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REVIEW

The Pharmacological Effects of *Salvia* species on the Central Nervous System

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***Salvia* is an important genus consisting of about 900 species in the family Lamiaceae. Some species of *Salvia* have been cultivated world wide for use in folk medicine and for culinary purposes. The dried root of *Salvia miltiorrhiza*, for example, has been used extensively for the treatment of coronary and cerebrovascular disease, sleep disorders, hepatitis, hepatocirrhosis, chronic renal failure, dysmenorrhea, amenorrhea, carbuncles and ulcers. *S. officinalis*, *S. leriifolia*, *S. haematodes*, *S. triloba* and *S. divinorum* are other species with important pharmacological effects. In this review, the pharmacological effects of *Salvia* species on the central nervous system will be reviewed. These include sedative and hypnotic, hallucinogenic, skeletal muscle relaxant, analgesic, memory enhancing, anticonvulsant, neuroprotective and antiparkinsonian activity, as well as the inhibition of ethanol and morphine withdrawal syndrome. Copyright © 2006 John Wiley & Sons, Ltd.**

Keywords: Salvia; CNS; sedative and hypnotic; hallucinogen; analgesic; memory enhancing; anticonvulsant; neuroprotective.

INTRODUCTION

It is estimated that nearly 25% of modern drugs directly or indirectly originated from plants. Several examples concern the CNS, and include caffeine, ephedrine, cannabinoids, opioids and reserpine. However, for the majority of CNS active plants, the active principles are not yet known (Carlini, 2003). The rational treatment of CNS disorders by plant extract-derived drugs is in its infancy due to the complex chemistry and organization of the CNS and also the complex chemistry and pharmacology of a plant extract (Houghton and Seth, 2003). This review article deals with the pharmacological effects of the genus *Salvia* on the CNS.

The name *Salvia* comes from the Latin word meaning 'to heal' which sums up the folkloric belief of its 'magical' therapeutic properties for many kinds of ailments and its popularity in traditional medicine (Kasimu *et al.*, 1998). *Salvia* (commonly called sage) is an important genus consisting of around 900 species in the family Lamiaceae. Some species of *Salvia* have been cultivated world wide for use in folk medicine and for culinary purposes. The dried root of *S. miltiorrhiza* (Danshen, or Red Sage root), for example, has been used extensively for the treatment of coronary disease, cerebrovascular disease, hepatitis, hepatocirrhosis, chronic renal failure, dysmenorrhea, amenorrhea, abdominal distension due to stasis of blood, carbuncles and ulcers (Du and Zhang, 2004). Studies on the chemical constituents of *Salvia miltiorrhiza* have been mainly confined to the tanshinones (diterpenes) (Fig. 1). Many effects that are attributed to these plants, such as antibacterial, antitumor, antioxidant, antimutagenic, antiinflammatory and antiplatelet aggregation activities, are due to the presence of these components in the genus *Salvia* (Ryu, 1997). For example, more than 30 kinds of tashinone compounds have so far been separated and identified from *S. miltiorrhiza* (Guanhua and Jun-tian, 2004). However, in recent years much attention has been directed to the biologically active, water-soluble components in the dried root decoction of these plants. These studies, particularly in China,

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a. monoterpenes

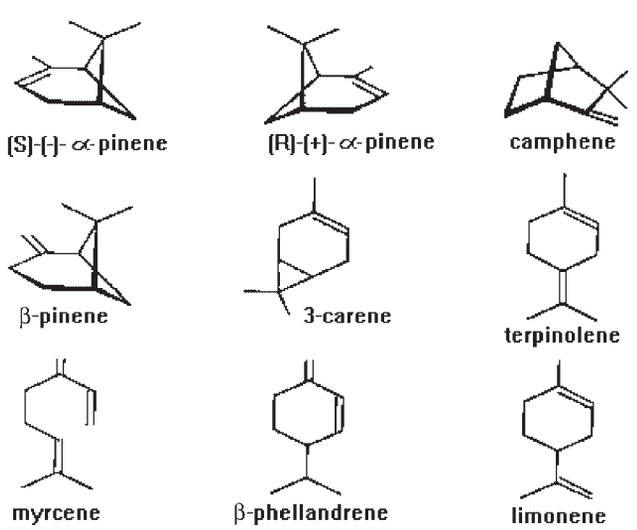

Figure 1. Structure of pharmacologically active compounds in genus *Salvia*.

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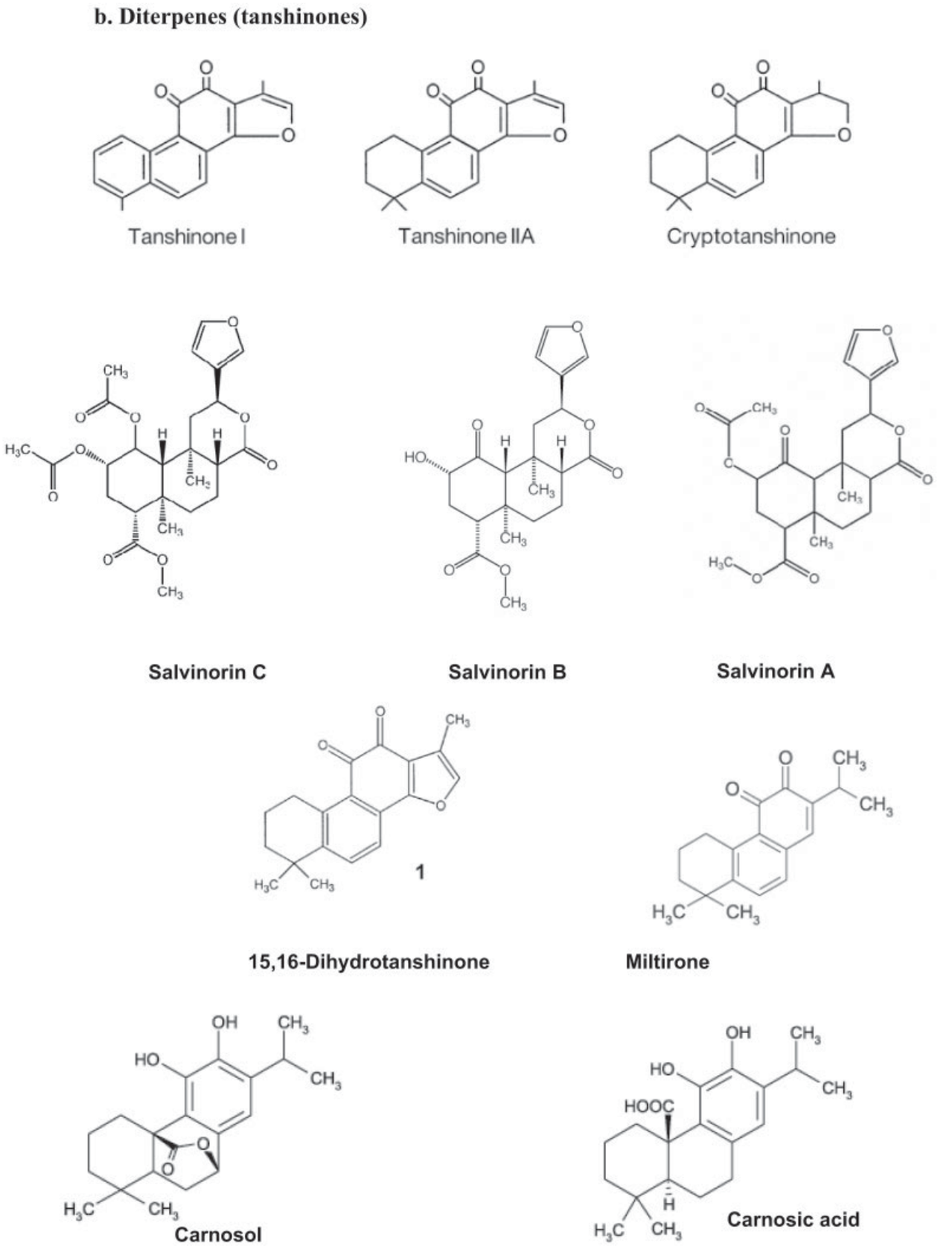

Figure 1. (*Continued*)

have led to the isolation and identification of a series of phenolic acids (Fig. 1), many of which possess a variety of biological activities including antioxidant, antiplatelet, antitumor and antiviral activity. The polar phenolic acids constitute the major part of the water-soluble components of *Salvia* decoction. The majority of the phenolic acids in *Salvia* species are exclusively those of caffeic acids derivatives, which are unique to *Salvia* except for rosmarinic acid and lithospermic acid (Lu and Foo, 2002). In this article the pharmacological

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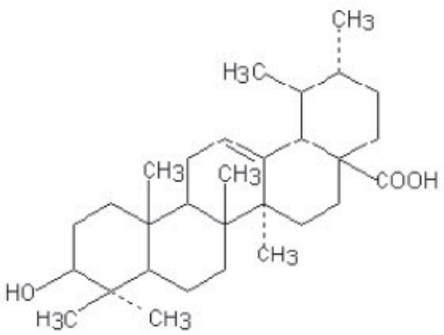
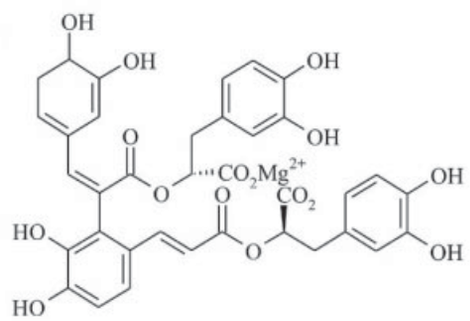
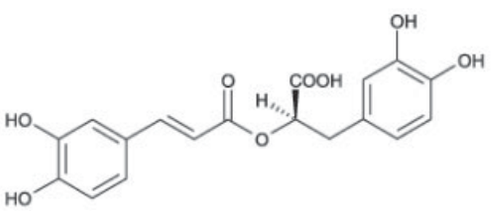


Urosolic acid

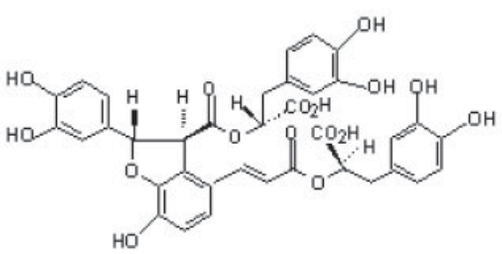
c. phenolic acids



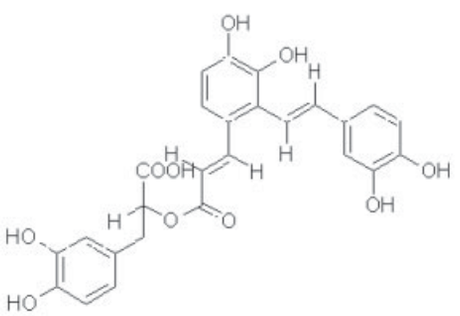
Lithospermate B



Rosmarinic acid

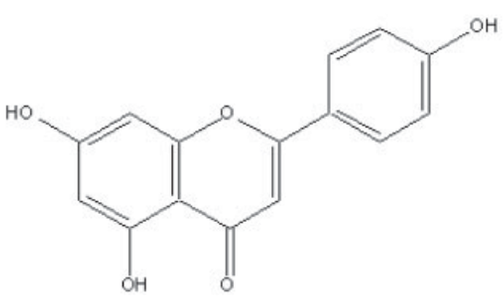


Salvianolic acid B

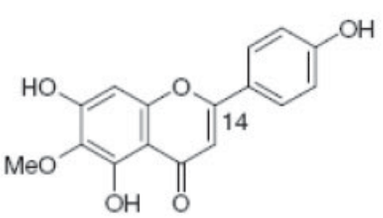


Salvianolic acid A

d. flavonoids



Apigenin



Hispidulin

Figure 1. (*Continued*)

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effects of *Salvia* species on the central nervous system is reviewed (Table 1).

SEDATIVE AND HYPNOTIC EFFECTS

Salvia guaranitica. This plant is a traditional medicinal plant used as a sedative in Latin America. In one study, it has been shown that cirsiliol (5, 3′, 4′-trihydroxy 6,7-dimethoxyflavone) and caffeic acid ethyl ester, which exist in the crude ethanol extract of the plant, are competitive low affinity benzodiazepine receptor ligands (Marder *et al.*, 1996). In another study, cirsiliol exhibited a dose-dependent hypnotic action in the pentobarbital-induced sleep test. Cirsiliol has been found to be more potent in displacing ^{3}H-zolpidem binding (K_i = 20 μM) than ^{3}H-flunitrazepam binding (K_i = 200 μM) to benzodiazepine receptors from the rat cerebral cortex. Therefore cirsiliol appears to possess sedative and hypnotic properties, probably by acting on the so-called type I benzodiazepine receptor (Viola *et al.*, 1997).

Salvia haematodes. The ethanol extract of *S. haematodes* significantly increased pentobarbital-induced sleep in mice and antagonized amphetamine-induced excitation in rats, suggesting a CNS depressant activity for the ethanol extract of this plant. The sedative effect is also evident from results that indicated an increase in the hypoxic survival time in mice (Akbar *et al.*, 1984).

Salvia leriifolia. The aqueous leaf extract of this species also increased significantly pentobarbital-induced sleep, at doses of 1.15 and 1.57 g/kg, but its effect was less than that of diazepam (Hosseinzadeh and Hassanzadeh, 2001). The sedative effect of this plant is also evident from results indicating an increase in the hypoxic survival time in mice (Hosseinzadeh and Imanshahidi, 1999).

Salvia miltiorrhiza. The root of *S. miltiorrhiza* has been used widely in China to treat neurasthenic insomnia. Ten diterpene quinones have been isolated from the ether extract of the root of this plant, which in radioligand studies inhibited the binding of [^{3}H]-flunitrazepam to central benzodiazepine receptors with IC_{50}s ranging from 0.3 to 36.2 μM. Among these compounds, miltirone had the highest potency (IC_{50} = 0.3 μM). Miltirone displayed an increase in its affinity in the presence of 100 μM GABA, although the GABA shift observed for it was less than that for diazepam, indicating that it might act as a partial agonist. On the other hand, using a similar method, 4-methylene miltirone appeared to be an antagonist. Miltirone, in a similar way to CG59896 (a partial agonist), but in contrast to diazepam (a full agonist), produced muscle relaxation, sedation, dependence and a withdrawal syndrome in mice at doses (10–60 mg/kg, p.o.) which were effective in the behavioral test (Lee *et al.*, 1991). Therefore, miltirone may represent a new class of tranquilizer isolated from a natural plant source and has the potential to be developed as a non-sedative and non-addictive anxiolytic.

In another study, 21 O-quinonoid-type compounds related to miltirone were synthesized with the aim of identifying the key structural elements involved in the interaction of miltirone at the central benzodiazepine receptor. The results were obtained on the basis of their inhibition of [^{3}H]-flunitrazepam binding to bovine cerebral cortex membranes, and indicate that ring A of miltirone is essential for affinity. Although increasing the size of ring A from being a six-membered to a seven- or eight-membered ring is well tolerated, the introduction of polar hydroxyl groups greatly reduces binding affinity. The presence of 1,1-dimethyl groups on ring A is, however, not essential. On the other hand, the isopropyl group on ring C appears to be critical for binding as its removal decreases affinity by more than 30-fold. It can, however, be replaced with a methyl group with a minimal reduction in affinity. Finally, linking ring A and B with a -CH_2-CH_2- bridge results in a compound which is 6 times more potent that miltirone at the central benzodiazepine receptor (IC_{50} = 0.05 μM) (Chang *et al.*, 1991).

Salvia officinalis. Carnosol and carnosic acid are two diterpenes isolated from the leaves of this plant which inhibited the binding of t-butylbicyclophosphoro [^{35}S] thionate (TBPS) to the chloride channel of the GABA/benzodiazepine receptor complex in brain tissue (with IC_{50} values of 57 ± 4 μM and 33 ± 3 μM, respectively), but had no effect on the binding of [^{3}H] muscimol, [^{3}H]-diazepam or [^{3}H]-flunitrazepam. Therefore the site of action of these compounds appears to be directly on the chloride channel, and therefore differs from miltirone (Rutherford *et al.*, 1992). In another study, a benzodiazepine receptor binding assay-guided fractionation of the methanol extract from sage leaves revealed three flavones and two abietane diterpenes functioning as benzodiazepine receptor-active components. The flavones, apigenin, hispidulin and cirsimaritin, competitively inhibited ^{3}H-flumazenil binding to the benzodiazepine receptor with IC_{50} values of 30, 1.3 and 350 mM, respectively. The IC_{50} value of abietane diterpenes, 7-methoxyrosmanol and galdosol, were 7.2 and 0.8 mM, respectively (Kavvadias *et al.*, 2003).

Salvia sclarea. An essential oil from this plant markedly potentiated the narcotic effects of 'Evipan' (N-methyl-cyclo-hexenyl-methyl-barbituric acid) at doses of less than 20% of the LD_{50} (520 mg/kg in male mice), but did not significantly affect spontaneous motor activity and statokinetic reflexes (Atanasova-Shopova and Rusinov, 1970).

Salvia triloba. Compounds isolated from this plant prolonged hexobarbital sleep in the rat (Todorov *et al.*, 1984). An ethanol extract of *S. triloba* showed a moderate affinity to the GABA(A)-benzodiazepine receptor site (Salah and Jager, 2005).

HALLUCINOGENIC EFFECTS

Salvia divinorum. This plant is used as a hallucinogen drug in Mexico. A neoclerodane diterpene, salvinorin A (also known as divinorin A), has been demonstrated in animals and humans to be its major active ingredient. When taken orally, this compound is essentially inactive because it is degraded in the gastrointestinal tract and only a small amount of the drug is absorbed

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Table 1. Summary of pharmacological effects of genus *Salvia* and active compounds

Plant	Pharmacologic effect(s)	Active compound(s) or extract	References
S. aegyptiaca	Antinociceptive, antiinflammatory and antipyretic	Acetone and methanol extracts	Al-Yousuf *et al.*, 2002
S. aethiopis	Antinociceptive and antiinflammatory	Aethiopinone	Perez *et al.*, 1995
S. africana-lutea	Antinociceptive	Aqueous extract	Amabeoku *et al.*, 2001
S. divinorum	Hallucinogen	Salvinorin A	Valdes, 1994; Vangapandu *et al.*, 2003; Munro *et al.*, 2005
S. guaranitica	Sedative and hypnotic	Cirsiliol	Marder *et al.*, 1996; Viola *et al.*, 1997
S. haematodes	Sedative and anticonvulsant	Ethanol and aqueous extracts	Akbar *et al.*, 1984; Akbar *et al.*, 1985
S. lavandulaefolia	Anticholinesterase	α-Pinene, 1,8-cineole and camphor	Perry *et al.*, 2000
S. leriifolia	Sedative and hypnotic	Aqueous leaf extract	Hosseinzadeh and Hassanzadeh, 2001
	Skeletal muscle relaxant	Aqueous leaf extract	Hosseinzadeh and Hassanzadeh, 2001
	Analgesic and antiinflammatory	Alcoholic and aqueous seed extracts; aqueous decoction leaf extract	Hosseinzadeh *et al.*, 2003; Hosseinzadeh and Yavary, 1999
	Anticonvulsant	Leaves and seed extracts	Hosseinzadeh and Arabsanavi, 2001
	Neuroprotective	Root	Hosseinzadeh *et al.*, 2002; Sadeghnia *et al.*, 2003
		Seed extracts	Khooei *et al.*, 2003
	Inhibition of opioid withdrawal syndrome	Ethanol leaf extract	Hosseinzadeh and Lari, 2000
S. mexicana	Antiinflammatory	β-Sitosterol, betulinic acid, ursolic acid	Delira *et al.*, 2003
S. miltiorrhiza	Sedative and hypnotic	Miltirone	Lee *et al.*, 1991; Chang *et al.*, 1991
	Analgesic	Root extract	Liu *et al.*, 1990
	Antiacetylcholinesterase	Dihydrotanshinone and cryptotanshinone	Ren *et al.*, 2004
	Neuroprotective	Acetylsalvianolic acid, tanshinones IIA and IIB Salvianic acid A and 15,16-dihydrotanshinone	Lam *et al.*, 2003; Dong and Xu, 1996
	Antiparkinson		Xin-Jian and Jian-Xing, 2005; Dittmann *et al.*, 2004
	Inhibition of ethanol withdrawal syndrome	Miltirone	Mostallino *et al.*, 2004
S. officinalis	Sedative and hypnotic	Carnosol and carnosic acid, apigenin, hispidulin and cirsimaritin	Rutherford *et al.*, 1992; Kavvadias *et al.*, 2003
	Antiinflammatory	Ursolic acid	Baricevic *et al.*, 2001
	Memory enhancing	Extract	Akhondzadeh *et al.*, 2003
	Antioxidant	Carnosic acid, carnosol, rosmanol and caffeic acid	Matsingou *et al.*, 2003 and Dorman *et al.*, 2003
S. sclarea	Sedative and anticonvulsant	Essential oil	Atanasova-Shopova and Rusinov, 1970
S. triloba	Sedative and hypnotic	Ethanol extract	Todorov *et al.*, 1984; Salah and Jager, 2005

through the mouth. Therefore, in common traditional use it has mild effects. However, when smoked (in a manner similar to free base cocaine), the compound is effective in doses of 200–500 μg and produces visions that last from 30 min to an hour or two, while doses over 2 mg are effective for much longer. At doses greater than 500 μg the subject is often no longer aware of their surroundings and may enter an uncontrollable delirium. This compound is the most potent naturally occurring hallucinogen thus far isolated. The extraction of salvinorin A from the plant is very easy and with care, about 1.5 g of pure salvinorin A per kilogram of air-dried *S. divinorum* leaves (about 8 kg fresh leaves) can be isolated. It is therefore of concern that both *S. divinorum* and salvinorin A are prime candidates to become drugs of widespread abuse, since a small investment in fertilizer and solvents, coupled with only a minimal mastery of laboratory techniques, would make the cultivation of *S. divinorum* and the isolation of salvinorin A potentially much more attractive than

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synthesizing LSD or phencyclidine derivatives (Valdes, 1994). Other neoclerodane diterpenoids, salvinorin C, salvinorins D, salvinorins E and salvinorins F have also been isolated from the leaves of *S. divinorum* (Munro and Rizzacasa, 2003). The site of pharmacological activity remained a mystery until recent reports identified salvinorin A as a potent and selective kappa-opioid receptor agonist, thus representing a unique structural class of non-nitrogenous opioid ligands (Vangapandu *et al.*, 2003). Other salvinorins, however, show a negligible binding affinity at the kappa-opioid receptor (Munro *et al.*, 2005). The chronic toxicity of salvinorin A has been evaluated in mice, by exposing the animals to 400, 800, 1600, 3200, or 6400 μg/kg of salvinorin A daily for 2 weeks. Histological studies of spleen, blood, brain, liver, kidney and bone marrow did not show any significant histological changes at any of the doses (Mowry *et al*., 2003).

SKELETAL MUSCLE RELAXANT EFFECTS

Salvia leriifolia. The muscle relaxant effect of the aqueous leaf extract of this plant was evaluated using a traction test, and demonstrated that the extract at a dose of 0.29 g/kg produced a relaxant effect similar to that of diazepam at a dose of 1 mg/kg (Hosseinzadeh and Hassanzadeh, 2001).

ANALGESIC AND ANTIINFLAMMATORY EFFECTS

Salvia aegyptiaca. The crude acetone and methanol extracts of the plant have been tested for antiinflammatory and antipyretic activity using several models of nociception. In treated mice, the extracts caused dose-related inhibition of acetic acid-induced abdominal constriction, and significantly reduced formalin-induced pain. Treatment with the extracts at doses of 0.5 and 1 g/kg significantly increased the reaction time in the hot-plate test. In treated mice both extracts caused a significant and dose-related impairment of the sensorimotor control and motor activity. Treatment with both extracts did not significantly affect the rectal temperature of normothermic mice. The methanol extract (0.5 and 1.0 g/kg) did not affect the rectal temperature of hyperthermic mice, but the acetone extract was effective in significantly reducing the rectal temperature of such mice, at 0.5 and 1 h after the administration of the extract at doses of 0.25–2 g/kg. The crude methanol and acetone extracts of *S. aegyptiaca* have antinociceptive, antiinflammatory and antipyretic actions, although the active constituents have not yet been identified (Al-Yousuf *et al.*, 2002).

Salvia aethiopis. An o-naphthoquinone diterpenoid, aethiopinone, isolated from *S. aethiopis* L. roots exhibited significant antinociceptive and antiinflammatory effects in rodents. Aethiopinone produced a strong antiinflammatory effect using an acute inflammatory model induced by carregeenan, which was of the same order of magnitude as that observed after piroxicam or ibuprofen administration. The antinociceptive effects was especially noticeable against thermal painful stimuli, indicating the presence of central analgesic action, and a moderate effect against a chemical stimulus (phenylquinone) was observed (Perez *et al.*, 1995).

Salvia africana-lutea. In traditional medicine, a decoction of the leaves of this plant is used to treat headache, fever and digestive disorders. The results of a study showed that a water extract of *S. africana-lutea* significantly antagonized acetic acid-induced writhing and attenuated the nociception produced by hot-plate thermal stimulation, as well as reducing the pyrexia induced by lipopolysaccharide from *Salmonella typhosa*. It is probable, therefore, that this plant might mediate its effects both peripherally and centrally (Amabeoku *et al.*, 2001).

Salvia leriifolia. The alcohol and aqueous seed extracts were studied for analgesic and antiinflammatory effects. The analgesic effect was studied using two thermic stimuli, the hot-plate and tail-flick tests. The acute antiinflammatory effect of the seed extract was studied using vascular permeability induced by acetic acid, and xylene-induced ear edema in mice. The chronic antiinflammatory effect was assessed using the cotton-plate test. The results showed that in the hot-plate test, the aqueous seed extract had significant and dose-dependent analgesic activity with 420 min duration of action, and naloxane inhibited the analgesic activity of the extract. The analgesic effect of the extract was comparable to that of morphine at 30 min, although the aqueous and alcohol seed extracts showed no analgesic activity in the tail-flick test. The aqueous seed extract showed a significant and dose-dependent acute antiinflammatory effect against inflammation induced by acetic acid: in this test, the effect of the extract was comparable to that of diclofenac. In the chronic antiinflammatory test (cotton-plate), the extract showed a significant and dose dependent antiinflammatory activity. From these results, it was concluded that the aqueous seed extract has a central (but not spinal) analgesic effect, and this may be mediated by opioid receptors. The aqueous seed extract also showed considerable acute and chronic antiinflammatory activity (Hosseinzadeh *et al.*, 2003), and the aqueous extract of the leaf of *S. leriifolia* also showed activity against acute and chronic inflammation (Hosseinzadeh and Yavary, 1999).

Salvia mexicana. The acetone and methanol extracts of aerial parts of this plant showed antiinflammatory properties in the TPA (tetradecanoyl phorbol acetate) model. Some common triterpenes including β-sitosterol, betulinol, betulinic acid and ursolic acid have been isolated as active compounds (Delira *et al.*, 2003).

Salvia miltiorrhiza. This plant has been used traditionally as an antiinflammatory herbal medicine in China. One study showed that tanshinone IIA, a diterpene isolated from *S. miltiorrhiza* root, has inhibitory effects on the production of nitric oxide (NO), interleukin-1b (IL-1b), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Therefore, the traditional use of *S. miltiorrhiza* as an antiinflammatory herbal medicine may be explained, in part, by the inhibition of NO, IL-1b, IL-6 and TNF-α production (Seon-il *et al.*, 2003). In another

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study, using an extracellular microelectrode method and a stereotaxic technique in the brain, the effects of the plant extract on visceral pain discharges in the posterior nucleus of the thalamus in cats were investigated. *S. miltiorrhiza* inhibited these, suggesting that the analgesic effect of Radix *S. miltiorrhiza* may be exerted via the central nervous system (Liu *et al.*, 1990).

Salvia officinalis. The hexane and ethylacetate fractions of garden sage (*S. officinalis* L.) were assayed for their effects on TNF-α and IL-6 production in LPS-stimulated RAW 264.7 macrophages. The extracts inhibited the protein and mRNA expression of TNF-α and IL-6 in LPS stimulated RAW 264.7 cells at a concentration of 100 mg/mL. These results suggest that the extract of sage may have antiinflammatory activity through the inhibition of pro-inflammatory cytokines (Eun-A *et al.*, 2004). In another study, the *n*-hexane and the chloroform extracts of the plant dose-dependently inhibited croton oil-induced ear oedema in mice, the chloroform extracts being the most active. Further investigation of this extract revealed ursolic acid as the main active component, with the antiinflammatory effect of ursolic acid (ID_{50} = 0.14 mmol/cm^2) being 2-fold more potent than that of indomethacin, the reference non-steroidal antiinflammatory drug (NSAID) (Baricevic *et al.*, 2001).

MEMORY ENHANCING EFFECT

Salvia lavandulaefolia. *Salvia* spp, especially *S. lavandulaefolia* (Spanish sage) and also *S. officinalis*, were reputed in European herbal encyclopedias to enhance memory. The anticholinesterase activity of *S. lavandulaefolia* and *S. officinalis* oil using human brain tissue (post mortem) has been reported and this could account, at least in part, for its memory enhancing reputation (Tildesley *et al.*, 2003). The results of a study demonstrated that the inhibition of acetylcholinesterase by *S. lavandulaefolia* is likely to be due to the presence of more than one monoterpenoid present in the essential oil, the chief compounds responsible being α-pinene, 1,8-cineole and camphor (Perry *et al.*, 2000). Another study has shown that eight terpenoid constituents of *S. lavandulaefolia* essential oil including 1,8-cineole, camphor, α-pinene, β-pinene, borneol, caryophyllene oxide, linalool and bornyl acetate have *in vitro* anticholinesterase activity. The inhibitory activity of the oil resulted from a complex interaction between its constituents, which produced both synergistic and antagonistic responses between the component terpenes (Savelev *et al.*, 2003). The essential oils of *S. lavandulaefolia* also show anti-butyrylcholinesterase activity, considered to be a target in the treatment of Alzheimer's disease (Savelev *et al.*, 2004). In a small clinical trial the effect of a standardized essential oil extract of *S. lavandulaefolia* on enhancing memory in young adult volunteers was evaluated and the results showed that *Salvia* essential oil significantly improved immediate word recall in healthy young adults (Tildesley *et al.*, 2003). A single dose of this oil was also capable of acute modulation of mood and cognition in healthy young adults (Tildesley *et al.*, 2005). In addition to anticholinesterase activity, the essential oil of this plant demonstrated antioxidant, antiinflammatory, oestrogenic and CNS depressant (sedative) effects which are currently relevant to the treatment of Alzheimer's disease (AD). In the light of these findings *S. lavandulaefolia* essential oil could be considered for further clinical studies in the symptomatic treatment of Alzheimer's disease (Perry *et al.*, 2003).

Salvia miltiorrhiza. The effect of tanshinone, the major active ingredient of *S. miltiorrhiza*, on the neuropathological changes induced by amyloid beta-peptide1–40 (Ab1–40) injection in the hippocampus in rats was evaluated. The results have showed that tanshinone significantly improved the changes caused by amyloid beta-peptide1–40 (Ab1–40) injection including a decrease in the level of AChE positive fibers (Longxuan *et al.*, 2004). In another study, two compounds, dihydrotanshinone and cryptotanshinone, were isolated from an acetone extract of Danshen (dried root of *S. miltiorrhiza*) and found dose-dependently to inhibit acetylcholinesterase. Their IC_{50} values were 1.0 mM and 7.0 mM, respectively (Ren *et al.*, 2004).

Salvia officinalis. On the basis of traditional medicine, the *in vitro* cholinergic binding properties and the modulation of mood and cognitive performance in humans it was thought that *Salvia officinalis* might potentially provide a novel natural treatment for Alzheimer's disease. In one placebo-controlled clinical trial, the efficacy and safety of *S. officinalis* extract in patients with mild to moderate Alzheimer's disease was evaluated using a fixed dose, over a 4-month period, in three centers in Tehran, Iran. The results indicated that after 4 months, the *S. officinalis* extract produced a significantly better outcome on cognitive function than placebo, and there were no significant differences in the two groups in terms of observed side-effects, except that agitation appeared to be more frequent in the placebo group (Akhondzadeh *et al.*, 2003).

ANTICONVULSANT ACTIVITY

Salvia haematodes. The ethanol extract of *S. haematodes* decreased the clonic and tonic extensor phases of electroshock seizures in mice (Akbar *et al.*, 1984). Also the aqueous extract of the root of this plant showed significant anticonvulsant activities (Akbar *et al.*, 1985).

Salvia leriifolia. The anticonvulsant activity of different parts of this plant was studied using electroshock and metrazol tests. The results indicated that in the metrazol test, the aqueous extract of the leaf and the alcohol extract of the seed showed maximal latency in convulsion initiation time and their effects were similar to pentobarbital, however, they could not prevent animal death. In the electroshock test, none of extracts exerted a significant protective effect. These results suggest that *S. leriifolia* may be useful in petit mal seizure as adjuvant treatment (Hosseinzadeh and Arabsanavi, 2001).

Salvia sclarea. The essential oil from this plant at a dose of 125 mg/kg showed activity against electroshock

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convulsions, but not with corazole- or strychnine-induced convulsions. At 400 mg/kg, the essential oil slightly prolonged the latency period of corazole convulsions and the survival time, and slightly increased the survival time in strychnine convulsions (Atanasova-Shopova and Rusinov, 1970).

NEUROPROTECTIVE EFFECT

Salvia leriifolia. For evaluation of the neuroprotective effect of this plant, ischemia was induced in rats using the four-vessel occlusion model for 20 min and evaluated pathologically using optical and transmission electronic microscopes (Hosseinzadeh *et al.*, 2002). Malonyldialdehyde (MDA) levels were also determined in the hippocampus of rats (as an index of lipid peroxidation) using the thiobarbituric acid (TBA) test (Sadeghnia *et al.*, 2003). The results of these studies showed the aqueous and especially the ethanol extracts of *S. leriifolia* radix had protective effects against ischemic injury and significantly decreased the lipid peroxide level in rat hippocampus following global cerebral ischemia. In the model of four-vessel occlusion global cerebral ischemia, it was shown that the aqueous extracts of *S. leriifolia* seed had a neuroprotective effect in the rat hippocampus (Khooei *et al.*, 2003).

Salvia miltiorrhiza. This plant is considered in Chinese medicine to have an action of 'quickening the blood' and 'dispelling stasis', and is frequently used to treat related disorders such as cerebrovascular accident and ischemic heart disease. A model of incomplete cerebral ischemia involving bilateral ligation of the common carotid arteries in the rat was used to examine the potential of *S. miltiorrhiza* to reduce cell damage following cerebral ischemia. The results showed that in this model of cerebral ischemia, the degree of lipid peroxidation could be lowered by pretreatment with an extract of this plant (Leung *et al.*, 1991). In another study, the potential neuroprotective effects of tanshinones IIA (TsIIA) and IIB (TsIIB) were examined in adult mice subjected to transient focal cerebral ischemia caused by middle cerebral artery occlusion (MCAO). The results revealed that 24 h after middle cerebral artery occlusion, brain infarct volume was reduced by 30% and 37% following treatment with TsIIA and TsIIB, respectively. The reduction in the brain infarct volume was accompanied by a significant decrease in the observed neurological deficit (Lam *et al.*, 2003). Also in one model of focal cerebral infarction developed by occluding both common carotid arteries and the right middle cerebral artery for 90 min, pretreatment with an intraperitoneal injection of *S. miltiorrhiza* reduced the area of cerebral infarct (Chih-Jui *et al.*, 2003). Acetylsalvianolic acid, a semisynthetic analogue of salvianolic acid A, significantly reduced the cerebral infarction and attenuated neurological deficits (87. 4%, $p < 0.01$) (Dong and Xu, 1996).

Several mechanisms have been considered for the anti-ischemic effects of this plant. Some studies have showed free radical scavenging activities (Huang and Zhang, 1992; Wang *et al.*, 1997; Leung *et al.*, 1991) and others have demonstrated an inhibitory effect on superoxide production (Byung-Soo *et al.*, 2004; Huang and Zhang, 1992). Different compounds, including lithospermate B (Do *et al.*, 2003; Zhi-xin *et al.*, 2004), (+)-1-hydroxypinoresinol-1-O-b-D-glucoside (Hye Sook *et al.*, 2003a), salvianic acid A (Xin-Jian and Jian-Xing, 2005), salvianolic acid B and rosmarinic acid (Huang and Zhang, 1992), have been suggested as active components of the plant. Other mechanisms that have been proposed for the neuroprotective effect of *S. miltiorrhiza* include the attenuation of monoamine neurotransmitters dysfunction (Cheng, 1999), reduction of NO production during reperfusion (Kuang, 1996), increase in GABA and a decrease in glutamate concentration during reperfusion (Kuang, 1994), antithrombotic effects (Yu, 1994; Tang *et al.*, 2002; Rong-jun *et al.*, 2004), reduction of platelet-derived growth factor A expression (Jiang *et al.*, 1999), inhibition of endothelin-1 gene expression (Wu, 1997a), reduction of neuron apoptosis induced by cerebral ischemia (Wu, 1997b), Ca^{2+} antagonistic action (Xiaohong *et al.*, 2003), N-methyl-D-aspartate (NMDA) receptor (NMDAR) antagonistic properties (Xiaoru *et al.*, 2003), reversion of the abnormal post-ischemic elevation in neuropeptide Y1-36 (Hong *et al.*, 2002), increasing cerebral blood flow (Liquan *et al.*, 1998; Shao, 1992) and decreasing extracellular fluid cysteine levels (Jingjun *et al.*, 1997). Also, a study of the protective effects of radix *S. miltiorrhiza* combined with nimodipine on the cochlea in an ischemia-reperfusion injury model of guinea-pigs showed that this combination can prevent the cochlea from ischemia reperfusion injury efficiently (Fanglei and Mingmin, 2003).

Other species. Sage (*S. officinalis*) has shown antioxidant activity in some studies. For example, administration of this plant to the rat improved the liver antioxidant potential (Lima *et al.*, 2005; Se Won and MiKyung, 2003). Carnosic acid, carnosol, rosmanol and caffeic acid are responsible for the free radical scavenging activity of sage (Matsingou *et al.*, 2003; Dorman *et al.*, 2003). Other species of *Salvia* that possess antioxidant activity include *S. sclarea*, *S. glutinosa*, *S. pratensis* (Miliauskas *et al.*, 2004), *S. fruticosa* (Oezcan, 2003; Saricoban and Ozcan, 2004), *S. plebeia* (Hye Sook *et al.*, 2003b) and *S. candelabrum* (Janicsak *et al.*, 2003).

ANTIPARKINSON AND MAO INHIBITORY EFFECTS

Salvia miltiorrhiza. The crude water extract (0.1 g/mL) of this plant significantly increased K^+-stimulated dopamine release ($p < 0.001$) from rat striatal slices and potentiated the effect of amphetamine on K^+-stimulated dopamine release. It seems that the extract may stimulate dopamine release in the same manner as amphetamine (Byung-Soo *et al.*, 2004). On the other hand, a study showed that *S. miltiorrhiza* does not alter dopamine (DA) and its metabolites [dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA)] in the corpus striatum in rats (Xu *et al.*, 2003). In another study, salvianic acid A had a protective effect on MPP+-induced cytotoxicity in human neuroblastoma SH-SY5Y cells. It has been suggested

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that this protective effect of salvianic acid A may be ascribed to its antioxidative properties and anti apoptotic activity via regulating the expression of Bcl-2 and Bax. These data indicate that salvianic acid A might provide a useful therapeutic strategy for the treatment of Parkinson's disease as a progressive neurodegenerative disease (Xin-Jian and Jian-Xing, 2005). Some studies have shown a monoamine oxidase (MAO) inhibi-tory effect for this plant. For example, four tanshinone-type diterpenoids isolated from this plant inhibited human recombinant MAO-A, with an IC_{50} of the most active compound (15,16-dihydrotanshinone) of 23 mM (Dittmann *et al.*, 2004). In another study *S. miltiorrhiza* showed inhibitory effects on MAO-B in rat brain homogenates (Lin *et al.*, 2003).

INHIBITION OF ETHANOL AND OPIOID WITHDRAWAL SYNDROME

Salvia leriifolia. The ethanol extract of the leaves of this plant reduced the number of jumps caused by withdrawal syndrome to morphine in mice. The extract at a dose of 500 mg/kg was as effective as diazepam at 5 mg/kg. The effect of the extract was antagonized by aminophylline, indicating a possible effect of the extract on the adenosine system (Hosseinzadeh and Lari, 2000).

Salvia miltiorrhiza. Recent research has demonstrated that extracts of the dried roots of *S. miltiorrhiza* were effective in reducing voluntary alcohol intake in selectively bred Sardinian alcohol-preferring rats which had the opportunity to consume alcohol for several weeks before the test with *S. miltiorrhiza* extracts (Brunetti *et al.*, 2003). A further experiment demonstrated that a combination of polysorbate 80 in water plus *S. miltiorrhiza* decreased alcohol intake even more effectively, suggesting that polysorbate 80 is a suitable vehicle for investigating the ameliorating effect of *S. miltiorrhiza* extracts on alcohol intake (Vacca *et al.*, 2003). Also, IDN 5082, a standardized extract of *S. miltiorrhiza*, dose-dependently delayed the acquisition of alcohol drinking behavior in Sardinian alcohol-preferring rats that had never experienced alcohol before the study. These results add further support to the preclinical anti-alcohol profile of *S. miltiorrhiza* extracts (Brunetti *et al.*, 2003). Miltirone (1–10 mM), characterized as a low-affinity ligand for central benzodiazepine receptors, also partially inhibited the increase in the abundance of the mRNA for the a4 subunit of the GABAA receptor induced by ethanol withdrawal in cultured hippocampal neurons. These results suggest that miltirone might attenuate the symptoms associated with the discontinuation of long-term administration of ethanol (Mostallino *et al.*, 2004).

CONCLUSION

Pharmacological and phytochemical research carried out during the past two decades confirms many traditional uses for plants of the genus *Salvia* in various CNS diseases. There is, however, a need for further studies to evaluate other folk uses of these plants and to test other less well-known and widespread species such as *S. leriifolia*. In some studies, the active ingredient and mode of action of the plants have been determined to some extent, and this will facilitate the steps needed to use these plants safely and perhaps to develop new medicines. In many other studies, only preliminary results using crude extract have been obtained. Despite showing good pharmacological or therapeutic effects, there is still a need for more precise studies to determine and separate the active compounds and elucidate their mechanisms of action where possible.

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