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Chemistry, Pharmacology and Medicinal Property of Sage (Salvia) to Prevent and Cure Illnesses such as Obesity, Diabetes, Depression, Dementia, Lupus, Autism, Heart Disease and Cancer

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Abstract- Sage (Salvia) species is known as the Functional Novel Natural Medicine, Salvia Extract are considered important for drug development, because they are reported to have Pharmacological activity in the Asia, Middle East especially China and India. For a long time Salvia has been used in traditional medicine for the relief of pain, protecting the body against oxidative stress, free radical damages, angiogenesis, inflammation, bacterial and virus infection, etc. Several studies suggest that sage might potentially provide novel natural treatments for the relief or cure of many serious and life threatening diseases in addition to treating minor common illnesses such as depression, dementia, obesity, diabetes, lupus, heart disease and cancer. This plant is used as Medicine in Asia, Africa, Middle East, South America, and some Countries in Europe. This article presents comprehensive analysis information on botanical, chemical and Pharmacological aspect of Sage (Saliva).

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Chemistry, Pharmacology and Medicinal Property of Sage (Salvia) to Prevent and Cure Illnesses such as Obesity, Diabetes, Depression, Dementia, Lupus, Autism, Heart Disease and Cancer

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Keywords: sage (salvia species), traditional remedies, pharmacological property.

I. Introduction

The genus Salvia, commonly known as sage is the largest member of Lamiacea or mint family containing over 900 species throughout the world (Nikavar, 2008; Itani, 2008). The plants are mostly aromatic, perennial, with flowers in different colors (Ayatollahi, 2009). Many species of Salvia, including Salvia officinalis (Common sage) are native to Mediterranean region and some of the salvia species have been used worldwide as flavoring spices as well as traditional herbal medicine (Ayatollahi, 2009; Smidling, 2008) Sage tea has been traditionally used for the treatment of digestive and circulation disturbances, bronchitis, cough, asthma, angina, mouth and throat inflammations, depression, excessive sweating, skin and many other diseases (Khalil, 2011; Walch, 2011; Khan, 2011). Salvia essential oils have been used in the treatment of large range of diseases like, nervous system, heart and blood circulation, respiratory, digestive, metabolic and endocrine diseases, and in addition sage essential oil have shown to have carminative, antispasmodic, antiseptic and astringent properties (Loizzo, 2007; Radulescu, 2004).

The essential oil of Salvia species can have various compositions depending on the genetic, climates, season and environmental factors (Hadri, 2010). There are some chemical compounds like flavonoids, terpenoids and essential oils present in different species of salvia (Ayatollahi, 2009). Essential oils are very important sources for the screening of anticancer, antimicrobial, antioxidant, and free radical scavenging agents (Hussain, 2011). Salvia officinalis (Common sage) is considered to have the highest amount of essential oil compared to the other species of Salvia (Khalil, 2011; Avato, 2005).

In all analyzed samples of S. officinalis, the major components, although in different extent are: 1, 8-cineole, camphor, borneol, bornyl acetate, camphene, α-and β-thujone, linalool, α-and β-caryophyllene, α-humulene, α-and β-pinene, viridiflorol, pimaradiene, salvianolic acid, rosmarinic acid, carnosolic acid, ursolic acid and etc. (Khan, 2011; Avato, 2005). Studies have shown that some biological properties of the essential oil of salvia, depend on camphor, 1, 8-cineole, α-thujone and β-thujone (Radulescu, 2004). The essential oil of sage contains about 20% camphor, and as the leaves expand, the camphor contents also increases (Crotea,1981) .The better radical scavenging activities of S. officinalis essential oil might be because of the high content of 1, 8-cineole (Hussain, 2011).

Sage is also a natural source of flavonoids and polyphenolic compounds (e.g. carnosic acid, rosmarinic acid and caffeic acid) possessing strong antioxidant, radical-scavenging and antibacterial activities (Baranauskiene, 2011). The majority of the phenolic acids in salvia species are derivatives of caffeic acid

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which is the building block of a variety of plant metabolites (Kamatou, 2009). Caffeic acid plays a central role in the biochemistry of the Lamiaceae and occurs mainly in dimmer form as rosmarinic acid (Kamatou, 2009). Carnosic acid and rosmarinic acid which are present at high concentration in the extract of sage plants, have shown strong antioxidant properties (Yurtseven, 2008). Ursolic acid, also as a component of sage, has strong anti-inflammatory properties and in sage preparations, is considered as a quality control measurement for the anti-inflammatory effects of different solutions (Baricevic, 2001).

Figure 1 : Salvia officinalis

Figure 2 : Salvia officinalis Flowers

Figure 3 : Salvia officinalis “sage Leaves”

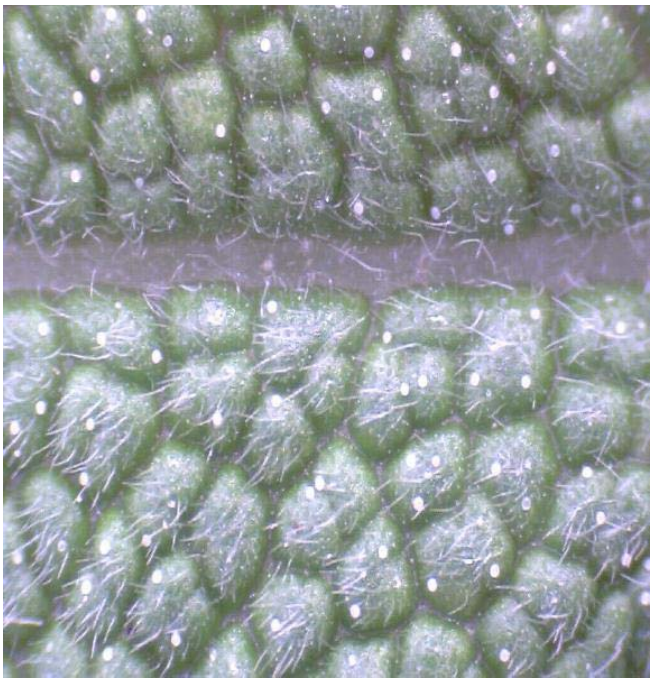
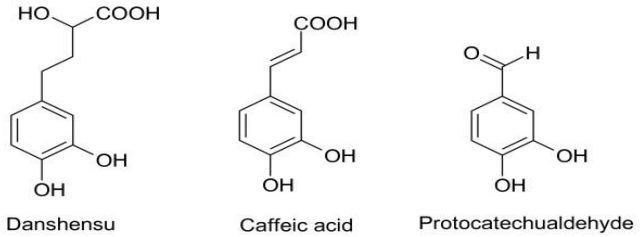


Figure 4 : Sage leaf - trichomes are visible

II. Common Names

Salvia officinalis has numerous common names. Some of the best known include sage, common sage, garden sage, golden sage, kitchen sage, true sage, culinary sage, Dalmatian sage, and broadleaf sage. Cultivated forms include purple sage and red sage. In Turkey, Salvia officinalis is widely known as adaçayı, meaning "island tea". In the Levant it’s called maramia.



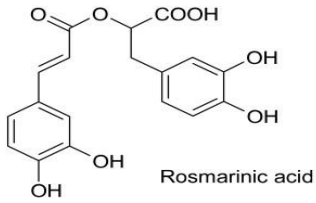
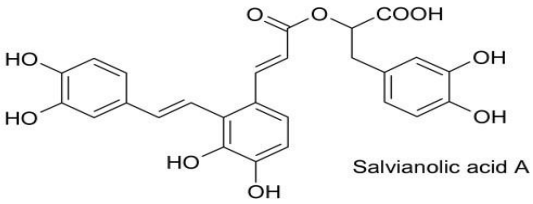


Figure 5 : Danshensu and monoterpenoids from *S. miltiorrhiza*. All of these compounds contain catechol functionalities

Adams *et al. Chinese Medicine* 2006 **1**:3 doi: 10.1186/1749-8546-1-3



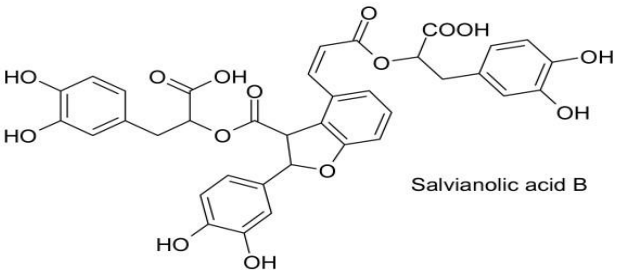


Figure 6 : Salvianolic acids from *S. miltiorrhiza*. All of these compounds contain catechol moieties.

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Table 1: Essential oil Composition (% of Major components) of Sage Salvia Officinalis collected as a sample (Khalil, 2011).

Compound*	S. Officinalis **	S. Officinalis ***
(1R)- (+)-a-Pinene	3.70	4.50
(-)- Camphene	2.60	5.00
B- Pinene	6.00	5.20
Sabinene	-	0.30
B- Myrcene	3.00	3.50
a-Terpinene	-	0.40
(R)- (+) Limonene	-	-
1, 8 – Cineole	62.0	55.0
Y- Terpinene	0.30	0.50
P-Cymene	0.60	0.60
Terpinolene	-	0.20
(-)-a-Thujone	1.38	1.80
B-Thujone	0.72	1.50
Camphor	8.0	10.0
(-)-Linalool	0.80	0.80
Linalyl acetate	0.60	0.30
(-)-Trans-Caryophyllene	2.00	1.00
Monoterpene	1.26	1.10
(+)-Menthol	-	-
Borneol	5.00	4.50
a- Terpineol	0.20	-
Geranyl acetate	0.30	-
Geraniol	0.10	0.25
Phytol	0.18	-
Thymol	0.80	0.70
Carvacrol	0.20	0.40
Farnesol	0.20	-
Trans-trans-Farnesol	0.06	0.15
Total Components	45	30

*compounds of essential oil extracted from fresh green leaves and flowering top. ** S. officinalis L. Collected at 100 m above the sea level; *** S. officinalis L. collected at 500 m above the sea level.

III. Chemical Composition

The commonly known from sage Salvia Officinalis a total of 28 components were identified (table 1). The principal components in the sage oils were 1, 8-cineole, camphor, alpha-thujone, beta-thujone, borneol, and viridiflorol. The chemo types of sage were not determined in investigated samples. The concentration of the main compounds in the drugs cultivated in different type of sage and different location varied in about the same range as the concentrations of these compounds in the oils of drugs obtained from other countries. The comparatively high concentration of toxic thujones seems to be characteristic to sage leaves cultivated in different location as well.

IV. Antioxidant

Antioxidants play a very important role to protect the body against the oxidative stress and free radical damages which are the cause of various ailments such as diabetes, heart diseases, cancer, brain dysfunction, weakened immune system and many more (Eidi, 2006; Yadav, 2011)

In a study done on the antioxidant activity of many plant extracts, like sage (Salvia officinalis), it was found that the phenolic and flavonoid compounds are mainly responsible for the antioxidant and free radical scavenging effect of these plants (Yadav, 2011; Nickavar, 2007). Phenolic compounds such as carnosol, carnosic and rosmarinic acids, rosmadial, rosmanol, epirosmanol, methyl carnosate and luteolin-7-*O*-beta-glucopyranoside have a high antioxidative activity and are usually extracted from sage with ethanol (Aleksovski, 2007). The phenolic compounds can either stimulate endogenous antioxidant defense systems or scavenge reactive species (Sa, 2009).

The antioxidant properties of sage have been studied intensively, and are found to be related to the presence of rosmarinic acid and carnosic acid (Lu, 2000; Lu, 2001). In addition, Salvianolic acid which is a rosmarinic acid dimmer, isolated from the sage extract showed a great antioxidant activity and is a very significant scavenger of free radicals (Lu, 2001). The aqueous extract of S. officinalis has shown to have antioxidant and antiviral effect and in a study, after drinking of sage tea for two weeks the liver antioxidant status improved as a result (Stanojevic, 2010).

V. Memory

Amongst many herbal extracts, Salvia species are known for the beneficial effects on memory disorders, depression and cerebral ischemia (Perry, 2003). Salvia officinalis (Common sage), Salvia lavandulaefolia (Spanish sage), and Salvia miltiorrhiza (Chinese sage) have been used for centuries as restoratives of lost or declining mental functions such as Alzheimer's disease (Perry, 2003; Eidi, 2006). In Alzheimer's disease (AD), the enzyme Acetyl cholinesterase (AChE) is responsible for degrading and inactivating acetylcholine, which is a neurotransmitter substance involved in the signal transferring between the synapses. Acetyl cholinesterase inhibitor drugs act by counteracting the acetylcholine deficit and enhancing the acetylcholine in the brain (Ferreira, 2006). Essential oil of Salvia officinalis have shown to inhibit 46% of acetylcholinesterase activity at a concentration of 0.5 mg ml^{-1} (Ferreira, 2006).

A study shows that salvia officinalis improves the memory and cognition, and with the increase of the dosage, the mood elevation increases as well as alertness, calmness and contentedness (Tildesley, 2005). A randomized, double blind clinical study has shown that an ethanolic extract from sage (S. officinalis) as well as Spanish sage (S. lavandulaefolia) is effective in the management of mild to moderate AD and study on patients did not show any adverse effect on them while taking sage (Akhondzadeh, 2003; Iuvone, 2006) . Administration of Salvia lavandulaefolia (Spanish sage) has been reported to be effective on the improving the speed of memory and mood. Salvia essential oil also has been reported to improve immediate word recall (Eidi, 2006).

A number of studies have investigated the effects of the aromas of plant essential oils on cognition and mood (Moss, 2010). Salvia officinalis aroma produced a significant enhancement effect for the quality of memory factor derived from CDR (Cognitive Drug Research) system (Moss, 2010) .The findings suggest that the aromas of essential oils of salvia species have some but not all of the effects found following the oral consumption of the herb (Moss, 2010). The antioxidant and anti-inflammatory properties of the S. officinalis or S. lavandulafolia may offer a long-term protection in the pathogenesis of the dementia (Tildesley, 2005). Also the mood enhancing properties of the herb may have applications in the treatment of advanced dementia, in which disturbed mood and agitation feature as a major problem (Tildesley, 2005). There is no report of negative side effects associated with S.officinalis or S. lavandulaefolia despite of many years of usage span (Tildesley, 2005).

The cytoprotective effect of sage against Aβ (amyloid beta plaques) toxicity in neuronal cells also has been proven by the data presented in a study which this provides the pharmacological basis for the traditional use of sage in the treatment of Alzheimer's disease (Iuvone, 2006). Rosmarinic acid as a component of sage has shown neuroprotective, antioxidative, and anti-apoptotic effects against Aβ toxicity and this could contribute, at least in part, to the neuroprotective effect of sage. Therefore, it is possible that rosmarinic acid, this very low toxic natural compound could be used as a

therapeutic agent in the treatment of Alzheimer's disease (Iuvone, 2006).

VI. Diabetes

Salvia officinalis has been used as a traditional remedy against diabetes in many countries and its glucose-lowering affects have been demonstrated in animal studies (Christensen, 2010). In a study, it was found that methanolic extracts of S. officinalis significantly decreased serum glucose in type I diabetic rats without affecting pancreatic insulin production (Christensen, 2010). An aqueous extract of Salvia officinalis have been found to exhibit insulin-like activities (Christensen, 2010).

In a study, drinking of sage tea, (300ml, twice a day) showed the increase in antioxidant defenses and improved the lipid profile, without causing any hepatotoxicity or inducing any adverse affects, such as changes in blood pressure, heart rate and body weight which these may indirectly improve the diabetic condition (Sa, 2009). Tea-infusions of Salvia officinalis have shown to be as effective as metformin, which is an oral anti-diabetic drug used for the treatment of type II diabetes and act by reducing liver glucose production as well as increases the action of insulin (Christensen, 2010).

VII. Cancer

Cancer is characterized by abnormal growth of cells which tend to proliferate in an uncontrolled way and in some cases spread to other parts of the body. The important factor in proliferating and spreading of cancer cells is the ability of tumors to produce large number of new blood vessels, known as angiogenesis (Keshavarz, 2011). Most primary solid tumors are dependent on angiogenesis for survival, growth, invasion, and metastasis (Keshavarz, 2011). In a study, it was found that Salvia officinalis extract at pharmacological concentrations inhibits angiogenesis in vivo which could be a novel starting point for the development of a new anti-angiogenic drug (Keshavarz, 2011). Ursolic acid found in sage effectively inhibits angiogenesis, invasion of tumor cells and metastasis and suppresses the lung colonization of B16 melanoma cells in vivo (Jedinak, 2006).

Colorectal cancer (CRC) is a common type of cancer and significant cause of mortality in Western societies. It develops by genetic and epigenetic alterations which transfer normal colon cells to proliferating cells. The study has shown that dietary compounds can change the epigenetic status. Many food plants are rich in bioactive compounds and have shown to posses anticancer properties (Pedro, 2010). The effect of sage (Salvia officinalis) herbal tea drinking was studied on the prevention of colon cancer in rats. It was found that Salvia officinalis water extract significantly decreased the oxidative H2O2-induced DNA damage in vitro (Pedro, 2010).

Some diterpenoids isolated from the roots of S. officinalis have shown to have cytotoxic and DNA-damaging activity in human colon carcinoma Caco-2 cells and human hepatoma HepG2 cells in vitro conditions (Hadri, 2010). The sesquiterpene fraction of S. officinalis with the presence of α-humulene, demonstrate a strong cytotoxic activity in human prostate carcinoma LNCaP cells (Hadri, 2010). Also trans-caryophyllene which is main component of sesquiterpene fraction in salvia officinalis shows high cytotoxic activity against the melanotic melanoma and renal adenocarcinoma cells (Loizzo, 2007). Presence of α-humulene as a component of S. officinalis demonstrated a strong cytotoxic activity on the human prostate carcinoma LNCaP cells (Loizzo, 2007).

Salvia libanotica (Lebanese sage) is one of the largely used sage species in traditional medicine which have been used for many years to cure diseases such as abdominal pains, headaches, indigestions and heart disorders (Itani, 2008). The oil extract of this species was shown to possess strong antimicrobial and anti tumor effects (Itani, 2008). The components of Lebanese sage essential oil was identified by gas chromatography and three of the components which contains on average, 9.1 % Camphor (Ca), 1.3%α-Terpineol (Te) and 1.1% Linalyl acetate(Ly) were found to be responsible for the oil antibacterial, antifungal, anti-inflammatory and antitumor effects (Itani, 2008) . In the study Ly, Te, and Ca synergistically induced cell cycle arrest and apoptosis resulting in the inhibition of the growth of human colon cancer cell lines, HCT-116 (P53+/+ and P53-/-) without any effect on the growth of normal human intestinal cell lines (Itani, 2008) .

VIII. Cholestrol

The metabolite profile of Salvia miltiorrhiza (SM) or Chinese sage is similar to common sage and recently it was shown that an extract of SM was able to lower plasma cholesterol, LDL, and triglycerides as well as increase HDL levels in lipidaemic rats (Christensen, 2010).

The extract of Salvia officinalis is found to activate PPARγ which is a regulator of genes involved in energy spending as well as lipid and glucose metabolism and its activation improves the HDL/LDL ratio and lowers triglycerides in serum, reduces insulin resistance and reduces size of adipose (fat) tissue (Christensen, 2010).

Extracts from some sage species have been shown to be effective in the prevention of cardiovascular disease due to, at least in part, prevention of LDL-C oxidation (Sa, 2009).

IX. Obesity

Overweight and obesity are recognized to be important risk factors for type II diabetes, dyslipidemia, hypertension and many other diseases (Tildesley, 2003). To regulate fat absorption, the effective way is, to reduce body weight and obesity (Tildesley, 2003).

Pancreatic lipase is well known to play an important role in lipid digestion (Tildesley, 2003). In several studies on anti-obese components from natural medicine, the effect of Salvia officinalis and its active components in pancreatic lipase activity and lipid digestion were investigated (Ninomiya et al, 2004). The methanolic (MeOH) extract from the leaves of Salvia officinalis L. significantly inhibited the pancreatic lipase activity, and suppressed serum triglyceride (TG) elevation in olive oil-loaded mice (Ninomiya et al, 2004). Carnosic acid and carnosol are two of the diterpenes isolated from the methanolic extract of the Salvia officinalis with inhibiting activity on pancreatic lipase. Carnosic acid also significantly inhibited triglyceride elevation in olive oil-loaded mice and reduced the gain of body weight and the accumulation of epididymal fat weight in high fat diet-fed mice after 14 days (Ninomiya et al, 2004). In the course of several studies on anti-obese components from natural medicine, the extract of salvia officinalis leaves showed inhibitory effect against the pancreatic lipase activity and eventually was effective to reduce body weight and obesity (Ninomiya et al, 2004).

X. Hot Flashes

Menopause is considered as physiological adjustment process to an altered hormonal balance (Bommer, 2011). Menopausal symptoms include hot flashes, insomnia, night-time sweating, dizziness, headaches and palpitations. These symptoms reflect adaptation of the body to estrogen deprivation which affects various central neurotransmitters.

Sage (Salvia officinalis) has been traditionally used to treat sweating and menopausal hot flashes, as well as to alleviate associated menopausal symptoms (Bommer, 2011). The efficacy of sage for the treatment of hot flashes during menopause was proven by multi center open clinical trial (Walch, 2011). A fresh sage preparation demonstrated clinical value in the treatment of hot flashes and associated menopausal symptoms (Bommer, 2011).Once-daily application of the fresh sage extract, demonstrated good clinical value in terms of safety, efficacy, and tolerability in the treatment of menopausal hot flashes and climacteric symptoms, validated by statistical analysis and the clinically relevant verdict of patients and physicians (Bommer, 2011). The study findings provide a scientific rationale for sage's use in folk medicine, offering a valuable option for patients and healthcare providers, seeking alternative approaches for the treatment of menopausal hot flashes and climacteric complaints (Bommer, 2011).

XI. Anti-Bacteria

In a study done on the antibacterial effect of sage against selected food spoiling bacteria in vitro, indicates that the sage aqueous extract exerted significant antibacterial activity and it was most effective against Bacillus mycoids, Bacillus subtilis, Enterobacter cloaceae and Proteus sp. (Itani, 2008) against bacteria, especially against resistant bacteria to the antibiotics (Khalil, 2011). This has made sage essential oil a good alternative to the traditional antibiotics as well as food preservatives (Khalil, 2011).

The finding of a study support the view that the hydroalcoholic extracts of salvia officinalis has growth inhibitory effect on some dental caries causing bacteria, such as Streptococcus mutans, Lactobacillus rhamnosus and Actinomyces viscosus. Based on this study and the world interest on using traditional treatments instead of chemical solutions, salvia officinalis with the bactericidal effect could be a natural remedy for the treatment of mouth and teeth diseases (Kermanshah et al, 2009).

The work showed that sage along with different plant extracts was comparable to synthetic preservatives and the result confirmed that the aqueous extract of Salvia officinalis can be used in biotechnological field as a natural preservative ingredient in food industry (Stanojevic, 2010).

The study of antibacterial activities of the essential oil of salvia officinalis proved that sage essential oil in higher concentration exhibited a better efficiency than antibiotics

XII. Anti-Diarrhea

Based on the medicinal use of sage in diarrhea and abdominal spasm, the crude extract of sage was tested for its anti-diarrheal and antispasmodic activities using the in-vitro and in-vivo assays. A study demonstrated that the crude extract provides protection against diarrhea through inhibitory effect on gut motility by the presence of some gut relaxant components (Khan, 2011).The data in a study suggests that the crude extract of S.officinalis possess anti-diarrheal and antispasmodic activities, mediated possibly through activation of voltage sensitive K+ channels together with weak Ca++ antagonist effect (Khan, 2011). Therefore, this study provides pharmacological basis for the medicinal use of S. officinalis in hyperactive gut disorders such as abdominal colic and diarrhea (Khan, 2011).

XIII. Toxicity of Sage

There are no reports of negative side effects as far we know associated with Salvia lavandulaefolia (or S.

officinalis) despite of their usages for many centuries (Tildesley, 2005).

The normal usage of sage is very safe; however, there might be an adverse effect for somebody using salvia officinalis in excessive amount, which can be caused by the high content of thujone (Walch, 2011). The studies have shown that Salvia lavandulaefolia (Spanish sage)compare to Salvia officinalis(common sage) has similar compositions without the thujone content, which makes it more suitable to use for somebody concerned about the excessive usage of sage as a treatment (Tildesley, 2003).

XIV. Conclusion

The objective of this paper has been the recent advance in the exploration of sage Salvia as phytotherapy and to illustrate its potential as a therapeutic agent. Salvia species may represent natural, safe and effective treatments for many diseases and their symptoms. In recent decades, with the increase of pharmacological knowledge about the beneficial effects of sage especially salvia officinalis, these herbal medicines with anti-bacterial, anti-oxidant, anti-inflammatory, free radical scavenging and anti-tumor activities, have found to be very effective in the development of novel natural drugs to prevent, control and treat many minor health problems as well as more serious and complicated diseases such as diabetes, Alzheimer's and cancer. It must be kept in mind that clinicians should remain cautious until more definite studies demonstrate the safety, quality and efficacy of salvia officinalis. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism should be focus of our next studies and further potential of salvia officinalis to be employed in new therapeutic drugs and provide a basis for future research on the application of medicinal plants.

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