-1-O-β-D-glucoside also efficiently scavenged DPPH, peroxynitrite, and ROS with EC50 values of: 32.3 3.23, and 2.26 μM respectively [100].

Several studies used lipid oxidation as target for antioxidants. Tanshinones (dihydrotanshinone I, tanshinone I, methylenetanshinquinone, miltirone, and cryptotanshinone, but not tanshinone IIA) were efficiently inhibiting (comparably to standard antiperoxidation agents BHT and BHA) lard rancidity caused by high temperature. Some structural prerequisites for the increased activity were suggested: additional conjugated double bonds in the A ring; a dihydrofuran ring rather than a furan ring; an isopropyl substituent in *ortho* position to a quinone carbonyl rather than a dihydrofuran ring. Weng and Gordon [108] proposed that the quinones act as primary antioxidants by addition of the lipid radical to the quinone to form a stabilized radical which interrupts the auto-oxidation chain reaction. However, in another paper [109], tanshinone IIA at 100 μM was able to almost completely inhibit LDL oxidation induced by copper, peroxyl radical and peroxynitrite. Mechanistically, the tanshinone was not acting via ROS scavenging or metal chelation, but through interaction and conformational changes within the oxidized substrate. Phenolic compounds have also exhibited liqid protection. Huang and Zhang [110] observed inhibition of NADPH-vitamin C and Fe(2+)-cysteine induced lipid peroxidation and superoxide scavenging by salvianolic acid A with the highest activity, followed by salvianolic acid B and rosmarinic acid.

Extracts and some compounds from *Salvia miltiorrhiza* are also able to protect cells from oxidative injury. For example, a standard solution of Dan shen attenuated hearing impairment following aminoglycoside (kanamycin) antibiotic administration in mice, but the applied doses were rather high (10 and 20 g/kg body weight). In cell cultures, Dan shen extract in higher doses (such as 1% to 5% in the assay medium) completely reduced gentamycin-induced oxidative stress markers such as: gentamycin-dependent lipid peroxidation (formation of conjugated dienes from arachidonic acid), as well as formation of superoxide and hydroxyl radicals [111].

Salvianolic acid A delivered intraperitoneally at 20mg/kg protected rats from carbon tetrachloride caused hepatotoxicity and reduced oxidative stress (lower level of markers such as MDA level and ROS production and increased SOD activity and GSH content) in the hepatocytes [112]. Dimethyl-lithospermate protected cells from protein nitration by scavenging native and donor-derived peroxynitrite [113]. Salvianolic acid B was able to protect various *in vitro* cultured mammalian cells or model animals from hydrogen peroxide or cupric ion induced oxidative injury. This compound also inhibited cellular lipid peroxidation, and stimulated activity of anti-ROS enzymes such as catalase, SOD, GPx, endogenous GSH levels [114-116]. *In vivo* cardioprotective effect in rats due to the antioxidant activity was also exerted by danshensu acid [117]. In human subjects with diabetes and chronic heart disease, treatment with 5 g twice a day of hydrophilic *Salviae miltiorrhizae radix* extract reduced the serum level of lipid peroxidation marker MDA, and increased endogenous antioxidant status significantly compared to the placebo group [118]. In the mentioned study the following markers were improved: GSH content, SOD, GSSG reductase, and paraoxonase (PONase) activity.

Some polysaccharide fractions [119] were able to scavenge free radicals such as DPPH, superoxide radical anion and hydroxyl radical. However, compared to other phytoconstituents, the concentration at which the effect was observed were much higher (4 mg/mL).

The cited examples are not all that reported direct or indirect antioxidant properties of various extracts and phytochemicals from Dan shen. However, these references demonstrate the broad spectrum of activity in various models, both *in vitro* and *in vivo*. In this respect, Danshen is one of the most extensively studied CHM and the results support its beneficial properties to a large extent.

Reynoutria japonica (Polygoni cuspidati rhizoma - Hu Zhang)

The botanical species *Reynoutria japonica* Houtt. (Polygonaceae) – Japanese knotweed, has been better known under the synonym *Polygonum cuspidatum* Sieb. & Zucc., another synonym that is used is *Fallopia japonica* (Houtt.) Ronse Decr. The species is indigenous to Eastern part of continental Asia and Japan. It is an extraordinarily large and vigorous perennial that has become a noxious invasive plant in Europe and other moderate climate regions in the world. The Chinese name reflects its size and vigor and means "Tiger's cane".

The underground, creeping, thick and remarkably strong rhizomes are used medicinally. In the TCM, it has bitter taste and cold temperature. The organ relationship is Liver, Gallbladder, and Lung. Similarly to Dan shen, it belongs to the "Blood invigorating" herbs and its primary indication is activating circulation, damp-heat clearing from the liver. Another indications include detoxifying (in snake bites or internal toxins), pain relieving (post traumatic, rheumatic and abdominal pain, phlegm transforming (in cough). The hepatic indications are also important and include jaundice and gallstones [5, 6]. Some of the TCM indications have been confirmed by pharmacological and clinical trials, in which Hu zhang was found effective in treatment of bile duct infection, infectious icteric jaundice, and chronic hepatitis.

Chemical Composition

As a member of knotweed family, *R. japonica* is rich in polyphenols such as stilbenes and tannins and contains considerable amount of anthraquinones.

The rhizome is known as a most abundant natural source of resveratrol and its glucoside – polydatin (also called piceid). Stilbenes can occur in two isomeric forms *trans* and *cis*, while the *trans* isomers are usually more active pharmacologically. The isomerization is caused by light and UV irradiation and is reversible in the dark. Several other stilbenoids have been found in this plant: glycosides of piceatannol and resveratrol, dimers, and galloylated glucosides of resveratrol [120]. Sulfated resveratrol glycosides have been found as well, where hydroxyl group of either aglyconic part (positions 5 or 4') or sugar were sulfated [49].

The other group of phenolics – tannins and tannin monomers, belong to both major classes – hydrolysable and condensed, the first fraction represented by gallotannins and the second by flavan-3-ols as oligomeric proanthocyanidins. In our phytochemical screening studies [121] we have evaluated the total content of polyphenols from different phytochemical classes in extracts and purified tannin fractions from Hu zhang. The acetone and butanol extracts were rich in total polyphenols (50% of which were tannins). Condensed

tannins constituted again from 42% (acetone extract) to 60% (butanol extract) of all tannins. The hydrolysable fraction contained gallic acid glycosides, while in the proanthocyanidin fraction, the presence of galloylated derivatives was observed (rhodanine assay) as well as epicatechin derivatives and other flavan-3-ols. The research is being continued for detailed analysis of tannin composition. Tachioside and isotachioside, caffeic acid dimeric glucosides, resembling gallotannins in the overall structural arrangement with caffeic acid molecules connected to sugar by ester bonds. Two lignans are also present in minor amounts [122], such as sulphates of (+)-isolariciresinol and (-)-lioniresinol.

Anthraquinones, another class typical for *Polygonaceae*, confer the laxative properties also to many other herbs. They have been also studied for other bioactivities such as estrogenic, antimutagenic, antitumor, tyrosinase inhibition [123-127]. Their biosynthetic origin is divert from that of phenylpropanoids, because they derive from polyketide (acetogenin) pathway. In Hu zhang, both glycosides and aglycons are present, for example physcion, emodin, chrysophanol, chrysophanic acid, citreorosein, and their respective glycosides [124]. Few minor naphtoquinones are also present in this herb – for example 2-methoxy-6-acetyl-7-methyljuglone [128].

Antioxidant Activity

In the existing literature supporting antioxidant properties of Hu zhang, a majority of papers consider resveratrol as the main antioxidant. As already mentioned in this review, the great number of reports exist on antioxidant activity of resveratrol from other sources or without any source cited. Therefore, we will focus more on other compounds that would add to the total antioxidant capacity of the herb, and on various mechanisms of antioxidant protection exerted by the phytochemical complex from Hu zhang.

The crude alcohol extract from the rhizomes scavenged DPPH free radical (IC_{50} = 110 μg/mL was calculated by the authors as the concentration of sample that reduced 50% of free radical – which is incorrect – the actual IC_{50} from the presented dose response curves would be around 70 μg/mL), completely reduced superoxide anion radical (EC_{50} about 3.2 μg/mL with the same remark as to DPPH test, but still over 10 times lower than catechin) as well as efficiently inhibited lipid peroxidation (with a relatively low IC_{50} – 8 μg/mL and maximum inhibition over 70%) and DNA strand breaks [129]. In another study [130], also using ethanol extraction, the extract was tested for DPPH and hydroxyl radical scavenging, heat-induced lipid peroxidation, and reducing power (phosphomolybdenum and ferricyanide assays). In these assays, that employ different mechanisms of antioxidant activity, the extract was similarly efficient or better than resveratrol used as reference within the concentration range between 0.2 mg/ml to 1.2 mg/ml. This again suggests contribution of other compounds to the final effect.

Some contribution from anthraquinones has been also postulated, revealed by *in vitro* cell based assays, DPPH scavenging, ferric ions reduction and ferrous ion chelation [131]. The anthraquinone-enriched fraction stimulated GPx activity and reduced malonyl dialdehyde level and hemolysis in hydrogen peroxide treated cells. The DPPH scavenging and ferric reducing capacity was higher than of ascorbic acid.

The naphtoquinone - 2-methoxy-6-acetyl-7-methyljuglone has been also studied for cytoprotective and antioxidant activity [128]. For example, pretreatment with 5 μM of 2-methoxy-6-acetyl-7-methyljuglone abolished the cytotoxic effect of tert-butyl hydroperoxide and the level of intracellular oxidants were significantly decreased. Similar effects were exerted by much higher doses of resveratrol (50 μM) and lipoic acid (100 μM).

In the recent study by Lee *et al.* [132], the extract fractionated with SPE on silica or XAD4 resin tested for DPPH scavenging and hydrogen peroxide reduction showed lack of correlation of these activities with resveratrol and emodin content. The most active were two primary MeOH extracts where the resveratrol and emodin content was low (about 6% and 8%, respectively) while total polyphenols high. Of three fractions rich in resveratrol (from 17 to over 30%), only one had comparable antioxidant efficacy to the crude extracts, that happened to be also the most abundant in total polyphenols measured with Folin-Ciocalteu method. These results clearly suggest the importance of other phenolic constituents to the antioxidant properties, but they remained unidentified. Surprisingly, there are no reports on antioxidant properties in *Polygoni cuspidati rhizoma* focused specifically on tannins or monomeric phenols such as phenolic acids, glycosides, or flavanols. It may result in a biased perception of the actual potential of this herb as source of preventive and therapeutic antioxidant activities.

In conclusion, Hu zhang seems to be one of the most promising sources of a variety of polyphenolic and hydroxyquinone antioxidants that act in concert. However, more data are required to fill the gap in understanding of actual contribution of different compounds, not just resveratrol, to antioxidant properties of *Polygoni cuspidati rhizoma*.

IS THERE ANY CLINICAL RELEVANCE OF CHM AS ANTIOXIDANTS?

Since the actual physiological role of herbal antioxidants *in vivo* is hard to pin down, clinical evidence specifically for their direct beneficial antioxidant activity is scarce, and the few existing are often ambiguous. Actually, antioxidant plant natural products may actually act as non-deleterious prooxidants by triggering the adaptive reaction of the organism – anti-ROS enzymes, thiols and other innate responses useful in combating oxidative stress [133].

Instead, there are much more clinical trials on the efficiency of CHMs in several disorders where antioxidant mechanisms of action may be involved. The evidence again, can only be indirectly supported by abundant data from aforementioned experimental pharmacological studies *in vitro* and in animal models. One of the still unresolved issues about the antioxidants *in vivo* is their limited bioavailability and quick pre- and post-absorption metabolism. The first metabolic transformation process depends on the gastrointestinal microflora and degradation during digestion, while the second results from the organism's xenobiotic detox system. Finally, only the small fraction of the orally administered compounds are actually absorbed and able to act on the cellular targets. Hypothetically, it could be the role of the experience-based combinations of CHMs, some of which are explained specifically by facilitating a proper directing/utilization of the main active herb by assistant (or messenger) herbs. In this aspect, an antioxidant could possibly serve in both categories, i.e. as a main active principle or for potentiating the therapeutic effect of another constituent or to temper its undesired effects. This approach is not unknown in Western pharmacotherapy and phytotherapy, but only in TCM it has been made to a sophisticated formalized scheme, even though it is based merely on functional visceral entities. This concept has not been actually approached on the clinical level, yet. In addition, many of the previously reported clinical trials are of insufficient quality in terms of study design: randomization, study group size, inclusion of proper placebo control, outcome measures [134].

Disorders that have been clinically studied for CHMs efficacy include cardiovascular and cerebrovascular conditions, influenced by Dan shen preparations. *Salviae miltiorrhizae radix* and thereof derived preparations are widely used clinically in China and have been proved to be effective in coronary heart disease and ischemic cerebral stroke [for example in [96, 135].

Several CHMs were also tested for efficacy against liver fibrosis [136], wherefrom antioxidant mechanism has been suggested for

such herbs or compounds as: *Salviae miltiorrhizae radix* (extract and salvianolic acid B), curcumin, berberine from *Coptis chinensis*, tetramethylpyrazine from *Ligusticum chuanxiong*, *Ginkgo extract*. Moreover, among several listed composite preparation of proved clinical efficiency, most contain at least one herb with pronounced antioxidant properties: *Salviae miltiorrhizae radix*, *Scutellariae baicalensis radix*, *Paeoniae lactiflorae radix, Rhei radix et rhizoma, Curcumae rhizoma, Sophorae flavescentis radix*. However, as we still cannot conclude about the *in vivo* relevance of antioxidant properties, more mechanistic studies on cellular level are needed.

With respect to cancer therapy, CHM can be considered only as complementary or modulating for the regular cytostatic treatments. A compound Chinese medicine manufactured as pharmaceutical grade version of traditional Huangqin Tang, consisting of two strong antioxidants (*Scutellariae baicalensis radix* – Huang qin and *Paeoniae lactiflorae radix* – Bai shao) and two other herbs that also have antioxidant properties - *Glycyrrhizae radix* – gan cao and *Jujubae fructus* – Da zao, was investigated in phase I clinical studies as complementary therapy in cytostatics-treated patients with gastrointestinal malignancies. In irinothecan-treated colorectal cancer patients [137] and in capecitabine-treated pancreatic and other gastrointestinal cancer patients [138], the preliminary results suggest no interference with the cytostatic therapy and some increase in tumor control rate was noted.

These are just few recent examples of the emerging trend in CHM research that increasingly involves clinical and *in vivo* pharmacological studies, and at the same time the most advanced instrumental analytic methods for quality of herbs. In the near future, we would certainly witness more well designed clinical studies on CHMs, even if the antioxidants will not remain in the central point of interest of such research [134].

CONCLUSIONS

A great number of CHMs has antioxidant properties and many strong antioxidant compounds have been isolated from them. However, their usefulness in prevention or alleviation of oxidative stress is still not completely verified. Most of the screening studies use *in vitro* assays, either cell free or in cell cultures, that are not necessarily relevant to the *in vivo* conditions. On the other hand, the results from *in vivo* experiments often lack a convincing explanation of cellular or molecular mechanisms underlying observed effects. Moreover, the results depend highly on the physiological conditions of the test system. One of the likely paradox mechanism of plant antioxidant action in an animal organism is in fact based on their pro-oxidant properties related to ferric or cupric ion reduction that provoke adaptive reaction of the cell – upregulation of innate antioxidant system: anti-ROS enzymes (SOD, CAT, GPx etc), increase of reduced thiol pool etc. The traditional Chinese medicine philosophy does not contradict such phenomena due to its fundamental rule of retaining or restoring balance. This may explain the abundance of herbs rich in antioxidant principle. Some of the compounds obtained from CHM are exceptionally active in various systems and have attracted great interest worldwide. Baikal skullcap lipophilic flavones (baicalein, wogonin), stilbenes and tannins from *Polygoni cuspidati rhizoma*, caffeic acid oligomers and tanshinones from *Salviae miltiorrhizae radix* are only few examples. Most other herbs or compounds are still not sufficiently studied, though. Some of the potentially important antioxidant herbs and compounds requiring more investigation are for example: *Belamcandae rhizoma* (lipophilic isoflavones and xanthone C-glycosides), *Epimedii herba* (prenylflavonols), *Forsythiae fructus* (phenylethanoid glycosides), and many others. The existing results are also frequently scattered through various pharmacological and phytochemical literature and difficult to reliably interpret.

The adaptation of modern scientific approach to the research on traditional Chinese herbs without losing its experience-based merit is a challenging mission. Yet, the simple example of antioxidants reveals the huge number of variables and data that have to be considered for the complete picture of diverse pharmacological effects reflecting the formalized traditional classification such as taste, temperature, organ relationships and direction.

To capture the complete picture of complex relations between the organism response to herbal treatment, including antioxidant activity, the advanced analytical, pharmacological, and statistical methods are essential as well as metabolomic approach towards both herbs phytochemistry and *in vitro* or *in vivo* response to treatment [139, 140]. With this review we hope to, at least partially, contribute to the better awareness of a potential usefulness of traditional Chinese herbs as the scientifically provable resource for preventing and combating oxidative stress.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT

Declared none.

REFERENCES

[1] Li, H.B.; Li, D.; Zhang, Y.; Gan, R.Y.; Song, F.L.; Cheng, F. Antioxidant Properties of Chinese Medicinal Plants. In *Reactive Oxygen Species and Antioxidants in Higher Plants*; Dutta Gupta, S., Ed.; Sci., ence Publishers: Enfield, NH, USA, **2011**; pp. 331-362.

[2] Cai, Y.; Luo, Q.; Sun, M.; Corke, H. Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. *Life Sci*., **2004**, *74*, 2157-2184.

[3] Cai, Y.-Z.; Sun, M.; Xing, J.; Luo, Q.; Corke, H. Structure-radical scavenging activity relationships of phenolic compounds from traditional Chinese medicinal plants. *Life Sci*., **2006**, *78*, 2872-2888.

[4] Matkowski, A. Plant Phenolic Metabolites as Antioxidants and Mutagenesis Inhibitors. In *Cell Biology and Instrumentation: UV Radiation, Nitric Oxide and Cell Death in Plants*; Blume, Y.; Durzan, D. J.; Smertenko, P., Eds.; IOS Press: Amsterdam, **2006**; pp. 129-148.

[5] Chen, J.K.; Chen, T.T. *Chinese Medical Herbology and Pharmacology*; Art of Medicine Press: City of Industry, CA, USA, **2006**.

[6] Hempen, C.-H.; Fischer, T. *A Materia Medica for Chinese Medicine*.; Churchill Livingstone Elsevier: Edinburgh, London, Philadelphia, **2009**.

[7] Ou, B.; Huang, D.; Hampsch-Woodill, M.; Flanagan, J. When East meets West: the relationship between yin-yang and antioxidation-oxidation. *FASEB J*., **2003**, *17*, 127-129.

[8] Wong, C.-C.; Li, H.-B.; Cheng, K.-W.; Chen, F. A systematic survey of antioxidant activity of 30 Chinese medicinal plants using the ferric reducing antioxidant power assay. *Food Chem*.., **2006**, *97*, 705-711.

[9] Szeto, Y.-T.; Benzie, I.F.F. Is the yin-yang nature of Chinese herbal medicine equivalent to antioxidation-oxidation? *J. Ethnopharmacol*., **2006**, *108*, 361-366.

[10] Liao, H.; Banbury, L.K.; Leach, D.N. Antioxidant activity of 45 Chinese herbs and the relationship with their TCM characteristics. *Evid. Based Complement Alternat. Med*., **2008**, *5*, 429-434.

[11] Liao, H.; Banbury, L.K.; Leach, D.N. Elucidation of danzhixiaoyao wan and its constituent herbs on antioxidant activity and inhibition of nitric oxide production. *Evid. Based Complement. Alternat. Med*., **2007**, *4*, 425-430.

[12] Li, Y.; Gong, M.; Konishi, T. Antioxidant synergism among component herbs of Traditional Chinese Medicine formula, ShengMai San studied *in vitro* and *in vivo*. *J. Health Sci.,* . **2007**, *53*, 692-699.

[13] Xuejiang, W.; Ichikawa, H.; Konishi, T. Antioxidant potential of qizhu tang, a chinese herbal medicine, and the effect on cerebral oxidative damage after ischemia reperfusion in rats. *Biol. Pharm. Bull*. **2001**, *24*, 558-563.

[14] Dai, J.; Mumper, R. Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. *Molecules*, **2010**, *15*, 7313-7352.

[15] Wang, B.Q. *Salvia miltiorrhiza* chemical and pharmacological review of a medicinal plant. *J. Med. Plant Res*., **2010**, *4*, 2813-2820.

[16] She, G.-M.; Xu, C.; Liu, B.; Shi, R.-B. Polyphenolic acids from mint (the aerial of *Mentha haplocalyx* Briq.) with DPPH radical scavenging activity. *J. Food Sci*., **2010**, *75*, C359-362.

[17] Tang, D.; Li, H.-J.; Chen, J.; Guo, C.-W.; Li, P. Rapid and simple method for screening of natural antioxidants from Chinese herb *Flos Lonicerae Japonicae* by DPPH-HPLC-DAD-TOF/MS. *J. Sep. Sci.*, **2008**, *31*, 3519-3526.

[18] Xiong, Q.; Kadota, S.; Tani, T.; Namba, T. Antioxidative effects of phenylethanoids from *Cistanche deserticola*. *Biol. Pharm. Bull*., **1996**, *19*, 1580-1585.

[19] Sharma, R.A.; Steward, W.P.; Gescher, A.J. Pharmacokinetics and pharmacodynamics of curcumin. *Adv. Exp. Med. Biol*., **2007**, *595*, 453-470.

[20] Strimpakos, A.S.; Sharma, R.A. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid. Redox Signal*., **2008**, *10*, 511-546.

[21] Zhongfa, L.; Chiu, M.; Wang, J.; Chen, W.; Yen, W.; Fan-Havard, P.; Yee, L.D.; Chan, K.K. Enhancement of curcumin oral absorption and pharmacokinetics of curcuminoids and curcumin metabolites in mice. *Cancer Chemother. Pharmacol*., **2012**, *69*, 679-89.

[22] Ahsan, H.; Parveen, N.; Khan, N.U.; Hadi, S.M. Pro-oxidant, anti-oxidant and cleavage activities on DNA of curcumin and its derivatives demethoxycurcumin and bisdemethoxycurcumin. *Chem. Biol. Interact*., **1999**, *121*, 161-175.

[23] Amic, D.; Davidovic-Amic, D.; Beslo, D.; Rastija, V.; Lucic, B.; Trinajstic, N. SAR and QSAR of the antioxidant activity of flavonoids. *Curr. Med. Chem.*, **2007**, *14*, 827-845.

[24] Choi, C.-W.; Jung, H.A.; Kang, S.S.; Choi, J.S. Antioxidant constituents and a new triterpenoid glycoside from *Flos Lonicerae*. *Arch. Pharm. Res.*, **2007**, *30*, 1-7.

[25] Ślusarczyk, S.; Hajnos, M.; Skalicka-Woźniak, K.; Matkowski, A. Antioxidant activity of polyphenols from *Lycopus lucidus* Turcz. *Food Chem.*, **2009**, *113*, 134-138.

[26] Ma, H.; He, X.; Yang, Y.; Li, M.; Hao, D.; Jia, Z. The genus Epimedium: an ethnopharmacological and phytochemical review. *J. Ethnopharmacol*., **2011**, *134*, 519-541.

[27] Li, W.-W.; Gao, X.-M.; Wang, X.-M.; Guo, H.; Zhang, B.-L. Icariin inhibits hydrogen peroxide-induced toxicity through inhibition of phosphorylation of JNK/p38 MAPK and p53 activity. *Mutat. Res*., **2011**, *708*, 1-10.

[28] Jung, H.A.; Jeong, D.-M.; Chung, H.Y.; Lim, H. A.; Kim, J.Y.; Yoon, N.Y.; Choi, J.S. Re-evaluation of the antioxidant prenylated flavonoids from the roots of *Sophora flavescens*. *Biol. Pharm. Bull*., **2008**, *31*, 908-915.

[29] Lapcík, O. Isoflavonoids in non-leguminous taxa: a rarity or a rule? *Phytochemistry*, **2007**, *68*, 2909-2916.

[30] Barnes, S. The biochemistry, chemistry and physiology of the isoflavones in soybeans and their food products. *Lymphat. Res. Biol*., **2010**, *8*, 89-98.

[31] Bebrevska, L.; Foubert, K.; Hermans, N.; Chatterjee, S.; Van Marck, E.; De Meyer, G.; Vlietinck, A.; Pieters, L.; Apers, S. In vivo antioxidative activity of a quantified *Pueraria lobata* root extract. *J. Ethnopharmacol*., **2010**, *127*, 112-117.

[32] Xiong, F.-L.; Sun, X.-H.; Gan, L.; Yang, X.-L.; Xu, H.-B. Puerarin protects rat pancreatic islets from damage by hydrogen peroxide. *Eur. J. Pharmacol.*, **2006**, *529*, 1-7.

[33] Cherdshewasart, W.; Sutjit, W. Correlation of antioxidant activity and major isoflavonoid contents of the phytoestrogen-rich *Pueraria mirifica* and *Pueraria lobata* tubers. *Phytomedicine*, **2008**, *15*, 38-43.

[34] Guerra, M.C.; Speroni, E.; Broccoli, M.; Cangini, M.; Pasini, P.; Minghett, A.; Crespi-Perellino, N.; Mirasoli, M.; Cantelli-Forti, G.; Paolini, M. Comparison between chinese medical herb *Pueraria lobata* crude extract and its main isoflavone puerarin antioxidant properties and effects on rat liver CYP-catalysed drug metabolism. *Life Sci*., **2000**, *67*, 2997-3006.

[35] Park, K.; Jung, G.; Choi, J.; Lee, K.; Park, H. Potent antimutagenic and their anti-lipid peroxidative effect of kaikasaponin iii and tectorigenin from the flower of *Pueraria thunbergiana*. *Arch. Pharm. Res.*, **2002**, *25*, 320-324.

[36] Wozniak, D.; Janda, B.; Kapusta, I.; Oleszek, W.; Matkowski, A. Antimutagenic and anti-oxidant activities of isoflavonoids from *Belamcanda chinensis* (L.) DC. *Mutat. Res.*, **2010**, *696*, 148-153.

[37] Jeong, G.S.; An, R.B.; Oh, S.H.; Kang, D.G.; Lee, H.S.; Kim, Y.C. cytoprotective activity of *Belamcanda chinensis* rhizome against glutamate-induced oxidative injury in HT22 cells. *Natural Prod. Sci.,* **2007**, *13*, 101-104.

[38] Pervaiz, S.; Holme, A. L. Resveratrol: its biologic targets and functional activity. *Antioxid. Redox Signal*., **2009**, *11*, 2851-2897.

[39] Orallo, F. Trans-resveratrol: a magical elixir of eternal youth? *Curr. Med. Chem*., **2008**, *15*, 1887-1898.

[40] Kovacic, P.; Somanathan, R. Multifaceted approach to resveratrol bioactivity: Focus on antioxidant action, cell signaling and safety. *Oxid. Med. Cell. Longev.*, **2010**, *3*, 86-100.

[41] Szekeres, T.; Saiko, P.; Fritzer-Szekeres, M.; Djavan, B.; Jäger, W. Chemopreventive effects of resveratrol and resveratrol derivatives. *Ann. N.Y. Acad. Sci*., **2011**, *1215*, 89-95.

[42] Mikulski, D.; Molski, M. Quantitative structure-antioxidant activity relationship of trans-resveratrol oligomers, trans-4, 4'-dihydroxystilbene dimer, trans-resveratrol-3-O-glucuronide, glucosides: trans-piceid, cis-piceid, trans-astringin and trans-resveratrol-4'-O-beta-D-glucopyranoside. *Eur. J. Med. Chem.*, **2010**, *45*, 2366-2380.

[43] Wenzel, E.; Soldo, T.; Erbersdobler, H.; Somoza, V. Bioactivity and metabolism of trans-resveratrol orally administered to Wistar rats. *Mol. Nutr. Food Res.*, **2005**, *49*, 482-494.

[44] Ryu, G.; Ju, J.H.; Park, Y.J.; Ryu, S.Y.; Choi, B.W.; Lee, B.H. The radical scavenging effects of stilbene glucosides from *Polygonum multiflorum*. *Arch. Pharm. Res.*, **2002**, *25*, 636-639.

[45] Han, J.; Ye, M.; Xu, M.; Qiao, X.; Chen, H.; Wang, B.; Zheng, J.; Guo, D.-A. Comparison of phenolic compounds of rhubarbs in the section deserticola with *Rheum palmatum* by HPLC-DAD-ESI-MSn. *Planta Med*., **2008**, *74*, 873-879.

[46] Wang, Q.L.; Lin, M.; Liu, G.T. Antioxidative activity of natural isorhapontigenin. *Japan. J. Pharmacol*., **2001**, *87*, 61-66.

[47] Fang, Y.N.; Liu, G.T. Effect of isorhapontigenin on respiratory burst of rat neutrophils. *Phytomedicine*, **2002**, *9*, 734-738.

[48] El-Seedi, H.R.; El-Barbary, M.A.; El-Ghorab, D.M.H.; Bohlin, L.; Borg-Karlson, A.-K.; Goransson, U.; Verpoorte, R. Recent insights into the biosynthesis and biological activities of natural xanthones. *Curr. Med. Chem.*, **2010**, *17*, 854-901.

[49] Xiao, K.; Xuan, L.; Xu, Y.; Bai, D. Stilbene glycoside sulfates from *Polygonum cuspidatum*. *J. Nat. Prod*., **2000**, *63*, 1373-1376.

[50] Woźniak, D.; Kuś, P.; Góralska, E.; Jamiołkowska, W.; Matkowski, A. Antimutagenic and antioxidant properties of natural products from the Chinese Herbal Medicine — *Belamcandae rhizoma*. *Acta Biochim. Pol*., **2011**, *58*, 23-26.

[51] Shen, C.-C.; Ni, C.-L.; Shen, Y.-C.; Huang, Y.-L.; Kuo, C.-H.; Wu, T.-S.; Chen, C.-C. Phenolic constituents from the stem bark of *Magnolia officinalis*. *J. Nat. Prod*., **2009**, *72*, 168-171.

[52] Chen, X.; Li, J.; Li, W.; Han, L.; Liu, X.; Di, L.; Cai, B. Intestinal absorption of the effective components of *Schisandra chinensis* Baill by rats single-pass perfusion in situ. *Yao Xue Xue Bao*, **2010**, *45*, 652-658.

[53] Leong, P.K.; Chiu, P.Y.; Ko, K.M. Prooxidant-induced glutathione antioxidant response *in vitro* and *in vivo*: a comparative study between schisandrin b and curcumin. *Biol. Pharm. Bull*., **2012**, *35*, 464-472.

[54] Chiu, P.Y.; Mak, D.H.; Poon, M.K.; Ko, K.M. In vivo antioxidant action of a lignan-enriched extract of Schisandra fruit and an anthraquinone-containing extract of Polygonum root in comparison with schisandrin B and emodin. *Planta Med*., **2002**, *68*, 951-956.

[55] Piao, X.-L.; Jang, M.H.; Cui, J.; Piao, X. Lignans from the fruits of *Forsythia suspensa*. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1980-1984.

[56] Fu, X.-J.; Liu, H.-B.; Wang, P.; Guan, H.-S. A study on the antioxidant activity and tissues selective inhibition of lipid peroxidation by saponins from the roots of *Platycodon grandiflorum*. *Am. J. Chin. Med*., **2009**, *35*, 967-975.

[57] Lee, K. Protective effect of saponins derived from roots of *Platycodon grandiflorum* on tert-butyl hydroperoxide-induced oxidative hepatotoxicity. *Toxicol. Lett*., **2004**, *147*, 271-282.

[58] Chan, J.Y.; Koon, J.C.; Leung, P.-C.; Che, C.-T.; Fung, K.-P. Suppression of low-density lipoprotein oxidation, vascular smooth muscle cell proliferation and migration by a herbal extract of *Radix Astragali, Radix Codonopsis* and *Cortex Lycii*. *BMC Complement. Altern. Med*., **2011**, *11*, 32.

[59] Ng, T.B.; Liu, F.; Wang, H.X. The antioxidant effects of aqueous and organic extracts of Panax quinquefolium, Panax notoginseng, Codonopsis pilosula, Pseudostellaria heterophylla and Glehnia littoralis. J.Ethnopharmacol., **2004**, 93, 285-288.

[60] Qiu, L.-H.; Xie, X.-J.; Zhang, B.-Q. Astragaloside IV improves homocysteine-induced acute phase endothelial dysfunction via antioxidation. *Biol. Pharm. Bull*., **2010**, *33*, 641-646.

[61] Cho, W.C.S.; Chung, W.-S.; Lee, S.K.W.; Leung, A.W.N.; Cheng, C.H.K.; Yue, K.K.M. Ginsenoside Re of *Panax ginseng* possesses significant antioxidant and antihyperlipidemic efficacies in streptozotocin-induced diabetic rats. *Eur. J. Pharmacol*., **2006**, *550*, 173-179.

[62] Huong, N.T.T.; Matsumoto, K.; Kasai, R.; Yamasaki, K.; Watanabe, H. In vitro antioxidant activity of Vietnamese ginseng saponin and its components. *Biol. Pharm. Bull*., **1998**, *21*, 978-981.

[63] Chen, Y.; Zhang, H.; Tian, X.; Zhao, C.; Cai, L.; Liu, Y.; Jia, L.; Yin, H.-X.; Chen, C. Antioxidant potential of crocins and ethanol extracts of *Gardenia jasminoides* Ellis and *Crocus sativus* L.: A relationship investigation between antioxidant activity and crocin contents. *Food Chem*., **2008**, *109*, 484-492.

[64] Verma, S.; Bordia, A. Antioxidant property of Saffron in man. *Indian J. Med. Sci*., **1998**, *52*, 205-207.

[65] Melnyk, J.P.; Wang, S.; Marcone, M.F. Chemical and biological properties of the world's most expensive spice: Saffron. *Food Res. Int.*, **2010**, *43*, 1981-1989.

[66] Padmavathy, J.; Kumar, C.P.; Saraswathi, V.S.; Saravanan, D.; Lakshmi, I.A.; Bindu, N.H.S.; Hemafaith, V. Pharmacological, pharmacognostic and phytochemical review of saffron. *Intl J. Pharm. Technol*., **2011**, *3*, 1214-1234.

[67] Inbaraj, B.S.; Lu, H.; Hung, C.F.; Wu, W.B.; Lin, C.L.; Chen, B.H. Determination of carotenoids and their esters in fruits of *Lycium barbarum* Linnaeus by HPLC-DAD-APCI-MS. *J Pharm. Biomed. Anal*., **2008**, *47*, 812-818.

[68] Amagase, H.; Sun, B.; Borek, C. *Lycium barbarum* (goji) juice improves in vivo antioxidant biomarkers in serum of healthy adults. *Nutr. Res.*, **2009**, *29*, 19-25.

[69] Potterat, O. Goji (*Lycium barbarum* and *L. chinense*]: Phytochemistry, pharmacology and safety in the perspective of traditional uses and recent popularity. *Planta Med.*, **2010**, *76*, 7-19.

[70] Chen, Y.; Roan, H.; Lii, C.; Huang, Y. Relationship between antioxidant and antiglycation ability of saponins, polyphenols, and polysaccharides in Chinese herbal medicines used to treat diabetes. *J. Med. Plant. Res.*, **2011**, *5*, 2322-2331.

[71] Liu, W.; Wang, H.; Pang, X.; Yao, W.; Gao, X. Characterization and antioxidant activity of two low-molecular-weight polysaccharides purified from the fruiting bodies of *Ganoderma lucidum*. *Int. J. Biol. Macromol.*, **2010**, *46*, 451-457.

[72] Wang, L.; Wang, G.; Zhang, J.; Zhang, G.; Jia, L.; Liu, X.; Deng, P.; Fan, K. Extraction optimization and antioxidant activity of intracellular selenium polysaccharide by *Cordyceps sinensis* SU-02. *Carbohydr. Polym.*, **2011**, *86*, 1745-1750.

[73] Ye, C.-L.; Hu, W.-L.; Dai, D.-H. Extraction of polysaccharides and the antioxidant activity from the seeds of *Plantago asiatica* L. *Int. J. Biol. Macromol.*, **2011**, *49*, 466-470.

[74] Luo, A.; Fan, Y. In vitro Antioxidant of a Water-Soluble Polysaccharide from *Dendrobium fimhriatum* Hook.var.oculatum Hook. *Int. J. Mol. Sci*., **2011**, *12*, 4068-4079.

[75] Jang, M.H.; Kim, H.Y.; Kang, K.S.; Yokozawa, T.; Park, J.H. Hydroxyl radical scavenging activities of isoquinoline alkaloids isolated from *Coptis chinensis*. *Arch. Pharm. Res*., **2009**, *32*, 341-345.

[76] Jung, H.A.; Min, B.-S.; Yokozawa, T.; Lee, J.-H.; Kim, Y.S.; Choi, J.S. Anti-Alzheimer and antioxidant activities of *Coptidis Rhizoma* alkaloids. *Biol. Pharm. Bull.*, **2009**, *32*, 1433-1438.

[77] Shang, X.; He, X.; He, X.; Li, M.; Zhang, R.; Fan, P.; Zhang, Q.; Jia, Z. The genus Scutellaria an ethnopharmacological and phytochemical review. *J. Ethnopharmacol.*, **2010**, *128*, 279-313.

[78] Mladěnka, P.; Macáková, K.; Filipský, T.; Zatloukalová, L.; Jahodář, L.; Bovicelli, P.; Silvestri, I.P.; Hrdina, R.; Saso, L. *In vitro* analysis of iron chelating activity of flavonoids. *J. Inorg. Biochem*., **2011**, *105*, 693-701.

[79] Perez, C. a; Wei, Y.; Guo, M. Iron-binding and anti-Fenton properties of baicalein and baicalin. *J. Inorg. Biochem.*, **2009**, *103*, 326-332.

[80] Woźniak, D.; Lamer-Zarawska, E.; Matkowski, A. Antimutagenic and antiradical properties of flavones from the roots of *Scutellaria baicalensis* Georgi. *Nahrung*, **2004**, *48*, 9-12.

[81] Woźniak, D. Antimutagenic and antioxidant activity of *Scutellariae baicalensis radix* and *Belamcandae chinensis rhizoma*., PhD dissertation, Medical University in Wroclaw, June **2009**.

[82] Długosz, A.; Lembas-Bogaczyk, J.; Lamer-Zarawska, E. Antoxid increases ferric reducing antioxidant power (FRAP) even stronger than vitamin C. *Acta Pol. Pharm.*, **2006**, *63*, 446-448.

[83] Przybylska, D.; Długosz, A. The research on Antoxid activity in free radicals processes. *Acta Pol. Pharm.*, **2007**, *64*, 491-495.

[84] Sawicka, E.; Średnicka, D. *Scutellaria baicalensis* inhibits lipid peroxidation caused by chromium in human erythrocytes. *Adv. Clin. Exp. Med*., **2008**, *17*, 539-544.

[85] Gabrielska, J.; Oszmiański, J.; Zyłka, R.; Komorowska, M. Antioxidant activity of flavones from *Scutellaria baicalensis* in lecithin liposomes. *Z Naturforsch. C*, **1997**, *52*, 817-823.

[86] Gao, Z.; Huang, K.; Yang, X.; Xu, H. Free radical scavenging and antioxidant activities of flavonoids extracted from the radix of *Scutellaria baicalensis* Georgi. *Biochim. Biophys. Acta*, **1999**, *1472*, 643-650.

[87] Bochoráková, H.; Paulová, H.; Slanina, J.; Musil, P.; Táborská, E. Main flavonoids in the root of *Scutellaria baicalensis* cultivated in Europe and their comparative antiradical properties. *Phytother. Res.*, **2003**, *17*, 640-644.

[88] Huang, W.-H.; Lee, A.-R.; Yang, C.-H. Antioxidative and Anti-Inflammatory Activities of Polyhydroxyflavonoids of *Scutellaria baicalensis* GEORGI. *BioSci. Biotechnol. Biochem.*, **2006**, *70*, 2371-2380.

[89] Kang, K.A.; Zhang, R.; Piao, M.J.; Chae, S.; Kim, H.S.; Park, J.H.; Jung, K.S.; Hyun, J.W. Baicalein inhibits oxidative stress-induced cellular damage via antioxidant effects. *Toxic. Ind. Health*, **2012**, *28*, 412-421.

[90] Choi, J.; Conrad, C.C.; Malakowsky, C. a; Talent, J.M.; Yuan, C.-S.; Gracy, R.W. Flavones from *Scutellaria baicalensis* Georgi attenuate apoptosis and protein oxidation in neuronal cell lines. *Biochim. Biophys. Acta*, **2002**, *1571*, 201-210.

[91] Kim, D.H.; Cho, K.H.; Moon, S.K.; Kim, Y.S.; Kim, D.H.; Choi, J.S.; Chung, H.Y. Cytoprotective mechanism of baicalin against endothelial cell damage by peroxynitrite. *J. Pharmacy Pharmacol.*, **2005**, *57*, 1581-1590.

[92] Zhao, Y.; Li, H.; Gao, Z.; Gong, Y.; Xu, H. Effects of flavonoids extracted from *Scutellaria baicalensis* Georgi on hemin-nitrite-H2O2 induced liver injury. *Eur. J. Pharmacol.*, **2006**, *536*, 192-199.

[93] Shang, Y.-Z.; Miao, H.; Cheng, J.-J.; Qi, J.-M. Effects of amelioration of total flavonoids from stems and leaves of *Scutellaria baicalensis* Georgi on cognitive deficits, neuronal damage and free radicals disorder induced by cerebral ischemia in rats. *Biol. Pharm. Bull*., **2006**, *29*, 805-810.

[94] Woo, A.Y.H.; Cheng, C.H.K.; Waye, M.M.Y. Baicalein protects rat cardiomyocytes from hypoxia/reoxygenation damage via a prooxidant mechanism. *Cardiovasc. Res.*, **2005**, *65*, 244-253.

[95] Gasiorowski, K.; Lamer-Zarawska, E.; Leszek, J.; Parvathaneni, K.; Bhushan Yendluri, B.; Blach-Olszewska, Z.; Aliev, G. Flavones from root of *Scutellaria baicalensis* Georgi: Drugs of the future in neurodegeneration? *CNS Neurol. Disord. Drug Targets*, **2011**, *10*, 184-191.

[96] Cheng, T.O. Cardiovascular effects of Danshen. *Int. J. Cardiol.*, **2007**, *121*, 9-22.

[97] Jiang, R.-W.; Lau, K.-M.; Hon, P.-M.; Mak, T. C. W.; Woo, K.-S.; Fung, K.-P. Chemistry and biological activities of caffeic acid derivatives from *Salvia miltiorrhiza*. *Curr. Med. Chem*., **2005**, *12*, 237-246.

[98] Li, Y.-G.; Song, L.; Liu, M.; Hu, Z.-B.; Wang, Z.-T. Advancement in analysis of *Salviae miltiorrhizae Radix et Rhizoma* (Danshen). *J. Chromatogr. A*, **2009**, *1216*, 1941-1953.

[99] Ho, J.H.-C.; Hong, C.-Y. Salvianolic acids: small compounds with multiple mechanisms for cardiovascular protection. *J. Biomed. Sci*., **2011**, *18*, 30.

[100] Kang, H.S.; Chung, H.Y.; Byun, D.S.; Choi, J.S. Further Isolation of Antioxidative (+]-1-Hydroxypinoresinol-1-Q- fj-o-glucoside from the Rhizome of *Salvia miltiorrhiza* that Acts on Peroxynitrite, Total ROS and 1, 1-0iphenyl-2-picrylhydrazyl Radical. *Arch. Pharm. Res*., **2003**, *123*, 24-27.

[101] Chen, C.P.; Yokozawa, T.; Chung, H.Y. Inhibitory effect of caffeic acid analogues isolated from *Salviae Miltiorrhizae Radix* against 1, 1-diphenyl-2-picrylhydrazyl radical. *Exp. Toxicol. Pathol.*, **1999**, *51*, 59-63.

[102] Zhao, G.; Xiang, Z.; Ye, T.; Yuan, Y.; Guo, Z. Antioxidant activities of *Salvia miltiorrhiza* and *Panax notoginseng*. *Food Chem*., **2006**, *99*, 767-774.

[103] Zhao, G.-R.; Zhang, H.-M.; Ye, T.-X.; Xiang, Z.-J.; Yuan, Y.-J.; Guo, Z.-X.; Zhao, L.-B. Characterization of the radical scavenging and antioxidant activities of danshensu and salvianolic acid B. *Food Chem. Toxicol*., **2008**, *46*, 73-81.

[104] Sun, Y.; Zhu, H.; Wang, J.; Liu, Z.; Bi, J. Isolation and purification of salvianolic acid A and salvianolic acid B from *Salvia miltiorrhiza* by high-speed counter-current chromatography and comparison of their antioxidant activity. *J. Chromatogr. B Biomed. Sci. Appl*., **2009**, *877*, 733-737.

[105] Liu, J.-R.; Chen, G.-F.; Shih, H.-N.; Kuo, P.-C. Enhanced antioxidant bioactivity of *Salvia miltiorrhiza* (Danshen) products prepared using nanotechnology. *Phytomedicine*, **2008**, *15*, 23-30.

[106] Matkowski, A.; Zielińska, S.; Oszmiański, J.; Lamer-Zarawska, E. Antioxidant activity of extracts from leaves and roots of *Salvia miltiorrhiza* Bunge, *S. przewalskii* Maxim. and *S. verticillata* L. *Bioresour. Technol*., **2008**, *99*, 7892-7896.

[107] Kim, M.-H.; Kim, S.-I.; Seo, D.-W.; Ryu, J.-C.; Choi, H.-Y. Antioxidant activity of Salvia miltiorrhiza Bunge, a novel foodstuff. *Mol. Cell. Toxicol.*, **2010**, *6*, 65-72.

[108] Weng, X.C.; Gordon, M.H. Antioxidant activity of quinones extracted from tanshen (*Salvia miltiorrhiza* Bunge). *J. Agric. Food Chem*., **1992**, *40*, 1331-1336.

[109] Niu, X.; Ichimori, K.; Yang, X.I.A.; Hirota, Y.; Hoshiai, K.; LI, M.; NAKAZAWA, H. Tanshinone II-A inhibits low density lipoprotein oxidation *in vitro*. *Free Radic. Res*., **2000**, *33*, 305-312.

[110] Huang, Y.S.; Zhang, J.T. Antioxidative effect of three water-soluble components isolated from *Salvia miltiorrhiza in vitro*. *Acta Pharmaceutica Sinica*, **1992**, *27*, 96-100.

[111] Wang, A.-M.; Sha, S.-H.; Lesniak, W.; Schacht, J. Tanshinone (*Salviae miltiorrhizae* extract) preparations attenuate aminoglycoside-induced free radical formation *in vitro* and ototoxicity *in vivo*. *Antimicrob. Agents Chemother.*, **2003**, *47*, 1836-1841.

[112] Wu, Z.-M.; Wen, T.; Tan, Y.-F.; Liu, Y.; Ren, F.; Wu, H. Effects of salvianolic acid a on oxidative stress and liver injury induced by carbon tetrachloride in rats. *Basic Clin. Pharmacol. Toxicol*., **2007**, *100*, 115-120.

[113] Kim, J.Y.; Kim, H.S.; Kang, H.S.; Choi, J.S.; Yokozawa, T.; Chung, H.Y. Antioxidant potential of dimethyl lithospermate isolated from *Salvia miltiorrhiza* (red sage) against peroxynitrite. *J. Med. Food*, **2008**, *11*, 21-28.

[114] Yang, T.-L.; Lin, F.-Y.; Chen, Y.-H.; Chiu, J.-J.; Shiao, M.-S.; Tsai, C.-S.; Lin, S.-J.; Chen, Y.-L. Salvianolic acid B inhibits low-density lipoprotein oxidation and neointimal hyperplasia in endothelium-denuded hypercholesterolaemic rabbits. *J. Sci. Food Agric*., **2011**, *91*, 134-141.

[115] Zhang, J.; Zhao, G.; Liu, J.; Ji, X. Protection of salvianolic acid B for human endothelial cells against hydrogen peroxide-induced oxidative damage. *Tianjin Daxue Xuebao*, **2009**, *15*, 434-439.

[116] Liu, C.-S.; Chen, N.-H.; Zhang, J.-T. Protection of PC12 cells from hydrogen peroxide-induced cytotoxicity by salvianolic acid B, a new compound isolated from *Radix Salviae miltiorrhizae*. *Phytomedicine*, **2007**, *14*, 492-497.

[117] Tang, Y.; Wang, M.; Le, X.; Meng, J.; Huang, L.; Yu, P.; Chen, J.; Wu, P. Antioxidant and cardioprotective effects of Danshensu (3-(3, 4-dihydroxyphenyl)-2-hydroxy-propanoic acid from *Salvia miltiorrhiza*) on isoproterenol-induced myocardial hypertrophy in rats. *Phytomedicine*, **2011**, *18*, 1024-1030.

[118] Qian, Q.; Qian, S.; Fan, P.; Huo, D.; Wang, S. Effect of *Salvia miltiorrhiza* hydrophilic extract on antioxidant enzymes in diabetic patients with chronic heart disease: a randomized controlled trial. *Phytother. Res.*, **2012**, *26*, 60-6.

[119] Wu, W.; Zhu, Y.; Zhang, L.; Yang, R.; Zhou, Y. Extraction, preliminary structural characterization, and antioxidant activities of polysaccharides from *Salvia miltiorrhiza* Bunge. *Carbohydr. Polym.*, **2012**, *87*, 1348-1353.

[120] Xiao, K.; Xuan, L.; Xu, Y.; Bai, D. Dimeric stilbene glycosides from *Polygonum cuspidatum*. *Eur. J. Org. Chem*., **2002**, *3*, 564-568.

[121] Nawrot, I. Extraction and qualitative evaluation of tannin fractions from rhizomes of Reynoutria sp., MSc thesis, Medical University in Wroclaw, June, **2009**.

[122] Xiao, K.; Xuan, L.; Xu, Y.; Bai, D.; Zhong, D. Constituents from *Polygonum cuspidatum*. *Chem. Pharm. Bull*., **2002**, *50*, 605-608.

[123] Matsuda, H.; Shimoda, H.; Morikawa, T.; Yoshikawa, M. Phytoestrogens from the roots of *Polygonum cuspidatum* (Polygonaceae): structure-requirement of hydroxyanthraquinones for estrogenic activity. *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 1839-1842.

[124] Zhang, C.; Zhang, X.; Zhang, Y.; Xu, Q.; Xiao, H.; Liang, X. Analysis of estrogenic compounds in *Polygonum cuspidatum* by bioassay and high per-

formance liquid chromatography. *J. Ethnopharmacol*., **2006**, *105*, 223-228.
[125] Su, H.-Y.; Cherng, S.-H.; Chen, C.-C.; Lee, H. Emodin inhibits the mutagenicity and DNA adducts induced by. *Mutat. Res*., **1995**, *329*, 205-212.
[126] Lee, M.S.; Cha, E.Y.; Sul, J.Y.; Song, I.S.; Kim, J.Y. Chrysophanic acid blocks proliferation of colon cancer cells by inhibiting EGFR/mTOR pathway. *Phytother. Res.*, **2011**, *25*, 833-837.
[127] Leu, Y.; Hwang, T.; Hu, J. Anthraquinones from *Polygonum cuspidatum* as tyrosinase inhibitors for dermal use. *Phytother. Res*., **2008**, *556*, 552-556.
[128] Li, Y.B.; Lin, Z.Q.; Zhang, Z.J.; Wang, M.W.; Zhang, H.; Zhang, Q.W.; Lee, S.M.Y.; Wang, Y.T.; Hoi, P.M. Protective, antioxidative and anti-apoptotic effects of 2-methoxy-6-acetyl-7-methyljuglone from *Polygonum cuspidatum* in PC12 cells. *Planta Med*., **2011**, *77*, 354-361.
[129] Hsu, C.-Y.; Chan, Y.-P.; Chang, J. Antioxidant activity of extract from *Polygonum cuspidatum*. *Biol. Res.*, **2007**, *40*, 13-21.
[130] Pan, Y.; Zhang, X.; Wang, H.; Liang, Y.; Zhu, J.; Li, H.; Zhang, Z.; Wu, Q. Antioxidant potential of ethanolic extract of *Polygonum cuspidatum* and application in peanut oil. *Food Chem.*, **2007**, *105*, 1518-1524.
[131] Wang, G.Q.; Zheng, Y.C.; Qian, Jinfang, C. In vitro antioxidant activity of anthraquinones from rhizome of *Reynoutria japonica*. *J. Plant Resour. Environ*., **2011**, *20*, 43-48.
[132] Lee, M.; Kao, L.; Lin, C. Comparison of the antioxidant and transmembrane permeative activities of the different *Polygonum cuspidatum* extracts in phospholipid-based microemulsions. *J. Agric. Food Chem.*, **2011**, *59*, 9135-9141.
[133] Hu, M.-L. Dietary polyphenols as antioxidants and anticancer agents: more questions than answers. *Chang Gung Med. J*., **2011**, *34*, 449-460.
[134] Jiang, M.; Yang, J.; Zhang, C.; Liu, B.; Chan, K.; Cao, H.; Lu, A. Clinical studies with traditional Chinese medicine in the past decade and future research and development. *Planta Med.*, **2010**, *76*, 2048-2064.
[135] Li, Y.; Wang, Y.; Yu, Q.; Wei, K.; Li, M.; Zhao, S.; Kurabayashi, Y.; Fan, J.; Liu, E. Compound Danshen dripping pills for stable angina: Meta-analysis of randomized controlled trials. *J. Med. Plant. Res.*, **2011**, *5*, 2245-2251.
[136] Feng, Y.; Cheung, K.-F.; Wang, N.; Liu, P.; Nagamatsu, T.; Tong, Y. Chinese medicines as a resource for liver fibrosis treatment. *Chinese Med*., **2009**, *4*, 16.
[137] Kummar, S.; Copur, M.S.; Rose, M.; Wadler, S.; Stephenson, J.; O'Rourke, M.; Brenckman, W.; Tilton, R.; Liu, S.-H.; Jiang, Z.; Su, T.; Cheng, Y.-C.; Chu, E. A phase I study of the chinese herbal medicine PHY906 as a modulator of irinotecan-based chemotherapy in patients with advanced colorectal cancer. *Clin. Colorectal Cancer*, **2011**, *10*, 85-96.
[138] Saif, M.W.; Lansigan, F.; Ruta, S.; Lamb, L.; Mezes, M.; Elligers, K.; Grant, N.; Jiang, Z.-L.; Liu, S.H.; Cheng, Y.-C. Phase I study of the botanical formulation PHY906 with capecitabine in advanced pancreatic and other gastrointestinal malignancies. *Phytomedicine*, **2010**, *17*, 161-169.
[139] Wang, M.; Lamers, R.-J.N.; Korthout, H.J.; van Nesselrooij, J.H.J.; Witkamp, R.F.; van der Heijden, R.; Voshol, P.J.; Havekes, L.M.; Verpoorte, R.; van der Greef, J. Metabolomics in the context of systems biology: bridging traditional Chinese medicine and molecular pharmacology. *Phytother. Res.*, **2005**, *19*, 173-182.
[140] Zhang, A.; Sun, H.; Wang, Z.; Sun, W.; Wang, P.; Wang, X. Metabolomics: towards understanding traditional Chinese medicine. *Planta Med*., **2010**, *76*, 2026-2035.
[141] Predes, F.; Ruiz, A.; Carvalho, J.; Foglio, M.; Dolder, H. Antioxidative and in vitro antiproliferative activity of *Arctium lappa* root extracts. *BMC Complement. Altern. Med*., **2011**, *11*, 25.
[142] Woo, J.H.; Shin, S.L.; Jeong, H.S.; Lee, C.H. Antioxidant effect of extracts obtained from three chrysanthemum species. *J. Korean Soc. Food Sci. Nutr.*, **2010**, *39*, 631-636.
[143] Lee, J.-S.; Kim, G.-H.; Lee, H.G. Optimization of extraction conditions for *Elsholtzia splendens* and its antioxidant activity. *J. Food Biochem*., **2012**, *in press.*
[144] Han, T.; Cheng, G.; Liu, Y.; Yang, H.; Hu, Y.; Huang, W. In vitro evaluation of tectoridin, tectorigenin and tectorigenin sodium sulfonate on antioxidant properties. *Food Chem. Toxicol*., **2012**, *50*, 409-414.
[145] Chen, J.; Hu, T. Effects of rhubarb on scavenging active oxygen. *Chinese Pharm. J*., **1996**, *31*, 461-463.
[146] Bora, K.S.; Sharma, A. The genus Artemisia: a comprehensive review. *Pharm. Biol.*, **2011**, *49*, 101-109.
[147] Carvalho, I.S.; Cavaco, T.; Brodelius, M. Phenolic composition and antioxidant capacity of six artemisia species. *Ind. Crops Prod*., **2011**, *33*, 382-388.
[148] Tai, B.H.; Jung, B.Y.; Cuong, N.M.; Linh, P.T.; Tung, N.H.; Nhiem, N.X.; Huong, T.T.; Anh, N.T.; Kim, J.A.; Kim, S.K.; Kim, Y.H. Total peroxynitrite scavenging capacity of phenylethanoid and flavonoid glycosides from the flowers of *Buddleja officinalis*. *Biol. Pharm. Bull*., **2009**, *32*, 1952-1956.
[149] Mei Shan, P.; Mi -Ran, K.; Dong Gun, L.; Yoonkyung, P.; Kyung -Soo, H.; Young -Hee, M.; Eun -Rhan, W. Antioxidative constituents from *Buddleia officinalis*. *Arch. Pharm. Res.*, **2003**, *26*, 453-457.
[150] Forester, S.C.; Lambert, J.D. The role of antioxidant versus pro-oxidant effects of green tea polyphenols in cancer prevention. *Mol. Nutr. Food Res.*, **2011**, *55*, 844-854.
[151] Kim, D.-H.; Lee, H.-J.; Oh, Y.-J.; Kim, M.-J.; Kim, S.-H.; Jeong, T.-S.; Baek, N.-I. Iridoid glycosides isolated from *Oldenlandia diffusa* inhibit LDL-oxidation. *Arch. Pharm. Res.*, **2005**, *28*, 1156-1160.
[152] Ding, H.-Y.; Chou, T.-H.; Lin, R.-J.; Chan, L.-P.; Wang, G.-H.; Liang, C.-H. Antioxidant and antimelanogenic behaviors of *Paeonia suffruticosa*. *Plant Foods Hum. Nutr.*, **2011**, *66*, 275-284.
[153] Wang, W.; Zu, Y.; Fu, Y.; Reichling, J.; Suschke, U.; Nokemper, S.; Zhang, Y. *In vitro* antioxidant, antimicrobial and anti-herpes simplex virus type 1 activity of *Phellodendron amurense* Rupr. from China. *Am. J. Chin. Med*., **2009**, *37*, 195-203.
[154] Rajkumar, V.; Guha, G.; Kumar, R.A. Antioxidant and anti-neoplastic activities of *Picrorhiza kurroa* extracts. *Food Chem. Toxicol*., **2011**, *49*, 363-369.
[155] Li, L.; Huang, Z.; Xiao, H.; Chen, X.; Zeng, J. Effect of PBNA on the NO Content and NOS Activity in Ischemia/Reperfusion Injury in the Rat Retina. In *Retinal Degenerative Diseases*; Anderson, R.E.; Hollyfield, J.G.; LaVail, M.M.; Mandal, M.N.A. Eds.; Springer New York, **2010**; Vol. 664, pp. 501-507.
[156] Feng, L.; Jia, X.; Zhu, M.-M.; Chen, Y.; Shi, F. Antioxidant activities of total phenols of *Prunella vulgaris* L. in vitro and in tumor-bearing mice. *Molecules*, **2010**, *15*, 9145-9156.
[157] Liu, G.; Ding, L.; Yang, Y.; Yang, H.; Yang, Q.; Wang, H. Antioxidative action of ent-kaurene diterpenoids. *Res. Chem. Intermed*., **2006**, *32*, 787-794.
[158] Shin, S.W.; Park, C.I.; Yang, C.H.; Park, J.-W. Protective effect of *Rehmannia glutinosa* on the UV-induced apoptosis in U937 cells. *Am. J. Chin. Med*., **2008**, *36*, 1159-1170.
[159] Choi, D.G.; Yoo, N.H.; Yu, C.Y.; de Los Reyes, B.; Yun, S.J. The activities of antioxidant enzymes in response to oxidative stresses and hormones in paraquat-tolerant *Rehmannia glutinosa* plants. *J. Biochem. Mol. Biol.*, **2004**, *37*, 618-624.
[160] Li, Y.; Han, Z.; Jiang, S.; Jiang, Y. Fast repairing of oxidized OH radical adducts of dAMP and dGMP by phenylpropanoid glycosides from *Scrophularia ningpoensis* Hemsl. *Acta Pharm. Sinica*, **2000**, *21*, 1125-1128.
[161] Demir, H.; Bali, E. Antioxidant and antimicrobial activities of *Solidago virgaurea* extracts. *Afr. J. Biotechnol*., **2010**, *8*, 274-279.
[162] Hussain, A.I.; Anwar, F.; Iqbal, T.; Bhatti, I.A. Antioxidant attributes of four Lamiaceae essential oils. *Pakistan J. Bot*., **2011**, *43*, 1315-1321.
[163] Hsu, C.-H. Antioxidant activity of extract from *Polygonum aviculare* L. *Biol. Res.*, **2006**, *39*, 281-288.
[164] Kim, S.; Gao, J.; Lee, W.-C.; Ryu, K.; Lee, K.; Kim, Y. Antioxidative flavonoids from the leaves of *Morus alba*. *Arch. Pharm. Res*., **1999**, *22*, 81-85.
[165] Kim, G.-N.; Jang, H.-D. Flavonol content in the water extract of the mulberry (*Morus alba* L.) leaf and their antioxidant capacities. *J. Food Sci.*, **2011**, *76*, C869-C873.
[166] Hou, J.; Sun, T.; Hu, J.; Chen, S.; Cai, X.; Zou, G. Chemical composition, cytotoxic and antioxidant activity of the leaf essential oil of *Photinia serrulata*. *Food Chem.*, **2007**, *103*, 355-358.
[167] Gan, R.-Y.; Kuang, L.; Xu, X.-R.; Zhang, Y.; Xia, E.-Q.; Song, F.-L.; Li, H.-B. Screening of natural antioxidants from Traditional Chinese Medicinal Plants associated with treatment of rheumatic disease. *Molecules*, **2010**, *15*, 5988-5997.
[168] Rahman, S.; Salehin, F.; Iqbal, A. In vitro antioxidant and anticancer activity of young *Zingiber officinale* against human breast carcinoma cell lines. *BMC Complement. Altern. Med*., **2011**, *11*, 76.
[169] Kumari, A.; Yadav, S.K.; Pakade, Y.B.; Kumar, V.; Singh, B.; Chaudhary, A.; Yadav, S.C. Nanoencapsulation and characterization of *Albizia chinensis* isolated antioxidant quercitrin on PLA nanoparticles. *Colloids Surf. B Biointerfaces*, **2011**, *82*, 224-232.
[170] Cai, Y.-Z.; Xing, J.; Sun, M.; Zhan, Z.-Q.; Corke, H. Phenolic antioxidants (hydrolyzable tannins, flavonols, and anthocyanins) identified by LC-ESI-MS and MALDI-QIT-TOF MS from *Rosa chinensis* flowers. *J. Agric. Food Chem*., **2005**, *53*, 9940-9948.
[171] Guleria, S.; Tiku, A.K.; Singh, G.; Vyas, D.; Bhardwaj, A. Antioxidant activity and protective effect against plasmid DNA strand Sci., ssion of leaf, bark, and heartwood extracts from *Acacia catechu*. *J. Food Sci*., **2011**, *76*, C959-C964.
[172] Zhu, L.; Tan, J.; Wang, B.; He, R.; Liu, Y.; Zheng, C. Antioxidant activities of aqueous extract from *Agrimonia pilosa* Ledeb and its fractions. *Chem. Biodivers.*, **2009**, *6*, 1716-1726.
[173] KIM, M.-J.; KIM, D.-H.; LEE, K.I.W.O.N.; YOON, D.-Y.; SURH, Y.-J. Jaceosidin induces apoptosis in ras-transformed human breast epithelial cells through generation of reactive oxygen species. *Ann. N.Y. Acad. Sci*., **2007**, *1095*, 483-495.
[174] Lan, M.-B.; Zhang, Y.-H.; Zheng, Y.; Yuan, H.-H.; Zhao, H.-L.; Gao, F. Antioxidant and immunomodulatory activities of polysaccharides from moxa (*Artemisia argyi*) leaf. *Food Sci., Biotechnol*., **2010**, *19*, 1463-1469.
[175] Salem, N.; Msaada, K.; Hamdaoui, G.; Limam, F.; Marzouk, B. Variation in phenolic composition and antioxidant activity during flower development of safflower (*Carthamus tinctorius* L.). *J. Agric. Food Chem*., **2011**, *59*, 4455-4463.
[176] Ng, T.B. Pharmacological activity of sanchi ginseng (*Panax notoginseng*). *J. Pharmacy Pharmacol.*, **2006**, *58*, 1007-1019.
[177] Xia, W.; Sun, C.; Zhao, Y.; Wu, L. Hypolipidemic and antioxidant activities of Sanchi (*Radix Notoginseng*) in rats fed with a high fat diet. *Phy-*

tomedicine, **2011**, *18*, 516-520.

[178] Lodi, S.; Sharma, V.; Kansal, L. The protective effect of *Rubia cordifolia* against lead nitrate-induced immune response impairment and kidney oxidative damage. *Indian J. Pharmacol.*, **2011**, *43*, 441-444.

[179] Cai; Sun, M.; Xing, J.; Corke, H. Antioxidant phenolic constituents in roots of *Rheum officinale* and *Rubia cordifolia*: structure−radical scavenging activity relationships. *J. Agric. Food Chem.*, **2004**, *52*, 7884-7890.

[180] Nguyen, T.T.; Cho, S.O.; Ban, J.Y.; Kim, J.Y.; Ju, H.S.; Koh, S.B.; Song, K.S.; Seong, Y.H. Neuroprotective effect of *Sanguisorbae radix* against oxidative stress-induced brain damage: *in vitro* and *in vivo*. *Biol. Pharm. Bull.*, **2008**, *31*, 2028-2035.

[181] Kang, H.S.; Chung, H.Y.; Jung, J.H.; Kang, S.S.; Choi, J.S. Antioxidant effect of *Salvia miltiorrhiza*. *Arch. Pharm. Res.*, **1997**, *20*, 496-500.

[182] Kim, H.-J.; Kim, M.-K.; Shim, J.-G.; Yeom, S.-H.; Kwon, S.-H.; Lee, M.-W. Anti-oxidative phenolic compounds from *Sophorae Fructus*. *Nat. Prod. Sci.*, **2004**, *10*, 330-334.

[183] Chang, C.L.; Lin, C.S.; Lai, G.H. Phytochemical characteristics, free radical scavenging activities, and neuroprotection of five medicinal plant extracts. *Evid. Based Complement. Alternat. Med.*, **2012**, *2012*, 984295.

[184] Rehecho, S.; Hidalgo, O.; Cirano, M. G.-I. de; Navarro, I.; Astiasarán, I.; Ansorena, D.; Cavero, R. Y.; Calvo, M. I. Chemical composition, mineral content and antioxidant activity of *Verbena officinalis* L. *LWT - Food Sci. Technol.*, **2011**, *44*, 875-882.

[185] Jeong, C.-H.; Choi, G.N.; Kim, J.H.; Kwak, J.H.; Kim, D.O.; Kim, Y.J.; Heo, H.J. Antioxidant activities from the aerial parts of *Platycodon grandiflorum*. *Food Chem.*, **2010**,*118*, 278-282.

[186] Le, K.; Chiu, F.; Ng, K. Identification and quantification of antioxidants in *Fructus Lycii*. *Food Chem.*, **2007**, *105*, 353-363.

[187] Chen, T.; Guo, Z.; Jiao, X.; Zhang, Y.; Li, J.; Liu, H. Protective effects of peoniflorin against hydrogen peroxide-induced oxidative stress in human umbilical vein endothelial cells. *Can. J. Physiol. Pharmacol.*, **2011**, *89*, 445-453.

[188] Uikey, S.K.; Yadav, A.S.; Sharma, A.K.; Rai, A.K.; Raghuwanshi, D.K.; Badkhane, Y. The botany, chemistry, pharmacological and therapeutic application of *Psoralea corylifolia* L. - A review. *Int. J. Phytomed.*, **2010**, *2*, 100-107.

[189] Xiao, G.; Li, G.; Chen, L.; Zhang, Z.; Yin, J.-J.; Wu, T.; Cheng, Z.; Wei, X.; Wang, Z. Isolation of antioxidants from Psoralea corylifolia fruits using high-speed counter-current chromatography guided by thin layer chromatography-antioxidant autographic assay. *J. Chromatogr. A*, **2010**, *1217*, 5470-5476.

[190] Xia, D.; Shi, J.; Gong, J.; Wu, X.; Yang, Q.; Zhang, Y. Antioxidant activity of Chinese mei (*Prunus mume*) and its active phytochemicals. *J. Med. Plant Res.*, **2010**, *4*, 1156-1160.

[191] Djakpo, O.; Yao, W. Rhus chinensis and Galla Chinensis - Folklore to modern evidence: Review. *Phytother. Res.*, **2010**, *24*, 1739-1747.

[192] Xiao, K.-J.; Zhong, X.-K.; Wang, J.; Jiang, J.-G. Extraction of brown pigment from *Rosa laevigata* and its antioxidant activities. *Pharm. Biol.*, **2011**, *49*, 734-740.

[193] Ding, H.-Y. Extracts and constituents of *Rubus chingii* with 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity. *Int. J. Mol. Sci.*, **2011**, *12*, 3941-3949.

[194] Ponou, B.K.; Teponno, R.B.; Ricciutelli, M.; Quassinti, L.; Bramucci, M.; Lupidi, G.; Barboni, L.; Tapondjou, L.A. Dimeric antioxidant and cytotoxic triterpenoid saponins from *Terminalia ivorensis* A. Chev. *Phytochemistry*, **2010**, *71*, 2108-15.

[195] Kaisar, A.; Islam, M.R.; Rahman, M.S.; Hossain, K.; Rashid, M. . Total phenolic content, free radical scavenging activity and reducing power of *Quisqualis indica* Linn. *J. Pharm. Sci.*, **2009**, *8*, 173-175.

Received: July 26, 2012 **Revised: October 04, 2012** **Accepted: October 09, 2012**