NPC Natural Product Communications

2011
Vol. 6
No. 8
1205 - 1215

Biological Activity of Bicyclic and Tricyclic Diterpenoids from *Salvia Species* of Immediate Pharmacological and Pharmaceutical Interest

Maria Carmela Bonito[a], Carla Cicala[a], Maria Carla Marcotullio[b], Francesco Maione[a] and Nicola Mascolo[a*]

[a]*Department of Experimental Pharmacology, University of Naples Federico II, via Domenico Montesano 49, 80131 Naples, Italy*

[b]*Department of Pharmaceutical Chemistry and Technology, University of Perugia, via del Liceo 1, 06123 Perugia, Italy*

nicola.mascolo@unina.it

This paper is dedicated to the memory of Professor Ludovico Sorrentino

Received: February 3rd, 2011; Accepted: May 12th, 2011

Diterpenoids are a class of compounds that derive from the condensation of four isoprene units that leads to a wide variety of complex chemical structures, including acyclic bi-, tri-and tetra-cyclic compounds; in *Salvia* species, only bi-, tri-and tetra-cyclic compounds have been found. This review covers a wide range of biological activities and mode of action of diterpenoids isolated from *Salvia* species that might raise some pharmacological and pharmaceutical interest.

We have produced a synoptic table where the biological activities of the main active principles are summarized. Our analysis emphasizes that diterpenoids from *Salvia* species continue to be a plant defence system since their antimicrobic activity. Experimental studies show that most of diterpenoids considered have cytotoxic and / or antiproliferative activity. Some of them have also cardiovascular and central effects. In a less extended manner, diterpenoids from *Salvia* species show gastrointestinal, urinary, antinflammatory, antidiabetic, ipolipidemic and antiaggregating effects.

In the last decade, several clinical trials have been developed in order to investigate the real value of *Salvia* extracts treatment; results obtained are promising and confer scientific basis in the use of medicinal plants from folk medicine.

Keywords: Lamiaceae; *Salvia* species; terpenoids; diterpenoids; biological activities; natural compounds.

Introduction

Salvia genus, belonging to the Lamiaceae or Labiatae family, is composed of about 900 species. The plants are typically herbaceous or suffruticose and are mostly perennial. Although *Salvia* species are common throughout the world, they are most concentrated in temperate and subtropical regions [1].

The name *Salvia* comes from the Latin word *salvare*, verb salvare (to heal or to save), in reference to the well known curative properties of this specie. The Salerno Medical School (11th and 12th centuries), depositary of ancient medical knowledge, considered this plant to be the miracle herb par excellence and named it *Salvia salvatrix.* Later, in the middle of the '700, the Swedish biologist and naturalist Linneo (father of binomial nomenclature for the systemic classification of plants and animals) assigned the name *officinalis* to this plant. In folk medicine, *Salvia* species have been used to treat cold, bronchitis, tuberculosis, haemorrhage and menstrual disorders [2]. Today, there is a great interest in the study of biological properties of terpenes that are the main secondary metabolites of the plants of the genus *Salvia.* They include a wide range of di-, tri-, sesqui- and tetraterpenoids; most of them have been investigated for their pharmacological activities.

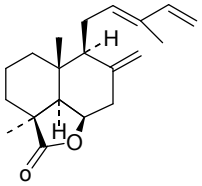
This review begins with the presentation of the major bi- and tricyclic secondary metabolites of several *Salvia* species, such as *S. leriaefolia*, *S. divinorum*, *S. splendens*, *S. leucantha*, *S. jamensis*, *S. polystachia*, *S. officinalis*, *S. alfricana-lutea*, *S. microphylla*, *S. sclarea*, *S. yunnanensis*, *S. prionitis*, *S. miltiorrhiza*, *S. przewalskii*, *S. lanigera*, *S. broussonetii*, *S. gilliessi*, *S. corrugate*, *S. pubescens*, *S. cinnabarina and S. hispanica*, that might raise pharmacological and pharmaceutical interest.

Diterpenoids Found in *Salvia* Species

Diterpenoids or diterpenes are compounds of plant and animal origin [3] and derive from condensation of four isoprene units that leads to a wide variety of complex chemical structures, including acyclic bi-, tri-and tetra-cyclic compounds; in *Salvia* species, only bi-, tri-and tetra-cyclic compounds have been found.

Bi-cyclic diterpenoids

Bi-cyclic diterpenoids from *Salvia* species are classified in labdanes and clerodanes types. The only labdane diterpenoid, 8 (17),12 *E*,14-labdatrien-6,19-olide (Figure 1), obtained from the chloroform extract of *Salvia leriaefolia*, has shown antimicrobial activity against the Gram-positive bacterium *Staphylococcus aureus* [4,5].



8(17),12 *E,*14-labdatrien-6,19-olide

Figure 1. A labdane diterpenoid from Salvia leriaefolia

Several clerodane diterpenoids have been isolated from *Salvia divinorum* (Figure 2), among them there are salvinorin A, divinatorin and salvinicin A [6]. All clerodanes from *Salvia divinorum* have been evaluated for their central effects, since hallucinogenic *Salvia divinorum* has been used as recreational drug. It has been demonstrated that most of clerodanes, such as salvinorin A, salvinorin B, salvinorin G, divinatorin D have agonistic activity to opioid receptor since they display significant binding at the Gαi-coupled human κ opioid receptor (KOR), salvinorin A being the most potent [7-9]. On the contrary, for salvinicin A and salvinicin B (Figure 2), other clerodanes found in *Salvia divinorum*, it has been described a partial agonistic activity on k opioid receptor and an antagonistic activity on μ opioid receptor, respectively [10].

Four clerodane compounds, salvisplendins A-D (Figure 3), isolated from *Salvia splendens* [11], have been tested for their affinity for human μ, δ and κ opioid receptors but none of them showed high affinity binding [12].

Recently, Capasso *et al*. [13,14] have shown that salvinorin A reduces inflammation – induced intestinal hypermotility in mice, revealing a functional interaction not only with KORs receptors but also with cannabinoid CB1 receptors. Salvileucalin B (Figure 4), a clerodane diterpenoid from *Salvia leucantha,* has shown cytotoxic activity in A549 (carcinomic human alveolar basal epithelial cells) and HT-29 (human colon adenocarcinoma) cell lines [15] while, 15,16-epoxy-cleroda-3-en-7α,10β-dihydroxy-12,17,19,18-diolide (Figure 4), a clerodane diterpenoids from *Salvia jamensis* has been found to increase adenosine-5'-diphosphate (ADP) – induced platelet aggregation *in vitro* [16]. Linearolactone (Figure 5), a clerodane diterpenoid isolated from *Salvia polystachia,* has shown to have antiprotozoal activity *in vitro* against *Entamoeba histolytica* and *Giardia Lamblia*, with IC_{50} of 22.9 and 28.2 μM respectively [17].

Tri-cyclic diterpenoids

Tri-cyclic diterpenoids, isolated from *Salvia* species, are classified in abietane and pimarane diterpenoids.

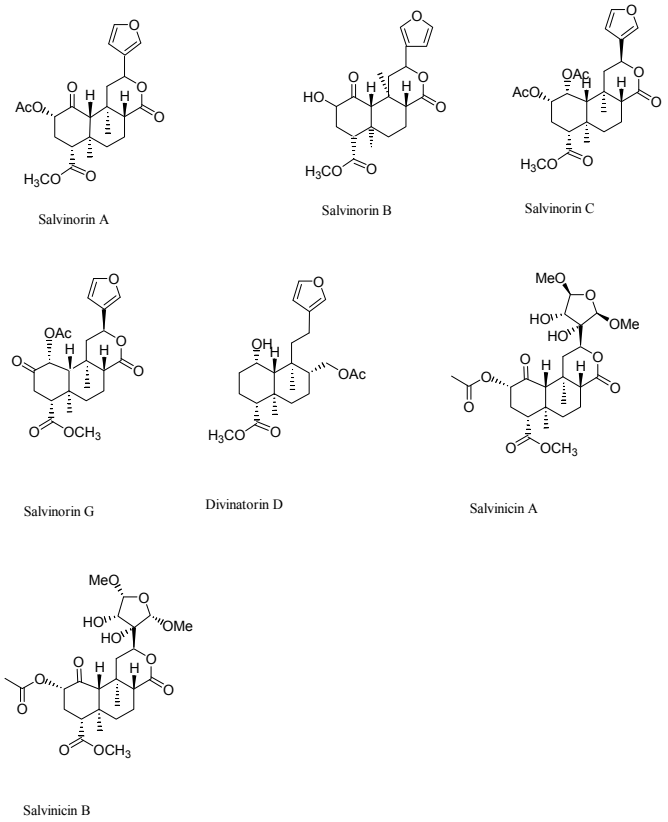
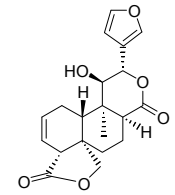
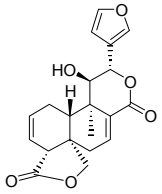


Figure 2. Clerodane diterpenoids from *Salvia divinorum*

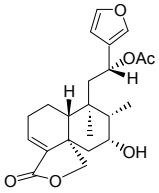
Abietane-type are further classified as phenolic, quinonic and icetaxane. It is know that phenolic diterpene compounds, including carnosic acid, carnosol, ferruginol, 7-methoxyrosmanol and galdosol (Figure 6), obtained from *Salvia* species, exhibit a variety of biological activities [2]. Experimental studies have demonstrated that carnosic acid and carnosol from *S. officinalis* and *S. africana-lutea* inhibited pancreatic lipase activity; however, only carnosic acid was able to inhibit serum triglyceride elevation in olive oil loaded mice [18]. Both compounds are activators of the human peroxisome proliferator-activated receptor gamma (PPAR-γ) and this activation increases the transcription of enzymes involved in primary metabolism, leading to low blood levels of fatty acids and glucose [19]. Carnosic acid and carnosol have



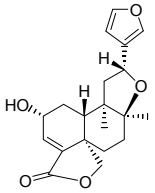
Salvisplendin A



Salvisplendin B

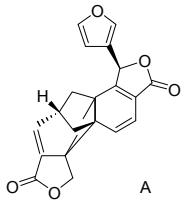


Salvisplendin C



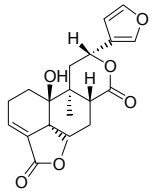
Salvisplendin D

Figure 3. Clerodanes from *Salvia splendens*



A

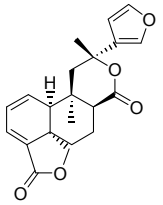
Salvileucalin B



B

15,16-epoxy-cleroda-3-en-7alpha,10beta-dihydrox y-12,17,19,18-diolide

Figure 4. Clerodane diterpenoids from *Salvia leucantha* (A) and from *Salvia Jamensis* (B)



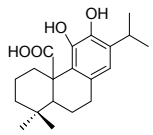
Linearolactone

Figure 5. A clerodane diterpenoid isolated from *Salvia polystachya*

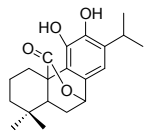
also shown pronounced antioxidant and anti-inflammatory effects. They inhibited pro-inflammatory leukotriene production in intact human polymorphonuclear leukocytes (PMNL) and they both potently antagonised intracellular Ca^{2+} mobilisation induced by a chemotactic stimulus [20].

Furthermore, carnosic acid from *Salvia africana-lutea* have shown antimicrobial activity exhibiting a MIC of 28 μM, against *Mycobacterium tuberculosis* and also cytotoxic activity against a breast human cancer cell line (MCF-7), with an IC_{50} of 69 μM [21]. In another study, carnosol from *Salvia officinalis* showed a weak antimicrobial activity; however, it is worth noting that it was able to greatly reduce MICs of various aminoglycosides and of some other types of antimicrobial agents in vancomycin-resistant enterococci, having a synergistic effect. A similar activity was also shown for carnosic acid [22]. A diterpene, carnosic acid 12-methyl ether (12-methoxycarnosic acid; Figure 6), isolated from the acetone extract of *Salvia microphylla*, possesses antimicrobial activity against *Staphylococcus aureus* [23]. 7-methoxyrosmanol and galdosol (Figure 6), isolated from *Salvia officinalis,* might have a potential activity on Central Nervous System (CNS) since their ability to bind the benzodiazepine receptor [24].

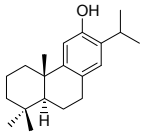
Ferruginol (Figure 6), isolated from *Salvia sclarea,* has been shown to possess bacteriostatic and bactericidal activity for the cultures of *Staphylococcus aureus* and *Staphylococcus epidermidis* [25].



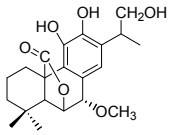
Carnosic acid



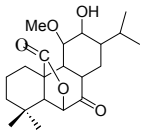
Carnosol



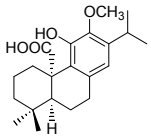
Ferruginol



7-methoxyrosmanol



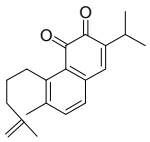
Galdosol



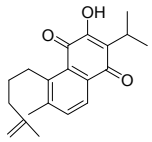
12-methoxycarnosic acid

Figure 6. Abietane type phenolic diterpenoids from different *Salvia species*

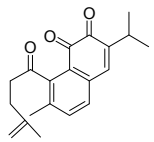
Among abietane-quinone type diterpenoids, aethiopinone, salvipisone, 1-oxoaethiopinone (Figure 7) obtained from *Salvia sclarea,* such as already described for ferruginol, have been shown to be bacteriostatic as well as bactericidal for the cultures of *Staphylococcus aureus* and *Staphylococcus epidermidis* [25,26].



Aethiopinone



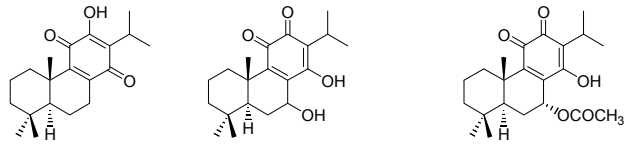
Salvipisone



1-oxoaethiopinone.

Figure 7 Abietane-quinone type diterpenoids from *Salvia sclarea*

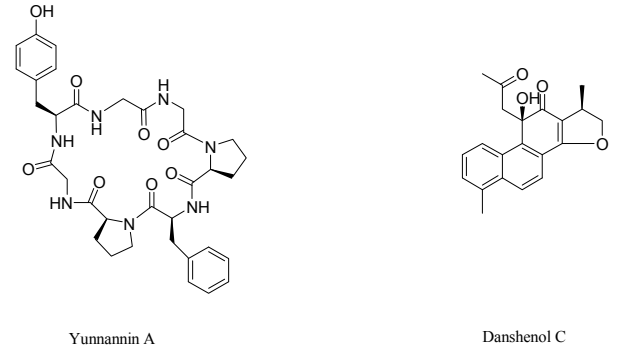
Royleanone, horminone and acetyl horminone (Figure 8), three abietanes quinoni isolated from *Salvia officinalis*, have been shown to have cytotoxic activity on human colonic carcinoma cells (Caco2) and human hepatoma cells (Hep G2) by damaging DNA; however, the underlying mechanism still needs to be clarified [27].



Royleanone Horminone Acethylhorminone

Figure 8. Abietane-quinoni from *Salvia officinalis*

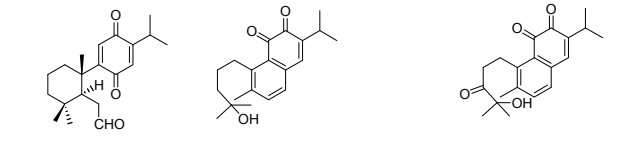
Other two abietane-quinone type diterpenoids, yunnannin A and danshenol C (Figure 9), isolated from *Salvia yunnanensis*, have shown antitumor activity when tested on several human cancer cell lines, T-24 (bladder carcinoma), K562 (erythromyeloblastoid leukaemia), Me180 (cervical cancer) and BIU87 (bladder cancer) [28].



Yunnannin A Danshenol C

Figure 9. Abietane-quinone from *Salvia yunnanensis*

Among abietane diterpene derivatives isolated from *Salvia prionitis*, compounds 7,8 – seco-para-furruginone has antimicrobial activity against *Staphylococcus aureus* and *Mycrococcus luteus*; 4-hydroxysaprorthoquinone has an inhibitory effect on topoisomerase I and the last, 3–keto-4-hydroxysaprorthoquinone (Figure 10), has shown cytotoxic activities against HL-60 human leukaemia cells and the SGC-7901 and MK-28 stomach cancer cell lines [29].



7,8-seco-para-ferruginone 4-Hydroxysaprorthoquinone 3-Keto-4-hydroxysaprorthoquinone

Figure 10. Abietane diterpene derivatives isolated from *Salvia prionitis*

Several quinone diterpenoids that have biological activity have been found in *Salvia miltiorrhiza,* used as therapeutic remedy in chinese traditional medicine [30]. Tanshinones (Figure 11) are the most bioactive compounds and their biological activities have been extensively investigated [31]. A recent study [32] has shown the anticancer activity of tanshinones, an effect associated to their ability to inhibit hypoxia-inducible factor-1 (HIF-1) accumulation. Authors report that sibiriquinone A, sibiriquinone B, cryptotanshinone and dihydrotanshinone I potently inhibit HIF-1 expression on AGS cells, a human gastric cancer cell line, and on Hep3B cells, a human hepatocarcinoma cell line. This finding has led to hypothesize an anticancer activity of these compounds since HIF-1 has been implicated in cancer cell proliferation [33].

Furthermore, recently, anti-cancer activity of tanshinone I (Figure 11) has also been reported by investigating the *in vitro* effect of tanshinone I on the induction of apoptosis in human breast cancer cells, MCF-7, oestrogen receptor positive, and MDA-MB-231, oestrogen receptor negative. Tanshinone I inhibited cell proliferation of both cell lines, MCF-7 and MDA-MB-231, in a concentration- and time-dependent fashion and significantly induced apoptosis of these cells. The effect was associated to the activation of caspase 3 and to the altered ratio between Bcl-2 and Bax protein levels [34]. Indeed, the Bcl-2 and Bax genes have been reported to be linked with the regulation of programmed cell death; in response to apoptotic stimuli, Bax oligomerizes and translocates to the outer mitochondrial membrane where it induces mitochondrial membrane permeabilization and cytochrome C release. Overexpression of the anti-apoptotic protein, Bcl-2, has been found to stabilize the outer membrane and to prevent the release of cytochrome C following a variety of insults [35].

Another work shows that tanshinone I significantly reduces adhesion of either monocyte U937 or MDA-MB-231 cells to human umbilical vein endothelial cells (HUVECs), by inhibiting ICAM-1 and VCAM-1 expressions in HUVECs. In addition, tanshinone I effectively inhibits TNFα-induced production of vascular endothelial growth factor (VEGF) and VEGF-mediated tube formation in HUVECs. Tanshinone I also inhibits TNFα -induced VEGF production in MDA-MB-231 cells and migration of MDA-MB-231 cells through extracellular matrix. Additionally, reduction of tumour mass volume and decrease of metastasis incidence by tanshinone I was observed *in vivo* [36].

A recent study performed, *in vitro*, on the highly invasive human lung adenocarcinoma cell line, CL1-5, and, *in vivo*, on genetically immunodeficient mice bearing CL1-5, shows that tanshinone I is able to significantly reduce tumorigenesis and metastasis through a mechanisms involving platelet derived growth factor β (PDGF –β) signal and its downstream pathway [37].

The effects of tanshinone derivatives (tanshinone I, cryptotanshinone, 15,16-dihydrotanshinone I) on prostaglandin (PG) and nitric oxide (NO) metabolism were also reported. Jeon *et al*. [38] have recently demonstrated

that cyclooxygenase-2 (COX-2)-mediated PGE_2 production, from lipopolysaccharide-treated RAW 264.7 cells, is inhibited by tanshinone I, cryptotanshinone and 15,16-dihydrotanshinone I (Figure 11), while only cryptotanshinone and 15,16-dihydrotanshinone I inhibit inducible NO synthase (iNOS)-mediated NO production and the activation of the transcription factors, such as nuclear transcription factor-kB (NFkB) and activator protein-1 (AP-1). Furthermore, cryptotanshinone down-regulates proinflammatory molecule expression, such as COX-2 and iNOS and, *in vivo*, it inhibits carrageenin – induced rat paw oedema, a well known inflammation model sustained by arachidonic acid metabolites [38]. Jin and co-workers [39] have shown that cryptotanshinone protects rats from myocardial ischemia – reperfusion injury by inhibiting inflammatory cytokine production, adhesion molecule expression and neutrophil migration.

Tanshinone IIA (Figure 11), a diterpene quinone extracted from *Salvia miltiorrhiza,* has been reported to have apoptotic inducing effects on a large variety of cancer cells with a mechanism involving the activation of caspase-3, down regulation of anti-antiapoptotic protein Bcl-2 and Bcl-xl and the up regulation of pro-apoptotic protein Bax [40], similarly to tanshinone I. A study performed on HeLa cell, a human epithelial carcinoma cell line, highly proliferative, has shown that in comparison with other anti-cancer drugs causing mitotic arrest by interfering with the microtubule structure (such as vincristine or taxol), tanshinone IIA destroys only the mitotic spindle during the M phase but not the microtubule structure in interphase cells [41]. More recently, Liu and co-workers [42] have confirmed the pro-apoptotic effect of tanshinone IIA on leukaemia THP-1 cell line; also in this case the effect is associated to Bcl-2 destruction and Bax up regulation.

In another work, Kim *et al*. [43] have shown that tanshinone IIA (Figure 11) completely inhibits osteoclastogenesis, indicating a correlation between *Salvia miltiorrrhiza* extract-inhibitory effect on osteoporosis and its chemical metabolites.

Several authors have extensively described cardiovascular beneficial effects of tanshinone IIA; it protects cardiac myocytes against oxidative stress-triggered damage and apoptosis [44] and reduces macrophage death induced by hydrogen peroxide by up regulating glutathione peroxidase [45]. Tanshinone IIA decreases the transcription level of microsomal triglyceride transfer protein gene, suggesting that it inhibits apoprotein B (ApoB) secretion via a proteasome-dependent pathway [46]. Recently, it has also been reported that tanshinone I, tanshinone IIA and 15,16-dihydrotanshinone I, from *Salvia miltiorrhiza*, enhance the activity of insulin on the tyrosine phosphorylation of the insulin receptor (IR) β-subunit and the activation of the downstream kinases signalling *in vitro* in chinese hamster ovary cells expressing human insulin receptors; furthermore, the three tanshinones stimulate glucose transporter 4 (GLUT4) translocation on adipocytes [47].

Tanshinone IIA has been shown to reduce atheroma in a rabbit model of atherosclerosis induced by high fat diet through a mechanism dependent on matrix metalloproteinases-2 and -9 (MMP-2 and MMP-9) expression down regulation, and to reduce serum levels of vascular cell adhesion molecule-1 (VCAM-1) and IL-1β [48].

Tanshinone IIA inhibits human aortic smooth muscle cell (HASMC) migration suggesting a beneficial effect in vascular remodelling triggered by several diseases [49].

Furthermore, tanshinone IIA has been shown to relax rat coronary artery *in vitro* with an endothelium dependent mechanism [50]; it has also a beneficial effect in a rat model of myocardial infarction [51].

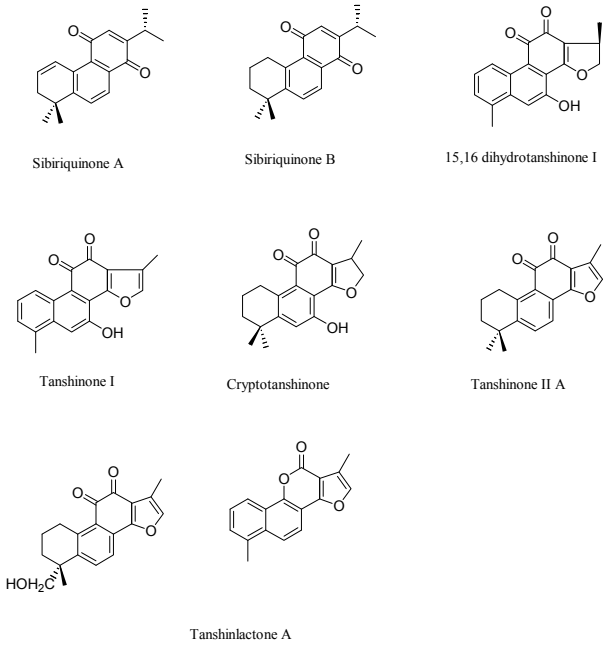


Figure 11. Tanshinones from *Salvia miltiorrhiza*

In order to investigate on compounds responsible for the vascular activity of the lipophilic fraction of *Salvia milthiorriza* and *Salvia przewalskii,* Wan *et al*. [52] performed an *in vitro* study on tanshinone IIA and criptothanshinone, that are present in both Salvia species, and on przewaquinone A (Figure 12), that is found only in *Salvia przewalskii*. They found that all three compounds were able to inhibit contraction of the isolated porcine coronary artery in response to the thromboxane A_2 analogue, U46619; however, the most active was przewaquinone A. Authors conclude that przewaquinone A is the most responsible for the vasorelaxant effect of the *Salvia przewalskii.*

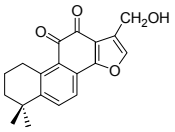
Tanshinone IIA and cryptotanshinone have also shown to have metabolic effect; indeed, they are able to induce CYP3A4 at transcriptional level, by activating human pregnane X receptor (PXR) on HepG2 cells [53].

Tanshinone IIB (Figure 11), a major active constituent from *Salvia miltiorrhiza*, whose roots are used in the treatment of acute stroke [54,55], protects rat brain from damage induced by experimental stroke, *in vivo* [56]. Successively, it has been demonstrated that tanshinone IIB inhibits apoptosis of rat primary cortical cells induced by staurosporine *in vitro*, suggesting a possible neuroprotective activity [57].

Tanshinone congeners, such as tanshinone I, tanshinone IIA, cryptotanshinone and 15,16-dihydrotanshinone I, significantly reverse scopolamine-induced cognitive impairments and ameliorate diazepam induced memory impairments in mice. The effect of cryptotanshinone and 15, 16-dihydrotanshinone I seems to be related to an increase of cholinergic signalling though acethylcholinesterase (AchE) inhibition; while, the effect of tanshinone I and tanshinone IIA, that do not affect AchE, has been speculated to be dependent on their ability to bind GABAA/benzodiazepine receptor [58]. More recently, it has been shown that tanshinone I enhance learning and memory in mice by activating extracellular signal-regulated kinase (ERK) / cAMP response element-binding (CREB) signalling [59].

Cryptotanshinone has been shown to modulate amyloid precursor protein metabolism and to attenuate beta-amyloid deposition through an up regulation of alpha-secretase activity, suggesting a protective role in Alzheimer disease [60].

Another compound named tanshinlactone A (Figure 11) was isolated from *Salvia miltiorrhiza* [61]. By an *in vitro* study performed on human peripheral blood mononuclear cells (PBMC) stimulated with phytohemagglutinin, it has been reported that tanshinlactone A has an antiproliferative effect; it reduces mitogen-activated protein kinases (MAPK) activation and interleukin-2 (IL-2) and interferon-gamma (IFN-γ) production suggesting a possible immunomodulatory activity [62].



Przewaquinone A

Figure 12. A tanshinone from *Salvia przewalskii*

Several compounds, deriving from abietane skeleton rearrangements, are named icetaxanes (Figure 13). Most of them possess activity against several strains of pathogens. The icetaxan lanigerol, from *Salvia lanigera,* is active against *Bacillus subtilis* and *Mycobacterium luteus* [63]. Brussonol, from Salvia broussonetii, was found to exert moderate citotoxicity against insect Sf9 cells [64,65]. 5-epi-icetexone, from *Salvia gilliessi,* has been found to exert an antiproliferative against *Trypanosoma cruzi* with low toxicity, only at very high concentration (more than 4.2 μM) for mammalian cells [66,67]. Two new icetaxane diterpenes quinones, fruticuline A and demethylfruticuline A (Figure 13), have been obtained from *Salvia corrugata*. In a recent work from Bisio *et al*. [68] the antibacterial activity of both compounds has been evaluated against 46 pathogens; it has been demonstrated that demethylfruticulin A is highly bactericidal against *Staphylococcus aureus* and *S. epidermidis* and bacteriostatic against *Enterococcus faecalis* and *E. faecium*. Fruticuline A manifests only bacteriostatic activity but against all strains tested [68].

Furthermore, demethylfruticulin A has been shown to induce a special form of apoptosis, named "anoikis", of mammalian cell line [69].

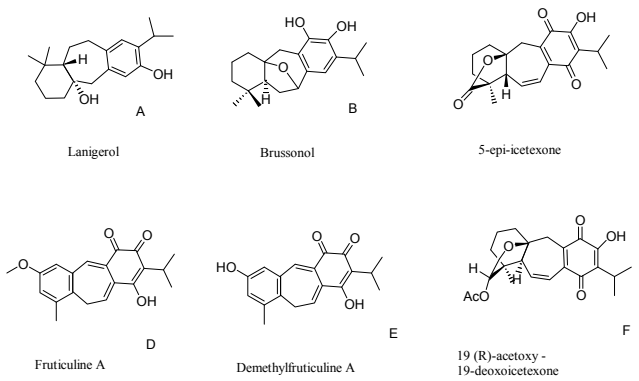


Figure 13. Icetaxanes isolated from *Salvia lanigera* (A), *Salvia broussonetii* (B), *Salvia gilliessi* (C), *Salvia corrugata* (D and E) and from *Salvia pubescens* (F).

Another icetaxane, the compound 19(R)-acetoxy-19-deoxoicetexone (Figure 13), has been isolated from *Salvia pubescens* and displays moderate antibacterial activity against *Escherichia coli* [65,70].

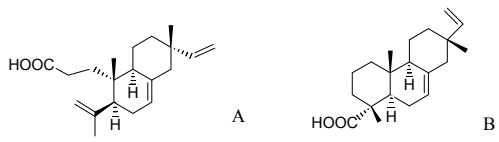


Figure 14. Abietane type phenolic diterpenoids from *Salvia cinnabarina* (A) and *Salvia jamensis* (B).

Among tri-cyclic diterpenoids with pimarane skeleton a new diterpenoid, the compound 3,4-secoisopimar-4(18),7,15-triene-3-oic acid (Figure 14), has been recently isolated from *Salvia cinnabarina.* 3,4-secoisopimar-4(18),7,15-triene-3-oic acid has intestinal spasmolytic activity *in vitro*, in rat, with an aspecific mechanism [71]. Successively, studies *in vivo*, have shown that the same compound inhibits mouse intestinal motility with a mechanism involving L-type Ca^{2+} channels [72] and, *in vitro*, it inhibits rat bladder contractility with the partial involvement of nitric oxide [73]. In addition, 3,4-secoisopimar-4(18),7,15-triene-3-oic acid has been shown to possess a weak hypotensive activity in vivo in rats [74]

and pronounced CNS depressant properties, manifested as sedation and anxiolytic effects [75]. More recently, the above secoisopimarane diterpenoid has been shown to be antimutagenic in Ames test [76].

Another compound with a pimarane skeleton, isopimaric acid (Figure 14), has been isolated from *Salvia jamensis* and it has been shown to inhibit ADP-induced rat platelet aggregation *in vitro* and to have phytotoxic activity against *Papaver rhoes* and *Avena sativa* [16,77].

Concluding Remarks

It is known that plants have played an important part in the development of new drugs and it is estimated that at least 25 % of the molecules currently used as prescribed drugs originate, directly or indirectly, from plant sources [78]. Efforts direct to obtain the active principle(s) from plants of genus *Salvia* have led to identify a class of compounds of diterpenoid and triterpenoid structures. Here, we have summarized the main diterpenoids from several *Salvia* species and their main biological activities.

Vegetal drugs might represent a precious source of therapeutically active substances, especially in those countries that reveal a strong vitality of traditional medicine, such as China, India and Japan. However, nowadays a renewed interest for vegetal drugs all around the world has been growing. Several clinical trials have been performed in order to confirm findings obtained from experimental studies and to evaluate the therapeutic potential of *Salvia* species. However, most of the clinical studies have investigated the effect of several *Salvia* species extracts. In the last ten years, clinical studies have

Table 1: Synoptic diagram of the biological activities of diterpenoids from Salvia species.

	antimicrobial	KOR agonist	μOR antagonist	GI effects	Urinary bladder effect	Cytotoxicity/anticancer activity	Antimutagenic effect	Abtiproliferative effect	Platelet aggregation	Serum fatty acids lowering effect	Blood Glucose Lowering effect	antioxidant	antinflammatory	CNS effects	Benzodiazepine receptor affinity	osteoclastogenesis	Cardiovascular effects
8(17),12E,14-labdatrien-6,19-olide	●																
Salvinorin A		●		●													
Salvinorin B		●															
Salvinorin G		●															
Divinatorin D		●															
Salvinicin A			●														
Salvinicin B			●														
Salvileucalin B						●											
15,16-epoxy-cleroda-3-en-7α,10β-dihydroxy-12,17,19,18-diolide									●								
Linearolactone	●																
Carnosic acid	●									●	●	●	●				
Carnosol	●									●	●	●	●				
Ferruginol	●																
7-methoxyrosmanol															●		
Galdosol															●		
12-methoxycarnosic acid	●																
aethiopinone	●																
1-oxoaethiopinone	●																
Salvipisone	●																
Royleanone						●											
Horminone						●											
Acetyl horminone						●											
Yunnannin A						●											
Danshenol C						●											
7,8-seco-para-furruginone	●																
4-hydroxysaprorthoquinone						●											
Sibiriquinone A						●											
Sibiriquinone B						●											
Cryptotanshinone						●							●	●			●
15,16 dihydrotanshinone I						●							●	●			
Tanshinone I						●							●	●	●		
Tanshinone IIA						●				●	●			●	●	●	●
Przewaquinone																	●
Tanshinone II B																	●
Tanshinlactone A								●									
Brossonol	●																
5-epi-icetexone	●																
Fruticuline A	●																
Demethylfruticuline A	●																
19(R)-acetoxy-19-deoxoicetexone	●																
3,4-secoisopimar-4(18),7,15-triene-3-oic acid				●	●		●							●			●

shown the potential therapeutic effects of *Salvia miltiorrhiza*, *Salvia officinalis* and *Salvia hispanica* for cardiovascular diseases [79-87]; for cognitive diseases [88-92]; for traumatic and inflammatory diseases [84,93-98]; for liver diseases [99-102]; for cancer [103]; for hypercholesterolemia [104]; in organ transplantation [105] and for treating vasovagal syncope [106] but there are only few trials evaluating the effect of active principles contained into the vegetal drugs. Among diterpenoids from *Salvia* species, the lipidic fraction of *Salvia officinalis*, rich in phenolic diterpenes, carnosic acid and carnosol (Figure 6), has been shown to protect from ultraviolet ray – induced skin erythema in volunteers [107]. More recently, sulphotanshinone, a semi synthetic derivative, have been analyzed in patients affected by angina pectoris [108]. Anyway, in the table (Table 1) we have made a synopsis of the biological activity of the diterpenes from *Salvia* species; as expected the antimicrobic activity and the cytotoxic activity are the most recurrent following by cardiovascular and antinflammatory activities.

In conclusion, diterpenoids from *Salvia* species continue to be a plant defence system and some of them are going to be promising candidates for the development of new therapeutic agents.

References

[1] Kintzios SE. (**2000**) *Sage: The Genus Salvia.(Ed)*. Kintzios SE. Harwood Academic Publishers, Amsterdam pp. 1-296.

[2] Topçu G. (**2006**) Bioactive triterpenoids from *Salvia* species. *Journal of Natural Products*, ***69***, 482-487.

[3] Capasso F, De Pasquale R, Grandolini G, Mascolo N. (**2000**) *Farmacognosia.* (Ed). Springer-Verlag Italia, Milano 1-189.

[4] Habibi Z, Fereshteh E, Keivandokht S, Abdolhossein R. (**2000**) Structure and antibacterial activity of a new labdane diterpenoid from *Salvia leriaefolia. Journal of Natural Products*, ***63***, 270-271.

[5] Rustaiyan A, Masoudi S, Tabatabaei-Anaraki M. (**2007**) Terpenoids from Iranian *Salvia species. Natural Product Communications*, ***2***,1031-1042.

[6] Hanson JR. (**2007**) Diterpenoids. *Natural Product Reports*, ***6***,1332-1341.

[7] Roth BL, Baner K, Westkaemper R, Siebert D, Rice KC, Steinberg S, Ernsberger P, Rothman RB. (**2002**) Salvinorin A: A potent naturally occurring non nitrogenous kappa opioid selective agonist. *Proceedings of the National Academy of Sciences*, ***99***, 11934-11939

[8] Chavkin C, Sud S, Jin W, Stewart J, Zjawiony J, Siebert DJ, Toth BA, Hufeisen SJ, Roth BL. (**2004**) Salvinorin A, an active component of the hallucinogenic sage *Salvia divinorum* is a highly efficacious kappa-opioid receptor agonist: Structural and functional considerations. *Journal of Pharmacology and Experimental Therapeutics*, ***308***, 1197-1203.

[9] Lee DYW, Ma Z, Liu C, Lee Y, Wang Y, Chen Y, Carlezon WA, Cohen B. (**2005**) New neoclerodane diterpenoids isolated from the leaves of *Salvia divinorum* and their binding affinities for human kappa - opioid receptors. *Bioorganic and Medicinal Chemistry,* ***13***, 5635-5639.

[10] Shirota O, Nagamatsu K, Sekita S. (**2006)** Neo-clerodane diterpenes from the hallucinogenic Sage *Salvia divinorum. Journal of Natural Products*, ***69***, 1782-1786.

[11] Fontana G, Savona G, Rodríguez B. (**2006**) Clerodane diterpenoids from *Salvia splendens*. *Journal of Natural Products*, ***69***, 1734-1738.

[12] Fontana G, Savona G, Rodríguez B, Dersch CM, Rothman RB, Prisinzano TE. (**2008**) Sintetic studies of neoclerodane diterpenoids from *Salvia splendens* and evaluation of opioid receptors affinity. *Tetrahedron*, ***64***, 10041-10048.

[13] Capasso R, Borrelli F, Zjawiony JK, Kutrzeba L, Aviello G, Capasso F, Izzo AA. (**2008**) The hallucinogenic herb *Salvia divinorum* and its active ingredient salvinorin A reduce inflammation-induced hypermotility in mice. *Neurogastroenterology Motility*, ***20***, 142-148.

[14] Capasso R, Borrelli F, Cascio MG, Aviello G, Huben K, Zjawiony JK, Marini P, Romano B, Di Marzo V, Capasso F, Izzo AA. (**2008**) Inibitory effect of salvinorina A, from *Salvia divinorum,* on ileitis-induced hypermotility: cross-talk between kappa-opioid and cannabinoid CB(1) receptors. *British Journal of Pharmacology*, ***155***, 681-689.

[15] Aoyagi Y, Yamazak A, Nakatsugawa C, Fukaya H, Takeya K, Kawauchi S, Izumi H. (**2008**) *Salvileucalin B,* a novel diterpenoid with an unprecedented rearranged neoclerodane skeleton from *Salvia leucantha Cav*. *Organic Letters*, ***10***, 4429-4432.

[16] Bisio A, Romussi G, Russo E, De Tommasi N, Mascolo N, Alfieri A, Bonito MC, Cicala C. (**2008**) Platelet antiaggregating activity and chemical constituents of *Salvia jamensis J. Compton. Natural Product Communications*, ***3***, 881-884.

[17] Calzada F, Yepez-Mulia L, Tapia-Contreras A, Bautista E, Maldonado E, Ortega A. (**2010**) Evaluation of the antiprotozoal activity of Neo-clerodane type diterpenes from *Salvia polystachya* against *Entamoeba histolytica* and *Giardia lamblia. Phytotherapy Research*, ***24***, 662-665.

[18] Ninomiya K, , Yoshino T, Morikawa T, Yoshikawa M. (**2004**) Carnosic acid, a new class of lipid absorption inhibitor from sage. *Bioorganic and Medicinal Chemistry Letters*, ***14***, 1943-1946.

[19] Rau O, Wurglics M, Paulke A, Zitzkowski J, Meindl N, Bock A, Dingermann T, Abdel-Tawab M, Schubert-Zsilavecz M. (**2006**) Carnosic acid and carnosol, phenolic diterpene compounds of the labiatae herbs rosemary and sage, are activators of the human peroxisome proliferator-activated receptor gamma. *Planta Medica*, ***72***, 881-887.

[20] Poeckel D, Greiner C, Verhoff M, Rau O, Tausch L, Hörnig C, Steinhilber D, Schubert-Zsilavecz M, Werz O. (**2008**) Carnosic acid and carnosol potently inhibit human 5-lipoxygenase and suppress pro-inflammatory responses of stimulated human polymorphonuclear leukocytes. *Biochemical Pharmacology*, ***76***, 91-97.

[21] Hussein AA, Mever JJ, Jimeno ML, Rodrìguez B. (**2007**) Bioactive diterpenes from *Orthosiphon labiatus* and *Salvia Africana-lutea. Journal of Natural Products*, ***70***, 293-295.

[22] Horiuchi K, Shiota S, Kuroda T, Hatano T, Yoshida T, Tsuchiya T. (**2007**) Potentiation of antimicrobial activity of aminoglycosides by carnosol from *Salvia officinalis. Biological & Pharmaceutical Bulletin*, ***30***, 287-290.

[23] Aydogmus Z, Yesilyurt V, Topçu G. (**2006**) Constituents of *Salvia microphylla. Natural Product Research*, ***20***, 775-781.

[24] Kavvadias D, Monschein V, Sand P, Riederer P, Schreier P. (**2003**) Constituents of sage (*Salvia officinalis*) with *in vitro* affinity to human brain benzodiazepine receptor. *Planta Medica*, ***69***, 113-117.

[25] Kuzma L, Rózalski M, Walencka E, Rózalska B, Wysokińska H. (**2007**) Antimicrobial activity of diterpenoids from hairy roots of *Salvia sclarea L.*: salvipisone as a potential anti-biofilm agent active against antibiotic resistant *Staphylococci. Phytomedicine*, ***14***, 31-35.

[26] Walencka E, Rózalska S, Wysokińska H, Rózalski M, Kuźma Ł, Rózalska B.(**2007**) Salvipisone and aethiopinone from *Salvia sclarea* hairy roots modulate Staphylococcal antibiotic resistance and express anti-biofilm activity. *Planta Medica*, ***73***, 545-551.

[27] Slamenová D, Masterová I, Lábaj J, Horváthová E, Kubala P, Jakubíková J, Wsólová L. (**2004**) Cytotoxic and DNA-damaging effects of diterpenoid quinones from the roots of Salvia officinalis L. on colonic and hepatic human cells cultured in vitro. *Basic & Clinical Pharmacology & Toxicology*, ***94***, 282-290.

[28] Xu G, Peng LY, Lu L, Weng ZY, Zhao Y, Li XL, Zhao QS, Sun HD. (**2006**) Two new abietane diterpenoids from *Salvia yunnanensis*. *Planta medica*, ***72***, 84-86.

[29] Chen X, Ding J, Yong-Mao Y, Zhang JS. (**2002**) Bioactive abietane and seco-abietane diterpenoids from *Salvia prionitis. Journal of Natural Products*, ***65***, 1016-1020

[30] Zhou L, Zuo Z, Chow MS. (**2005**) Danshen: an overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. *Journal of Clinical Pharmacology*, ***45***, 1345-1359.

[31] Han JY, Fan JY, Horie Y, Miura S, Cui DH, Ishii H, Hibi T, Tsuneki H, Kimura I. (**2008**) Ameliorating effects of compounds derived from *Salvia miltiorrhiza* root extract on microcirculatory disturbance and target organ injury by ischemia and reperfusion. *Pharmacology & Therapeutics*, ***17***, 280-295.

[32] Dat NT, Xuejun J, Lee JH, Lee D, Hong YS, Lee K, Kim YH, Lee JJ. (**2007**) Abietane diterpenes from *Salvia miltiorrhiza* inhibit the activation of hypoxia-inducible factor-1. *Journal of Natural Products*, ***70***, 1093-1097.

[33] Forsythe JA, Jiang BH, Iyer NV, Agani F, Leung SW, Koos RD, Semenza GL. (**1996**) Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. *Molecular and Cellular Biology*, ***16***, 4604-4613.

[34] Nizamutdinova IT, Lee GW, Son KH, Jeon SJ, Kang SS, Kim YS, Lee JH, Seo HG, Chang KC, Kim HJ. (**2008**) Tanshinone I effectively induces apoptosis in estrogen receptor-positive (MCF-7) and estrogen receptor-negative (MDA-MB-231) breast cancer cells. *International Journal of Oncology*, ***33***, 485-491.

[35] Wei MC, Zong WX, Cheng EH, Lindsten T, Panoutsakopoulou V, Ross AJ, Roth KA, MacGregor GR, Thompson CB, Koresmeyer SJ. (**2001**) Proapoptotic BAX and BAK: a requisite gateway to mitochondrial dysfunction and death. *Science*, ***292***, 727-730.

[36] Nizamutdinova IT, Lee GW, Lee JS, Cho MK, Son KH, JeoKuzma L, Rózalski M, Walencka E, Rózalska B, Wysokińska Hn SJ, Kang SS, Kim YS, Lee JH, Seo HG, Chang KC, Kim HJ.(**2008**) Tanshinone I suppresses growth and invasion of human breast cancer cells, MDA-MB-231, through regulation of adhesion molecules. *Carcinogenesis*, ***29***, 1885-18892.

[37] Lee CY, Sher HF, Chen HW, Liu CC, Chen CH, Lin CS, Yang PC, Tsay HS, Chen JJ. (**2008**) Anticancer effects of tanshinone I in human non-small cell lung cancer. *Molecular Cancer Therapeutics*, ***7***, 3527-3538.

[38] Jeon SJ, Son KH, Kim YS, Choi YH, Kim HP. (**2008**) Inhibition of prostaglandin and nitric oxide production in lipopolysaccharide-treated RAW 264.7 cells by tanshinones from the roots of *Salvia miltiorrhiza bunge. Archives of Pharmacal Research*, ***31***, 758-763.

[39] Jin YC, Kim CW, Kim YM, Nizamutdinova IT, Ha YM, Kim HJ, Seo HG, Son KH, Jeon SJ, Kang SS, Kim YS, Kam SC, Lee JH, Chang KC. (**2009**) Cryptotanshinone, a lipophilic compound of *Salvia miltiorrriza* root, inhibits TNF-alpha-induced expression of adhesion molecules in HUVEC and attenuates rat myocardial ischemia/reperfusion injury in vivo. *European Journal of Pharmacology*, ***614***, 91-97.

[40] Liu JJ, Lin DJ, Liu PQ, Huang M, Li XD, Huang RW. (**2006**) Induction of apoptosis and inhibition of cell adhesive and invasive effects by tanshinone IIA in acute promyelocytic leukemia cells *in vitro*. *Journal Biomedical Science*, ***13***, 813-823.

[41] Zhou L, Chan WK, Xu N, Xiao K, Luo H, Luo KQ, Chang DC. (**2008**) Tanshinone IIA, an isolated compound from *Salvia miltiorrhiza* Bunge, induces apoptosis in HeLa cells through mitotic arrest. *Life* Science, ***83***, 394-403.

[42] Liu JJ, Zhang Y, Lin DJ, Xiao RZ. (**2009**) Tanshinone IIA inhibits leukemia THP-1 cell growth by induction of apoptosis. *Oncology Reports*, ***21***, 1075-1081.

[43] Kim HK, Woo ER, Lee HW, Park HR, Kim HN, Jung YK, Choi JY, Chae SW, Kim HR, Chae HJ. (**2008**) The correlation of *Salvia* miltiorrhiza extract-induced regulation of osteoclastogenesis with the amount of components tanshinone I, tanshinone IIA, criptotanshinone and diidrotanshinone. *Immunopharmacology and Immonotoxicology*, ***30***, 347-364.

[44] Fu J, Huang H, Liu J, Pi R, Chen J, Liu P. (**2007**) Tanshinone IIA protects cardiac myocytes against oxidative stress-triggered damage and apoptosis. *European Journal of Pharmacology*, ***568***, 213-221.

[45] Li X, Du JR, Bai B, Yu Y, Zheng XY, Yang F, Zheng H. (**2008**) Inhibitory effects and mechanism of tanshinone IIA on proliferation of rat aortic smooth muscle cells. *China Journal of Chinese Materia Medica*, ***33***, 2146-2150.

[46] Kang YJ, Jin UH, Chang HW, Son JK, Lee SH, Son KH, Chang YC, Lee YC, Kim CH. (**2008**) Inhibition of microsomal triglyceride transfer protein expression and atherogenic risk factor apolipoprotein B100 secretion by tanshinone IIA in HepG2 cells. *Phytotherapy Research*, ***22***, 1640-1645.

[47] Jung SH, Seol HJ, Jeon SJ, Son KH, Lee JR. (**2009**) Insulin-sensitizing activities of tanshinones, diterpene compounds of the roots of *Salvia miltiorrhiza Bunge. Phytomedicine*, ***16***, 327-335.

[48] Fang ZY, Lin R, Yuan BX, Liu Y, Zhang H. (**2007**) Tanshinone IIA inhibits atherosclerotic plaque formation by down-regulating MMP-2 and MMP-9 expression in rabbits fed a high-fat diet. *Life Sciences*, ***81***, 1339-1345.

[49] Jin UH, Suh SJ, Chang HW, Son JK, Lee SH, Son KH, Chang YC, Kim CH. (**2008**) Tanshinone IIA from *Salvia miltiorrhiza BUNGE* inhibits human aortic smooth muscle cell migration and MMP-9 activity through AKT signalling pathway. *Journal of Cellular Biochemistry*, ***104***, 15-26.

[50] Wu GB, Zhou EX, Qing DX. (**2009**) Tanshinone II(A) elicited vasodilation in rat coronary arteriole: roles of nitric oxide and potassium channels. *European Journal of Pharmacology*, ***617***, 102-107.
[51] Ren ZH, Tong YH, Xu W, Ma J, Chen Y. (**2010**) Tanshinone II A attenuates inflammatory responses of rats with myocardial infarction by reducing MCP-1 expression. *Phytomedicine*, ***17***, 212-218.
[52] Wan AK, Leung SW, Zhu DY, Man RY. (**2008**) Vascular effects of different lipophilic components of "Danshen", a traditional Chinese medicine, in the isolated porcine coronary crtery. *Journal of Natural Products*, ***71***, 1825-1828.
[53] Yu C, Ye S, Sun H, Liu Y, Gao L, Shen C, Chen S, Zeng S. (**2009**) PXR-mediated transcriptional activation of CYP3A by cryptotanshinone and tanshinone IIA. *Chemico-Biological Interactions*, ***177***, 58-64.
[54] Zhu YP. (**1998**) In Chinese Materia Medica: Chemistry, Pharmacology and Applications, Harwood Academic Publishers.
[55] Wu B, Liu M, Zhang S. (**2004**) Danshen agents for acute ischaemic stroke. *Cochrane Database of Systematic Review.* CD004295.
[56] Yu XY, Lin SG, Zhou ZW, Chen X, Liang J, Duan W, Yu XQ, Wen JY, Chowbay B, Li CG, Sheu FS, Chan E, Zhou SF. (**2007**) Tanshinone IIB, a primary active constituent from *Salvia miltiorrhiza*, exhibits neuro-protective activity in experimentally stroked rats. *Neuroscience Letters*, ***417***, 261-265.
[57] Yu XQ, Xue CC, Zhou ZW, Li CG, Zhou SF. (**2008**) Tanshinone IIB, a primary active constituent from *Salvia miltiorrhiza,* exerts neuroprotective effect via inhibition of neuronal apoptosis in vitro. *Phytotherapy Research*, ***22***, 846-850.
[58] Kim DH, Jeon SJ, Jung JW, Lee S, Yoon BH, Shin BY, Son KH, Cheong JH, Kim YS, Kang SS, Ko KH, Ryu JH. (**2007**) Tanshinone congeners improve memory impairments induced by scopolamine on passive avoidance tasks in mice. *European Journal of Pharmacology*, ***574***, 140-147.
[59] Kim DH, Kim S, Jeon SJ, Son KH, Lee S, Yoon BH, Cheong JH, Ko KH, Ryu JH. (**2009**) Tanshinone I enhances learning and memory, and ameliorates memory impairment in mice via the extracellular signal-regulated kinase signalling pathway. *British Journal of Pharmacology*, ***158***, 1131-1142.
[60] Mei Z, Zhang F, Tao L, Zheng W, Cao Y, Wang Z, Tang S, Le K, Chen S, Pi R, Liu P. (**2009**) Cryptotanshinone, a compound from *Salvia miltiorrhiza* modulates amyloid precursor protein metabolism and attenuates beta-amyloid deposition through upregulating alpha-secretase *in vivo* and *in vitro*. *Neuroscience Letters*, ***452***, 90-95.
[61] Sun CM, Chin TM, Lin YL, Chen CJ, Chen WC, Wu TS, Don MJ. (**2006**) Isolation, structure elucidation, and syntheses of isoneocryptotanshinone II and tanshinlactone A from *Salvia miltiorrhiza*. *Heterocycles*, ***68***, 247-255.
[62] Wu MH, Tsai WJ, Don MJ, Chen YC, Chen IS, Kuo YC. (**2007**) Tanshinlactone A from *Salvia* miltiorrhiza modulates interleukin-2 and interferon-gamma gene expression. *Journal of Ethnopharmacology*, ***113***, 210-217.
[63] El-Lakany, AM, Abdel-Kader MS, Sabri NN, Stermitz FR. (**1995**) Lanigerol: a new antimicrobial icetexane diterpene from *Salvia lanigera. Planta Medica*, ***61***, 559-560.
[64] Fraga, BM, Díaz CE, Guadaño A, González-Coloma A. (**2005**) Diterpenes from *Salvia broussonetii* transformed roots and their insecticidal activity. *Journal of Agricultural and Food Chemistry*, ***53***, 5200-5206.
[65] Simmons EM, Sarpong R. (**2009**) Structure, biosynthetic relationships and chemical synthesis of the icetexane diterpenoids. *Natural Product Reports*, ***26***, 1195-1217.
[66] Nieto M, García EE, Giordano OS, Tonn CE. (**2000**) Icetexane and abietane diterpenoids from *Salvia gilliessi*. *Phytochemistry*, ***53***, 911-915.
[67] Sanchez AM, Jimenez-Ortiz V, Sartor T, Tonn CE, García EE, Nieto M, Burgos MH, Sosa MA. (**2006**) A novel icetexane diterpene, 5-epi-icetexone from Salvia gilliessi is active against *Trypanosoma cruzi. Acta Tropica*, ***98***, 118-124.
[68] Bisio A, Romussi G, Russo E, Cafaggi S, Schito AM, Repetto B, De Tommasi N. (**2008**) Antimicrobial activity of the ornamental species *Salvia corrugata*, a potential new crop for extractive purposes. *Journal Agricultural Food Chemistry*, ***56***, 10468-10471.
[69] Giannoni P, Narcisi R, De Torero D, Romussi G, Quarto R, Bisio A. (**2010**) The administration of demethyl fruticulin A from *Salvia corrugata* to mammalian cells lines induces "anoikis", a special form of apoptosis. *Phytomedicine*, ***17***, 449-456.
[70] Esquivel B, Calderon JS, Flores E, Chavez C, Juarez M. (**1997**) Abietane and icetaxane diterpenoids from *Salvia pubescens*. *Natural Product Research*, ***10***, 87-93.
[71] Romussi G, Ciarallo G, Bisio A, Fontana N, De Simone F, De Tommasi N, Mascolo N, Pinto L. (**2001**) A new diterpenoid with antispasmodic activity from *Salvia cinnabarina. Planta Medica*, ***67***, 153-155.
[72] Capasso R, Izzo AA, Capasso F, Romussi G, Bisio A, Mascolo N. (**2004**) A diterpenoid from *Salvia cinnabarina* inhibits mouse intestinal motility *in vivo*. *Planta Medica*, ***70***, 375-377.
[73] Capasso R, Izzo AA, Romussi G, Capasso F, De Tommasi N, Bisio A, Mascolo N. (**2004**) A seicoisopimarane diterpenoid from *Salvia cinnabarina* inhibits rat urinary bladder contractility *in vitro. Planta Medica*, ***70***, 185-188.
[74] Alfieri A, Maione F, Bisio A, Romussi G, Mascolo N, Cicala C. (**2007**) Effect of a diterpenoid from *Salvia cinnabarina* on arterial blood pressure in rats. *Phytotherapy Research*, ***21***, 690-692.
[75] Maione F, Bonito MC, Colucci MA, Cozzolino V, Bisio A, Romussi G, Cicala C, Pieretti S, Mascolo N. (**2009**) First evidence for anxiolitic effect of a diterpenoid from *Salvia cinnabarina*. *Natural Product Communications*, ***4***, 469-472.
[76] Di Sotto A, Mastrangelo S, Romussi G, Bisio A, Mazzanti G. (**2009**) Antimutagenic activity of a secoisopimarane diterpenoid from *Salvia cinnabarina* M. Martens et Galeotti in the bacterial reverse mutation assay. *Food and Chemical Toxicology*, ***47***, 2092-2096.
[77] Bisio A, Fraternale D, Damonte G, Millo E, Lanteri AP, Russo E, Romussi G, Parodi B, Ricci D, De Tommasi N. (**2009**) Phytotoxic activity of *Salvia x jamensis. Natural Product Commununications*, ***4***, 1621-1630.
[78] De Smet PA. (**1997**)The role of plant-derived drugs and herbal medicines in healthcare. *Drugs*, ***54***, 801-840.
[79] Shi X, Xia Z, Fang J. (**2000**) Effects of *Salvia miltiorrhiza* compound injection on serum endothelin, prostaglandin I_2/thromboxane A_2 ratio alteration following myocardial ischemia-reperfusion in patients undergoing intracardiac surgery. *Chinese Journal of Integrated Traditional and Western Medicine*, ***20***, 896- 898.
[80] Yu W, Shen F, Ma Z. (**2000**) Observation of therapeutic effect of *Salvia miltiorrhiza* and cytosine diphosphate-choline injection on patients with hypertensive cerebral hemorrhage. *Chinese Journal of Integrated Traditional and Western Medicine*, ***20***, 94-96.
[81] Jiang FX, Wang SJ, Zhong L. (**2001**) Clinical observation of compound *Salvia* injection in treating mid-severe infantile hypoxic-ischemic encephalopathy. *Chinese Journal of Integrated Traditional and Western Medicine*, ***21***, 903-905.

[82] Xia Z, Gu J, Ansley DM, Xia F, Yu J. (**2003**) Antioxidant therapy with *Salvia miltiorrhiza* decreases plasma endothelin-1 and thromboxane B2 after cardiopulmonary bypass in patients with congenital heart disease. *Journal of Thoracic and Cardiovascular Surgery*, ***126***, 1404-1410.

[83] Vuksan V, Whitham D, Sievenpiper JL, Jenkins AL, Rogovik AL, Bazinet RP, Vidgen E, Hanna A. (**2007**) Supplementation of conventional therapy with the novel grain Salba (*Salvia hispanica L.*) improves major and emerging cardiovascular risk factors in type 2 diabetes: results of a randomized controlled trial. *Diabetes Care*, ***30***, 2804-2810.

[84] Zhang SJ, Cheng ZX, Lin YW, Qin J, Cheng YH, Liu SL. (**2007**) Effection of compositie *Salvia* e dropping pill on hyperlipemia patients with phlegm and blood stasis syndrome *China Journal of Chinese Materia Medica*, ***32***, 440-443.

[85] Li YQ, Jin M, Qiu SL, Wang PL, Zhu TG, Wang CL, Li TC, Liu HX, Bian H, Yao LF, Shi DZ. (**2009**) Effect of Chinese drugs for supplementing Qi, nourishing Yin and activating blood circulation on myocardial perfusion in patients with acute myocardial infarction after revascularization. *Chinese Journal of Integrated Medicine*, ***15***, 19-25.

[86] Tam WY, Chook P, Qiao M, Chan LT, Chan TY, Poon YK, Fung KP, Leung PC, Woo KS. (**2009**) The efficacy and tolerability of adjunctive alternative herbal medicine (*Salvia miltiorrhiza* and *Pueraria lobata*) on vascular function and structure in coronary patients. *Journal of Alternative and Complementary Medicine*, ***15***, 415-421.

[87] Xu G, Zhao W, Zhou Z, Zhang R, Zhu W, Liu X. (**2009**) Danshen extracts decrease blood C reactive protein and prevent ischemic stroke recurrence: a controlled pilot study. *Phytotherapy Research*, ***23***, 1721-1725.

[88] Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. (**2003**) *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. *Journal of Clinical Pharmacy and Therapeutics*, ***28***, 53-59.

[89] Perry NS, Bollen C, Perry EK, Ballard C. (**2003**) *Salvia* for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial. *Pharmacology Biochemistry and Behavior*, ***75***, 651-659.

[90] Tildesley NT, Kennedy DO, Perry EK, Ballard CG, Wesnes KA, Scholey AB. (**2005**) Positive modulation of mood and cognitive performance following administration of acute doses of *Salvia lavandulaefolia* essential oil to healthy young volunteers. *Physiology & Behavior*, ***83***, 699-709.

[91] Kennedy DO, Pace S, Haskell C, Okello EJ, Milne A, Scholey AB. (**2006**) Effects of cholinesterase inhibiting sage (*Salvia officinalis*) on mood, anxiety and performance on a psychological stressor battery. *Neuropsychopharmacology*, ***31***, 845-852.

[92] Scholey AB, Tildesley NT, Ballard CG, Wesnes KA, Tasker A, Perry EK, Kennedy DO. (**2008**) An extract of *Salvia* (sage) with anticholinesterase properties improves memory and attention in healthy older volunteers. *Psychopharmacology*, ***198***, 127-139.

[93] Peng B, Du J, Jia Q, Qiao A, Wu Y, Liu X, Qiang Q. (**2001**) The effect of *Salvia miltiorrhiza* and Shengmai on inflammatory mediator and renal function of post-operative patients with obstructive jaundice. *Journal of West China University of Medical Sciences*, ***32***, 587-589.

[94] Hubbert M, Sievers H, Lehnfeld R, Kehrl WV. (**2006**) Efficacy and tolerability of a spray with *Salvia officinalis* in the treatment of acute pharyngitis - a randomised, double-blind, placebo-controlled study with adaptive design and interim analysis. *European Journal of Medical Research*, ***11***, 20-26.

[95] Pu C, Yang YB, Sun QL. (**2006**) Effects of *Salvia miltiorrhiza* on oxidative stress and microinflammatory state in patients undergoing continuous hemodialysis. *Chinese Journal of Integrated Traditional and Western Medicine*, ***26***, 791-794.

[96] Peng GL, Zhang XY. (**2007**) Effects of *Salvia miltiorrhiza* on serum levels of inflammatory cytokines in patients with severe acute pancreatitis *Journal of Chinese Integrative Medicine*, ***5***, 28-31.

[97] Schapowal A, Berger D, Klein P, Suter A. (**2009**) Echinacea/sage or chlorhexidine/lidocaine for treating acute sore throats: a randomized double-blind trial. *European Journal of Medical Research*, ***14***, 406-412.

[98] Sun M, Zhang JJ, Shan JZ, Zhang H, Jin CY, Xu S, Wang YL. (**2009**) Clinical observation of Danhong injection (herbal TCM product from Radix *Salvia miltiorrhizae* and *Flos Carthami tinctorii*) in the treatment of traumatic intracranial hematoma. *Phytomedicine*, ***16***, 683-689.

[99] Liang YG, Chu XJ. (**2002**) Effect of compound *Salvia* pill combined with propranolol on liver fibrosis and portal hypertension. *Chinese Journal of Integrated Traditional and Western Medicine*, ***22***, 382-383.

[100] She SF, Huang XZ, Tong GD. (**2004**) Clinical study on treatment of liver fibrosis by different dosages of *Salvia* injection. *Chinese Journal of Integrated Traditional and Western Medicine*, ***24***, 17-20.

[101] Ye F, Liu Y, Qiu G, Zhao Y, Liu M. (**2005**) Clinical study on treatment of cirrhosis by different dosages of *Salvia* injection. *Journal of Chinese Medicinal Materials*, ***28***, 850-854.

[102] Jin CX, Yang J, Sun HF. (**2006**) Comparative study of the clinical effects of S*alvia miltiorrhiza* injection and Shengmai injection on chronic hepatitis B. *Chinese Journal of Integrated Traditional and Western Medicine*, ***26***, 936-938.

[103] Wong CK, Bao YX, Wong EL, Leung PC, Fung KP, Lam CW. (**2005**) Immunomodulatory activities of Yunzhi and Danshen in post-treatment breast cancer patients. *American Journal of Chinese Medicine*, ***33***, 381-395.

[104] Ji KT, Zhang HQ, Tang JF, Li HY. (**2007**) Effects of Danshen on number and activity of endothelial progenitor cells of patients with hypercholesterolemia. *China Journal of Chinese Materia Medica*, ***32***, 1214-1217.

[105] Tian XH, Xue WJ, Ding XM. (**2005**) Application of Danshen injection on early stage of renal transplantation. *Chinese Journal of Integrated Traditional and Western Medicine,* ***25***, 404-407.

[106] Han Y, Wang ZK, Wang ZD. (**2004**) Observation on therapeutic effect of compound *Salvia* drop-pill in treating vasovagal syncope. *Chinese Journal of Integrated Traditional and Western Medicine*, ***24***, 452-454.

[107] Reuter J, Jocher A, Hornstein S, Mönting JS, Schempp CM. (**2007**) Sage extract rich in phenolic diterpenes inhibits ultraviolet-induced erythema in vivo. *Planta Medica*, ***73***, 1190-1191.

[108] Yan FF, Liu YF, Liu Y, Zhao YX. (**2009**) Sulfotanshinone Sodium Injection could decrease fibrinogen level and improve clinical outcomes in patients with unstable angina pectoris. *International Journal of Cardiology*, ***135***, 254-255.