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The Pharmacological Properties of *Salvia* Essential Oils

Zhiming Fu, Hang Wang, Xiaofei Hu, Zhaolin Sun, Chunchao Han*
School of Pharmacy, Shandong University of Traditional Chinese Medicine, Jinan250355, People's Republic of China.

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ABSTRACT

Salvia essential oils isolated by hydrodistillation from the plant's commercial dried aerial parts(Fig.1), have powerful biological activity and pharmacological properties. The oils contain more than 100 different bioactive compounds, which mainly include Monoterpene hydrocarbons, Oxygenated monoterpenes, Sesquiterpene hydrocarbons, Diterpenes, Not iso-prenoid compounds and Oxygenated sesquiterpenes. It has a number of pharmacological effects including antimicrobial, antioxidant, anti-cholinesterase, improvement of cognitive performance and mood, reducing work-related stress, anti-mutagenic, anticancer, anti-inflammatory, choleretic activities and so on. The present review focuses on the pharmacological activities of *Salvia* essential oils.

INTRODUCTION

The genus *Salvia* is one of the largest genera of the Lamiaceae family and is represented by more than 900 species spread throughout the world. Numerous species of the *Salvia* genus are economically important since they are used as spices and flavouring agents in the field of perfumery and cosmetics (Felice Senatore *et al.*, 2004 and 2006). *Salvia* has also been used since ancient times in folk medicine and has been subjected to extensive pharmacognostic research intended to identify biologically active compounds.

There are some significant activities and properties of *Salvia* essential oils, including antimicrobial, antioxidant, anti-cholinesterase, improvement of cognitive performance and mood, reducing work-related stress, antimutagenic, anticancer, anti-inflammatory, choleretic activities (Fig.2). The pharmacological effects of *Salvia* essential oils are based on the presence of more than 100 active elements which can be categorized into Monoterpene hydrocarbons, Oxygenated monoterpenes, Sesquiterpene hydrocarbons, Diterpenes, Not iso-prenoid compounds and Oxygenated sesquiterpenes. The major components contain 1, 8-cineole, camphor, borneol, β-pinene, α-pinene, camphene and α-thujene and each of them has their own outstanding medicinal effects. Because of its presumed health benefits and apparent absence of side-effects, the present review will focus on the pharmacological activities of *Salvia* essential oils.

** Corresponding Author*
Email: shandongtcmh@126.com

Antimicrobial activity

The antimicrobial properties of the essential oils have been well recognized for many years, and as naturally occurring antimicrobial agents, they have been applied to pharmacology, pharmaceutical botany, phytopathology, medical and clinical microbiology, and food preservation. Furthermore, the essential oils of some *Salvia* species have recently been investigated, showing strong antimicrobial activity. Morteza Yousefzad *et al.* demonstrated that *S. chloroleuca* oil exhibited moderate to high antimicrobial activity, especially for Bacillus subtilis, Staphylococcus epidermidis and *S. aureus* with inhibition zones of 21, 19, 15 mm and MIC values of 3.75, 3.75 and 7.5 mg/ml, respectively. Moreover, the study showed the antimicrobial activity of five major components of the oil, included 1, 8-cineole, α-pinene, β-pinene, β-caryophyllene and carvacrol. Among of these components, the antimicrobial activity of carvacrol was superior compared to the other components (Morteza Yousefzadi *et al.*, 2007). The MICs values (ranged from 0.015 to 0.25μL/mL) and the MIC/MCC ratio (close to 1) confirmed that *S. officinaliscs* had inhibitive effect on a large panel of bacterial strains including Gram+ and Gram– of rods and cocci (Mohamed Bouaziz *et al.*, 2009).

S. przewalskii oil also showed an antimicrobial activity against Staphylococcus aureus and *S. epidermidis* strains (MIC values ranged from 2.5 to 10 mg/ml) (Morteza Yousefzadi *et al.*, 2007). Ali Sonboli *et al.* performed bioassays with the oils of *S. santolinifolia*, *S. hydrangea* and *S. mirzayanii*, and the results proved that these oils have the antimicrobial property. Furthermore, the antimicrobial property of *S. myrzayanii* oil was superior to others (Ali Sonboli *et al.*, 2006). Besides, *S. fruticosa*, *S. tomentosa*, *S. officinalis* and *S. lavandulifolia* were testified the property of inhibiting the growth of bacteria (C. Rota *et al.*, 2004 and Nurdan Sarac *et al.*, 2008). The essential oils of *Salvia* species not only have the antibacterial activity, but also have the antifungal activity.

Danae Pitarokili *et al.* had already demonstrated the antifungal activity of the *S. fruticosa* essential oils and the main components that is 1, 8-cineole and camphor. In this study, 1, 8-cineole was the most abundant component (16.9-48.3% of total oil) in all analyzed oils. The constituents were evaluated in vitro against five phytopathogenic fungi and the result revealed that they owned slightly effective against Fusarium oxysporum f. sp. dianthi and Fusarium proliferatum, but had exhibited high antifungal activities when against Rhizoctonia solani, Sclerotinia sclerotiorum, and Fusarium solanif. sp. cucurbitae. Mycelial growth of R. solani, which was found to be the most sensitive fungus, was completely inhibited by the essential oils at a concentration of 2000μL/L (Pitarokili D *et al.*, 2003). Nurhayat Tabanca *et al.* reported some researches about the antifungal activity of *S. Macrochlamys* and *S. recognita* essential oils. The consequence displayed that the antifungal activity of the essential oils of *Sal via* species was nonselective at inhibiting growth and development of reproductive stroma of the plant pathogens, including Colletotrichum acutatum, Colletotrichum fragariae, and Colletotrichum gloeosporioides. *S.macrochlamys* oil was researched that could exert good antimycobacterial activity against Mycobacterium intracellulare. However, the oil showed no antimicrobial activity against human pathogenic bacteria or fungi at concentrations up to 200μg/Ml (Tabanca N *et al.*, 2006). Factors influencing the antimicrobial activity of essential oils *in vitro* and the mechanisms of essential oils action on microorganisms are reported. D. Kalemba *et al.* gave an overview on the susceptibility of human and food-borne bacteria and fungi with different essential oils and their constituents. Essential oils of spices and herbs were found to possess the strongest antimicrobial properties in many tests (Kalemba D *et al.*, 2003).

Salvia officinalis *Salvia fruticosa* *Salvia przewalskii*

Fig. 1: The aerial parts of the genus *Salvia*.

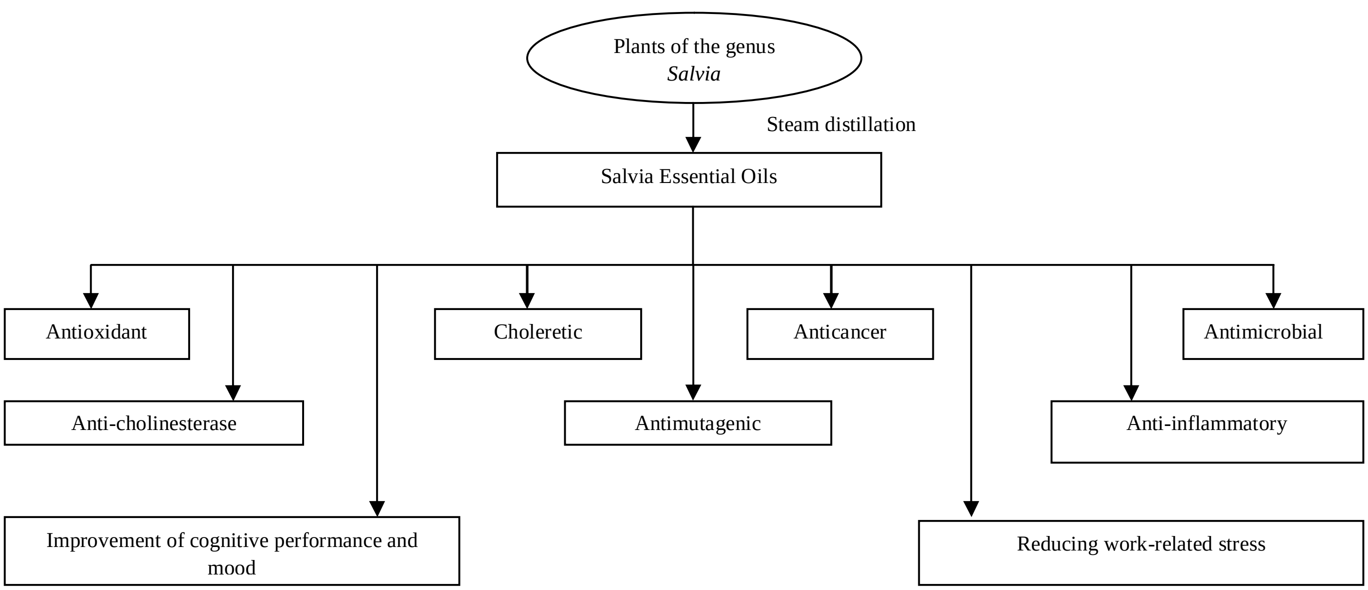

Fig. 2: The Pharmacological properties of *Salvia* essential oils.

Antioxidant activity

One of bioactivities of the *Salvia* essential oils is attributed mainly to antioxidant activity and the major effective content are polyphenols and terpenes. Some polyphenolic extracts from *Salvia* were examined by Dimitrios Stagos *et al.* for antioxidant activity in correlation with their polyphenolic content. The results revealed that the tested polyphenolic extracts had strong free radical scavenging activity against DPPH_ and ABTS_+ radicals and protected from hydroxyl and peroxyl radical-induced DNA damage. Moreover, the results showed that the total polyphenolic content is not correlated with the above activity (Stagos D *et al.* 2012).

Gian Carlo Tenore *et al.* evaluated the antioxidant activities of *S. lanigera Poir*. essential oil using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and FRAP methods together with three antioxidant standards, L-ascorbic acid, tert-butyl-4-hydroxy toluene (BHT) and gallic acid.

The results of DPPH test and FRAP assay are indicative of the capacity of the oil to scavenge free radicals. This capacity could be attributed to oil phenolic components (mainly, carvacrol and thymol) and to their hydrogen donating ability by which they are considered potent free radical scavengers (Tenore GC *et al.,* 2011). *S. euphratica* , *S. Fruticosa* and *S. eremophila* essential oils were also turned out to have antioxidant activities (Yumrutas O *et al.,* 2012, Papageorgiou V *et al.,* 2008 and Ebrahimabadi AH *et al.,* 2010) .

Anti-cholinesterase activity

David O Kennedy and N. S. L. Perry performed an *in vitro* investigation of the cholinesterase inhibitory properties respectively, which demonstrated the *S. lavandulaefolia* essential oil was a highly potent selective inhibitor of AChE (David O Kennedy *et al.,* 2011, Perry NS *et al.,* 2000). Moreover, N. S. L. Perry(2000) found that the main monoterpenoids of *S. lavandulaefolia* essential oil (1,8-cineole and α-pinene) exhibited considerably great inhibition of human erythrocyte AChE with IC50 values of 0.67mM and 0.63mM, respectively(Perry NS *et al.,* 2000). N. S. L. Perry (2002) reported *S. lavandulaefolia* oil decreased the rat brain AChE activity *in vivo* at doses of 20 and 50μl. It suggested that constituents of *S. lavandulaefolia* oil or their metabolites reaching the brain inhibit cholinesterase in select brain areas, consistent with evidence of inhibition of the brain enzyme *in vitro* (N. S. L. Perry *et al.,* 2002).

In addition, the essential oil of *S. officinalis* exhibited a moderate inhibition towards AChE with 63.8% inhibition. *S. officinalis* and *S. sclarea* oils displayed a notable inhibition towards BChE having 66.3 and 76.0 % inhibition, respectively (Ilkay Orhan *et al.,* 2008).

The essential oil of *S. fruticosa* also showed high inhibition against acetylcholinesterase activity at 100μg/mL , whereas the oil only had a lower inhibitory effect on butyrylcholinesterase (Senol FS *et al.,* 2011). The property of *Salvia* oils may help explain its traditional use for ailing memory.

Improvement of cognitive performance and mood

Members of the *Salvia* family have a longstanding reputation in British herbal encyclopaedias as an agent that enhances memory. Several experiments had showed that *Salvia* essential oils may be relevant to the amelioration of the mood and cognition.

Lucy Moss *et al.* evaluated the potential for the aromas of the essential oils of *S. officinalis* and *S. lavandulaefolia* to affect cognition and mood in healthy adults. Cognitive performance was assessed via the Cognitive Drug Research (CDR) System and the participants' mood was measured with Bond–Lader mood scales. These findings revealed *S. officinalis* aroma produced a significant enhancement effect for the quality of memory factor derived from the CDR System. However, no significant effects were found for *S. lavandulaefolia* aroma on any of the cognitive performance factors (Lucy Moss *et al.,* 2010).

Tildesley *et al.* showed that administration of *S. lavandulaefolia* resulted in significant improvements in word recall and the quality of memory factor scores. Significant improvements in 'calm', 'content' and 'alert' aspects of mood assessed via the Bond–Lader scale were also recorded (N.T.J. Tildesley *et al.,* 2005). Oral consumption of *S. lavandulaefolia* essential oil led to improved performance of secondary memory and attention tasks, most notably at the 1-h post-dose testing session, and reduced mental fatigue, meanwhile increased alertness which were more pronounced 4-h post-dose (David O Kennedy *et al.,* 2011).

Reducing work-related stress

Most of the volatile oil from the nature have been revealed the action of making people feel relax and reduce stress. Erin Pemberton *et al.* reported the combination of *Lavandula angustifolia* and *S. sclaria* essential oils had a positive effect on reducing work-related stress of nurses in an ICU setting (Erin Pemberton *et al.,* 2008). Furthermore, *S. sclaria* also had been proved the relaxing and calming effects in the clinical application (Buckle J *et al.,* 2003).

Antimutagenic activity

Antimutagenic effect of the essential oil of *S. officinalis* and its monoterpenes against UV-induced mutations were studied with Escherichia coli and Saccharomyces cerevisiae （B. Vukovic´-Gacˇic´ *et al.,* 2006.

The result showed that essential oil of *S. officinalis* significantly decreased the number of UV-induced revertants in a concentration-dependent manner, reaching 50–70% of inhibition at the maximum non-toxic concentrations: 3μl/plate (TA102), 5μl/plate (WP2), 7.5μl/plate (IB112), 30μl/plate (E. coli K12 SY252) and 60μl/plate (D7). Whilst, the antimutagenic activity of oxygen-containing monoterpenes, tested with SY252 and D7, reached 40–50% at 15–20μl/plate of thujone, 10μl plate of cineole and 1–10μg /plate of camphor. And limonene showed antimutagenic effect only in D7.

Anticancer activity

Biological studies have demonstrated that the essential oils of *Salvia* species have potential anticancer activity. *S. officinalis* oil was able to inhibit the growth of renal cell adenocarcinoma with IC50 of 100.70μg/ml. The oil was unable to react with human breast cancer cell (MCF-7) and hormone dependent prostate carcinoma cell (LNCaP) (Loizzo MR *et al.,* 2007). Additionally, the cytotoxicity of the essential oil on the squamous human cell carcinoma cell line of the oral cavity (UMSCC1) was also assessed with the XTT assay. It revealed that low concentrations of the essential oil increased vitality of the UMSCC1 cells. Beyond the concentration of the IC50 of 135μg/ml, *S. officinalis* oil reduced UMSSC1 cells viability to a minimum (Sertel S *et al.,* 2011).

Wafica S. Itani *et al.* found that combining the three bioactive compounds of *S. libanotica* essential oil, Linalyl acetate (Ly) Terpeniol (Te) and Camphor (Ca) caused significant growth suppression of HCT116 p53+/+ cells in PreG1 (64% at 48 hours). In p53-/- cells, Ly + Te + Ca caused cell accumulation in PreG1 and G2/M phases. In response to the three components, 58% apoptosis occurred in p53+/+ cells and 38% in p53-/- cells (Itani WS *et al.* 2008). In addition, the anti-proliferative activity of *Salvia* oils on human cancer cell lines was investigated. *S. leriifolia* exhibited a strong inhibitory activity on renal adenocarcinoma ACHN, large cell carcinoma COR-L23, amelanotic melanoma C32, and malignant melanoma A375 with IC50 values of 6.8, 7.5, 9.1, and 12.5μg/mL respectively. *S. acetabulosa* inhibited the viability of C32 and COR-L23cell lines with IC50 values of 6.3 and 6.5μg/mL. However, both *S. acetabulosa* and *S. leriifolia* couldn't exert anti-proliferative activity against human skin fibroblast 142BR (Loizzo MR *et al.,* 2010).

Anti-inflammatory activity

Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids which affect the brain. Š. JUHÁS showed anti-inflammatory activity of borneol on TNBS-induced colitis in mice, which is one of the active components of *S. officinalis* essential oil. They evaluated cytokine mRNA expression in colonic tissue using quantitative real-time RT-PCR, and found that borneol was able to significantly decrease pro-inflammatory cytokine (IL-1β and IL-6) mRNA expression in colonic inflammation at two concentrations (0.09% and 0.18%) in comparison to the control group. (Juhás S *et al.,* 2008).

Choleretic activity

Components of plant essential oils have been reported that they have health benefit properties, including antioxidative, anti-tumour, antimicrobial, and anti-stress. However, few papers reported the choleretic activity of the genus *Salvia*. Alessandra Peana's study showed that the essential oil of *S. desoleana* had a strong choleretic effect (Peana A *et al.,* 1994). The male Wistar rats was administered with the essential oil and its oxygen-containing fractions (esteric: B, alcoholic: C). One hour after administration of essential oil and fraction C, the bile flux increased respectively 35% compared to basal value. This result could explain its efficacy in the empirical treatment of some digestive problems.

Toxicological property

Experimental studies on the toxicity of the essential oil of *Salvia* species are scarce despite its wide use in traditional medicine. G.N. Farhat *et al.* investigated the relationship between seasonal changes in *S. libanotica* oil composition and toxicity (G.N. Farhat *et al.,* 2001). The toxicity of the oil was investigated following intraperitoneal (i.p.) injection into mice. Essential oil extracted from plants collected in the winter season (January), which contained higher levels of camphor (12.3%), α, β-thujone (1.9%), and camphene (4.8%), was found to be the most toxic, (LD50: 839 mg/kg body weight) and exhibited powerful convulsant properties. However, the spring extract was the least toxic (LD50: 1200 mg/kg body weight) and contained lower levels of camphor (7.7%), α, β-thujone (1.3%) and camphene (3.1%). These data indicated that there was a strong correlation between the contents of camphor, thujones and camphene and the oils' toxicity.

C.F.Lima *et al.* evaluated toxic/protective effects of the essential oil of *S. officinalis* on freshly isolated rat hepatocytes by measuring cell viability (LDH leakage), lipid per-oxidation and glutathione status. The results showed that essential oil (EO) of *S. officinalis* did not exhibit toxic effect on the rat hepatocytes at concentrations below 200nl/ml, whereas a significant LDH leakage and GSH decrease were observed at the concentration of 2000nl/ml, which indicated cell damage (Lima CF *et al.,* 2004).

Other beneficial aspects of *Salvia* essential oils

Salvia essential oils are economically and ecologically important not only as a source of medicinal but its role in cosmetic products. Taking into account the increasing interest for new and safe essential oils and considering that many species belonging to the *Salvia* genus have not been fully investigated yet, C. Villa *et al.* evaluated the *S. somalensis Vatke* essential oil in terms of chemical composition, scent and safety. The odour evaluation of the essential oil revealed peculiar olfactive characteristics interesting in alcoholic male perfumery and body detergents. And *in vitro* cytotoxicity assays displayed slight cytotoxic effects. The promising results indicated that this essential oil as an interesting potential functional ingredient was useful in a cosmetic context (C. Villa *et al.,* 2009).

CONCLUSION

Essential oils, aromatic oily liquids obtained from plants, may be an alternative source of mosquito larval control agents, since they are rich sources of biologically active compounds that are biodegradable and potentially suitable for use in integrated management programs. The genus *Salvia* (*Lamiaceae*) is one of the largest genera of flowering plants, with more than 900 species spread throughout the world, largely cultivated for ornamental, aromatic, and culinary usage. Therefore, the essential oils of *Salvia* species also exert many various pharmacological activities. The present review reported the main and significant pharmacological activities of *salvia* essential oils, including antimicrobial, antioxidant, anticholinesterase, improvement of cognitive performance and mood, reducing work-related stress, antimutagenic, anticancer, anti-inflammatory, and choleretic activities (Table 1). Although *Salvia* essential oils appear to serve as an effective adjuvant role in the treatment of memory deficits, the mechanism of this effect is unknown. It appears that there are a number of biologically active compounds explored in *Salvia* essential oil and the future research may be oriented in that direction.

Table. 1: Pharmacological Effects of *Salvia* essential oils Reported in the Literature.

Pharmacological activities	*Salvia* essential oils	References
Antimicrobial activity	*S. officinalis, S. chloroleuca, S. przewalskii, S. santolinifolia, S. hydrangea, S. mirzayanii, S. fruticosa, S. tomentosa , S. recognita, S. Macrochlamys* and *S. lavandulifolia*	Mohamed Bouaziz *et al.*, 2009; Morteza Yousefzadi *et al.*, 2007; Morteza Yousefzad *et al.*, 2007; Ali Sonboli *et al.*, 2006; C. Rota *et al.*, 2004; Pitarokili D *et al.*, 2003 and Nurdan Sarac *et al.*, 2008.
Antioxidant activity	*S.lanigera Poir, S. officinalis, S.euphratica, S. fruticosa*, and *S.eremophila*	Stagos D *et al.*, 2012; Tenore GC *et al.*, 2011; Ben Farhat M *et al.*, 2009. Yumrutas O *et al.*, 2012; Papageorgiou V *et al.*, 2008 and Ebrahimabadi AH *et al.*, 2010.
Anti-cholinesterase activity	*S.lavandulaefolia, S. officinalis,* and *S. fruticosa*	David O Kennedy *et al.*, 2011; Perry NS *et al.*, 2000; N. S. L. Perry *et al.*, 2002; Ilkay Orhan *et al.*, 2008 and Senol FS *et al.*, 2011
Improvement of cognitive performance and mood	*S.officinalis,* and *S.lavandulaefolia*	Lucy Moss *et al.*,2010; N.T.J. Tildesley *et al.*, 2005 and David O Kennedy *et al.*, 2011.
Reducing work-related stress	*S. sclaria*	Erin Pemberton *et al.*, 2008 and Buckle J *et al.*, 2003.
Antimutagenic activity	*S. officinalis*	B. Vukovic´-Gacˇic´ *et al.*, 2006
Anticancer activity	*S.officinalis, S. libanotica S. leriifolia* and *S. acetabulosa*	Loizzo MR *et al.*, 2007; Loizzo MR *et al.*, 2010 and Itani WS *et al.*, 2008.
Anti-inflammator activity	*S. officinalis*	Juhás S *et al.*, 2008
Choleretic activity	*S. desoleana*	Peana A *et al.*, 1994
Toxicological property	*S. officinalis* and *S. libanotica*	Lima CF *et al.*, 2004 and G.N. Farhat *et al.*, 2001

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