

Article

# Sage Species Case Study on a Spontaneous Mediterranean Plant to Control Phytopathogenic Fungi and Bacteria

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**Abstract:** Sage species belong to the family of *Labiatae/Lamiaceae* and are diffused worldwide. More than 900 species of sage have been identified, and many of them are used for different purposes, i.e., culinary uses, traditional medicines and natural remedies and cosmetic applications. Another use of sage is the application of non-distilled sage extracts and essential oils to control phytopathogenic bacteria and fungi, for a sustainable, environmentally friendly agriculture. Biocidal propriety of non-distilled extracts and essential oils of sage are well documented. Antimicrobial effects of these sage extracts/essential oils depend on both sage species and bacteria and fungi species to control. In general, it is possible to choose some specific extracts/essential oils to control specific phytopathogenic bacteria or fungi. In this context, the use of nanotechnology techniques applied to essential oil from salvia could represent a future direction for improving the performance of eco-compatible and sustainable plant defence and represents a great challenge for the future.

**Keywords:** essential oils; extracts; *Salvia Africana*; *S. rutilans*; *S. munzii*; *S. mellifera*; *S. greggii*; *S. officinalis* “Icterina”; *S. officinalis*

## 1. Introduction

Medicinal plants are recently getting growing attention worldwide as important sources of bioactive compounds, and hence for their potential beneficial properties [1–23]. The World Health Organization (WHO) reported that about 80% of the world's population use herbal medicine for the treatment of many diseases, referring to traditional drugs only as a second choice, due to diffidence for chemical origin pharmaceuticals [24]. A lot of plants and herbs have been cultivated for their aromatic and medicinal proprieties. In particular, the interest for aromatic plants has increased not only in medicine but also in agriculture, since their essential oils are among the eco-compatible compounds potentially useful to control dangerous biotic agents of the crops, which makes them extremely interesting in view of eco-sustainable and environmentally friendly agriculture practices [25–28].

*Main Features of Some Sage Species (Salvia africana, Salvia rutilans, Salvia munzii, Salvia mellifera, Salvia greggii, Salvia officinalis "Icterina", Salvia officinalis)*

*Salvia* genus belongs to the family of *Labiatae/Lamiaceae* [29,30] and is widespread in various regions around the world, being particularly present in Mediterranean regions of Europe, South Africa, Central and South America, and South-East Asia [31,32]. It includes more than 900 species, which are used for different purposes, i.e., culinary uses, traditional medicines and remedies, and cosmetic applications. Plants of the genus *Salvia* have been reported to have a wide range of biological activities and are used for the prevention and treatment of various diseases, due to the presence of a peculiar profile of secondary metabolites/bioactive components isolated in several parts of the plants (i.e., flowers, leaves, stem), in particular, essential oils, with a large spectrum of terpenoids (i.e.,  $\alpha$ - and  $\beta$ -thujone, camphor, 1,8-cineole,  $\alpha$ -humulene,  $\beta$ -caryophyllene and viridiflorol) as well as di- and tri-terpenes (i.e., carnosic acid, ursolic acid, carnosol and tanshinones), polyphenols, comprising an array of phenolic acids (i.e., caffeic acid and its derivatives, rosmarinic acid, salvianolic acids, sage coumarin, lithospermic acids, sagerinic acid, and yunnaneic acids) and flavonoids (i.e., luteolin, apigenin, hispidulin, kaempferol and quercetin) [33].

The most common species, namely the *Salvia officinalis* L., represents an important medicinal and aromatic plant, with antioxidant, antimicrobial, anti-inflammatory and anticancer properties. Poullos et al. [34] well summarized the current advances on the extraction and identification of bioactive components of sage; further, the same authors gave a current state-of-the-art on the antioxidant activity of sage (*Salvia* spp.) and its bioactive components [35].

The study of Craft et al. [36] revealed the presence of five major chemotypes of sage (*Salvia officinalis* L.) leaf essential oils, with several subtypes: most sage oils belonged to the "typical" chemotype composition containing, in percentages (*w/w*),  $\alpha$ -thujone > camphor > 1,8-cineole; however, the essential oil composition can vary widely and may have a profound effect on flavour and fragrance profiles, as well as on biological activities.

An update overview of pharmacological properties of *Salvia officinalis* and its components was exploited in the recent review of Ghorbani and Esmailizadeh [37].

*S. officinalis* 'Icterina' is a cultivar of *S. officinalis* characterised by yellow-green variegated leaves, as reported by Pop et al. [38]. *Salvia Africana* L., commonly known as Bruinsalie or beach sage, is distributed from Namaqualand to the Eastern Cape Province of South Africa [39]. Etsassala et al. [40] reported how the methanolic extract of *S. africana-lutea* L. is a rich source of terpenoids, especially abietane diterpenes, with strong antioxidant and anti-diabetic activities, that can be helpful to modulate the redox status of the body and could be, therefore, an excellent candidate for the prevention of diabetes.

The phytochemical composition and bioactive effects of *Salvia Africana* and *Salvia officinalis* 'Icterina', was recently reported by Afonso et al. [41]; particularly, rosmarinic acid was the dominant phenolic compound in all the extracts, yet that of *S. africana* origin was characterised by the presence of yunnaneic acid isomers, which overall accounted for about 40% of total phenolics, whereas *S. officinalis* 'Icterina' extract presented glycosidic forms of apigenin, luteolin and scutellarein [41].

*Salvia mellifera* Greene, known as Black sage, is a traditional medicine of the Chumash Indians. De Martino et al. [42] reported that *Salvia mellifera* essential oils contain fifty-four monoterpenoids and several diterpenoids, such as carnosol (41%), carnosic acid (22%), salvicanol (15%) and rosmanol (9%). Adams et al. [43] reported how several chronic pain patients have reported long-term improvements in their pain after treatment with sun tea, made from the stems and leaves of the *Salvia mellifera*.

*S. greggii* A. Gray was studied for its terpenic compounds content [44,45], and the anti-germinative properties of its essential oils [42]. Pereira et al. [46] suggested that decoctions of *S. greggii* (*S. elegans*, *S. officinalis*) could be an effective natural antidiabetic and anti-obesity agent and help to control the glucose levels through the modulation of the  $\alpha$ -glucosidase activity.

*Salvia rutilans* Carrière (synonym *S. elegans* Vahl) is native to Mexico, known as “pineapple-scented sage”. The plant is used in traditional Mexican medicine for the treatment of Central Nervous System discomforts [47], and this species has been reported as a possible source of anxiolytic and antidepressant compounds [48]. The essential oil of this plant has been studied by Makino et al. [49], and its antigerminative activity was reported [50].

*Salvia munzii* Epling is present in xeric coastal sage scrub in Northern Baja California. Its essential oil was previously studied [50] and it was also studied for its antigerminative effects [50].

## 2. Sage Plants to Control Fungal and Bacterial Diseases

Sage-based phytochemicals have showed a great potential to face phytopathogens causing diseases and very important economic losses in agricultural systems worldwide. Several studies indicated the suitability of these natural substances to implement conventional crop management protocols and match the pressing sustainability challenge about safe foods and organic productions, launched by the political institutions and the large-scale distribution. In addition, the consumers' preference toward no-pesticides of chemical origin-treated crops needs to be considered. In order to reduce or eliminate the use of chemical fungicides for plant protection, research is moving toward the study and implementation of new eco-friendly non-synthetic tools able to effectively replace them in sustainable producing contests. All the plants are a source of secondary metabolites belonging to several chemical groups, that, once extracted, may be exploitable for their antifungal properties [51] alone or in integration with antagonistic microorganisms in controlling plant pathogens [52].

Aromatic plants have been extensively investigated as potential sources of natural compounds with antimicrobial activity, which can be effectively used to replace conventional environment unfriendly pesticides. This topic also includes all the bioactive sage species. Due to the natural origin, many of the sage-derived antifungal compounds could be included into the “generally recognised as safe (GRAS)” classification [53] for plant protection and food preservation. The antimicrobial compounds from sage tissues are currently extracted in raw blends, in which the activity is based on all the phytochemicals [54], such as solvent-extracts and essential oils that are among the main promising tools to totally replace or integrate chemicals for disease management.

### 2.1. Solvent Sage Extracts

The bioactive antimicrobial molecules are extracted from dried plant sage material to obtain their raw blends or purified compounds through water or other solvents, expression under pressure, supercritical CO<sub>2</sub>, and solvent-free microwave methods [55,56].

Recently, Nutrizio et al. [57] explored an innovative process based on high-voltage electrical discharge for the eco-friendly recovery of bioactive compounds from Dalmatian sage. Sage extracts are characterised by antioxidant activity, high phenolic content and steroids, alkaloids and saponins to a lesser extent [58,59]. For example, caffeic acid and rosmarinic acid, reported as the most abundant phenolic compounds in sage extracts [60–62], have been associated to the control ability of *Fusarium* root rot in asparagus [63] and against *Fusarium* wilt in cyclamen [64]. The antifungal activity of *S. fruticosa* Mill. ethyl acetate extract against *B. cinerea* and *P. digitatum* has been supported by three major constituents, carnosic acid, carnosol and hispidulin [65].

As a hypothetical mechanism of action, sage extracts have been reported to affect cellular processes associated with changes in the membrane functionality involved in feeding and growth of the pathogen. A cytological study performed on *Candida albicans* yeast revealed the leakage of intracellular contents caused by membrane lipid bilayer alteration after treatment with the ethanol extract of *Salvia miltiorrhiza* [66].

A literature survey indicated a wide range of pathogens that are susceptible to the sage extract exposure (Table 1).

**Table 1.** Sage extracts exhibiting antimicrobial activity against phytopathogens, their extraction methods, susceptible microorganisms and bioassay to test the control efficacy.

Sage Species ( <i>Salvia</i> spp.)	Extraction Methods	Target Phytopatogens	Efficacy on Bioassay	Reference
<i>S. aegyptiaca</i>	Ethanol and water extraction	<i>Phyptora infestans</i>	In vitro and in vivo on tomato	[67]
<i>S. africana-lutea</i>	Dichloromethane: Methanol extraction	<i>Fusarium verticillioides</i> and <i>F. proliferatum</i>	In vitro determination of MIC and MFC	[68]
<i>S. cryptantha</i> , <i>S. officinalis</i> , <i>S. tomentosa</i>	Water, ethanol and methanol extraction	<i>Fusarium oxysporum</i> f. sp. <i>radicis</i>	In vitro mycelial growth inhibition	[69]
<i>S. cryptantha</i> <i>S. officinalis</i> , <i>S. tomentosa</i>	Methanol and ethanol extraction	<i>Botrytis cinerea</i> , <i>Monilia laxa</i> , <i>Aspergillus niger</i> , and <i>Penicillium</i> sp.	In vivo on apple	[70]
<i>S. fruticosa</i>	Crude water extraction	<i>Alternaria solani</i>	In vitro mycelial growth inhibition	[71]
<i>S. fruticosa</i>	Extraction in semi-automated Soxlet system	<i>B. cinerea</i>	In vivo on grape	[72]
<i>S. fruticosa</i>	Ethanol extraction	<i>Sclerotinia sclerotiorum</i>	In vitro mycelial growth inhibition	[73]
<i>S. officinalis</i>	Extracted in 90% methanol + 9% water + 1% acetic acid	<i>Alternaria alternata</i> , <i>A. niger</i> , and <i>A. parasiticus</i>	In vitro mycelial growth inhibition	[74]
<i>S. officinalis</i>	Metanolic extraction	<i>A. alternata</i> , <i>B. cinerea</i> , <i>Phytophthora cambivora</i> , and <i>F. oxysporum</i>	In vitro mycelial growth inhibition	[75]
<i>S. officinalis</i>	Ethanol and methanol extraction	<i>A. alternata</i> , <i>A. solani</i> , <i>Fusarium solani</i> , <i>F. oxysporum</i> f.sp. <i>lycopersici</i> , <i>P. infestans</i> , <i>Rhizoctonia solani</i> , <i>B. cinerea</i> , <i>Colletotrichum coccoides</i> , <i>Verticillium albo-atrum</i>	In vitro determination of MIC and MFC	[76]
<i>S. officinalis</i>	Ethanol extraction	<i>Plasmopora viticola</i>	In vivo on grape	[77]
<i>S. officinalis</i>	Water extraction	<i>F. oxysporum</i> f.sp. <i>asparagi</i>	In vitro on conidia germination	[63]
<i>S. officinalis</i>	Hydroethanol, ethanol and water infusion	<i>S. sclerotiorum</i>	In vitro and in vivo on lettuce	[78]
<i>S. officinalis</i>	Water extraction	<i>F. oxysporum</i> f.sp. <i>cyclaminis</i>	In vitro density of conidia	[64]
<i>S. officinalis</i>	Ethanol extraction	<i>Pseudoperonospora cubensis</i>	In vivo on cucumber	[79]
<i>S. officinalis</i> , <i>S. sclarea</i>	Aqueous, saline Buffer and acid extraction	<i>Alternaria</i> spp.	In vitro determination of MIC and MFC	[80]

Table 1. Cont.

Sage Species ( <i>Salvia</i> spp.)	Extraction Methods	Target Phytopatogens	Efficacy on Bioassay	Reference
<i>S. officinalis</i> , <i>S. sclarea</i>		<i>Pantoea agglomerans</i> , <i>Erwinia chrysanthemy</i>	In vitro growth inhibition	[81]
<i>S. verticillata</i>	Methanol extraction	<i>F. oxysporum</i> , <i>A. alternata</i> , <i>Aureobasidium pullulans</i> , <i>Trichoderma harzianum</i> , <i>Penicillium canescens</i>	In vitro determination of MIC and MFC	[82]
<i>S. virgata</i>	Methanol and n-hexane extraction	<i>R. solani</i> , <i>A. solani</i> , <i>F. oxysporum</i> f.sp. <i>radicis</i> , <i>lycopersici</i> , <i>Verticillium dahliae</i>	In vitro mycelial growth inhibition	[83]
<i>S. tigrina</i>	Ethanol extraction	<i>B. cinerea</i> , <i>F. oxysporum</i> , <i>A. alternata</i>	In vitro determination of MIC and MFC	[84]

MIC: Minimal inhibitory concentration; MFC: Minimum fungicidal concentration.

*S. officinalis* ethanolic extracts have proven to be able to control *Plasmopara viticola* on grapevine [77] and *Pseudoperonospora cubensis* on organic cucumber [79]. *Salvia aegyptiaca* L. ethanolic extracts have resulted as effective both in vitro and in vivo against *Phytophthora infestans*, the causal agent of late blight disease of tomato [67]. Dellavalle et al. [80] assessed the minimum inhibition concentration (MIC) and migration inhibitory factor (MIF) values of *Salvia officinalis* L. and *Salvia sclarea* L. respectively, foliar and seed acid extracts against *Alternaria* spp. quite comparable to values obtained with the conventional fungicide captants ( $2.5 \mu\text{g mL}^{-1}$ ). In vitro inhibitory effects were also found on *Fusarium proliferatum* and *F. verticilloides* by *Salvia africana-lutea* extracts [68] and on *Aspergillus flavus*, *Penicillium frequentans*, *Botrytis cinerea*, *Geotrichum candidum*, *Fusarium oxysporum* and *Alternaria alternata* by treatments with ethanolic extracts of *Salvia tigrina* Hedge & Hub.-Mor. [84]. All these fungi are able to produce many metabolites [85–89]. Water, ethanol and methanol extracts of *S. officinalis*, *S. cryptantha* Montbret and Aucher and *S. tomentosa* Mill. have been found effective against *F. oxysporum* f. sp. *radicis-lycopersici* [69] and *Sclerotinia sclerotiorum*, *Alternaria solani*, *Ascochyta rabiei*, *Botrytis cinerea*, *Rhizoctonia solani*, *Penicillium italicum*, *Aspergillus niger* and *Monilia laxa* [70]. The mycelium development of *Rhizoctonia solani*, *Alternaria solani*, *Fusarium oxysporum* f. sp. *radicis lycopersici* and *Verticillium dahliae* were repressed by methanol and n-hexane extracts of *Salvia virgate* Jacq. [83], while ethanol, hexane and aqueous extracts of *S. sclarea* have shown in vitro antifungal activity against pathogenic fungi *Epicoccum nigrum* and *Colletotrichum coccodes* [90]. *Salvia fruticosa* Mill. (sage Greek) has sourced very active extracts against the mycelial growth and sclerotial formation and germination of *Sclerotinia sclerotiorum* [73] and against the early blight fungus, *Alternaria solani* [71].

The formulation of sage extracts aimed at improving their safe use and antimicrobial efficacy is a very active research field. Ghaedi et al. [91] have made available preparations based on the incorporation in  $\text{Zn(OH)}_2$  nanoparticles and Hp-2-minh of extracts of *Salvia officinalis*. Chitosan-based edible coating was combined with the acetonic extract of *Salvia fruticosa*. Carrying the flavonoids hispidulin, salvigenin and cirsimaritin and the diterpenes carnosic acid, carnosol and the 12-methoxycarnosic acid as major constituents, showed encouraging efficacy against the grey mould of table grapes [72]. Salević et al. [92] recently characterised electrospun poly( $\epsilon$ -caprolactone) films containing a solid dispersion of *Salvia officinalis* extract for their antimicrobial potential.

## 2.2. Sage Essential Oils

The genus *Salvia*, as all the aromatic plant species from *Lamiaceae*, is a noble source of essential oils (EOs), obtained by the steam or hydro-distillation of different vegetative parts of the plant, including leaves, flowers, seeds and stems [93,94]. The super critical fluid-mediated extraction of bioactive EOs has also been achieved: it utilizes carbon dioxide at fluid state as the solvent in the same extractor model by merely lowering the extraction temperatures. EOs contain a wide variety of hydrophobic secondary metabolites, such as mainly terpenes, that can enhance the antimicrobial

activity through synergic action [95,96] and are reported to be responsible for antiseptic properties of the phytochemical [97]. For example, Džamić et al. [98] found linalyl acetate, linalool,  $\alpha$ -terpineol,  $\alpha$ -pinene, 1,8-cineole, limonene,  $\beta$ -caryophyllene and  $\beta$ -terpineol as the main components of *S. sclarea* EO that affect the moderate to high antimicrobial activity against a plethora of phytopathogens. Three major constituents,  $\alpha$ -thujone,  $\beta$ -thujone and myrcene, have been identified, instead, in the wide-spectrum fungistatic *S. pomifera* subsp. *calycina* EO [99,100]. The major compounds in the antimicrobial EOs of *Salvia mirzayanii* Rech. F. and Esfand were  $\alpha$ -terpinyl acetate, eudesm-7(11)-en-4-ol, bicyclogermacrene,  $\delta$ -cadinene, 1,8-cineole, germacrene D-4-ol, cis-dihydroagarofuran, linalyl acetate,  $\alpha$ -cadinol, linalool and  $\alpha$ -terpineol [101]. While, 1,8-cineole,  $\alpha$ -pinene, camphene, borneol, camphor and  $\beta$ -pinene have been indicated among the most abundant constituents of *Salvia brachyodon* Vandas antifungal EOs [102]. The presence of cis-thujone and camphor has been associated to the fungicidal activity of *S. officinalis* EO against filamentous fungi, belonging to *Penicillium*, *Aspergillus*, *Cladosporium* and *Fusarium* genera [103].

EOs antimicrobial activity exploitable in the control of phytopatogenic diseases is due to these single constituents and their synergistic interactions [104]. Lipophilic volatile molecules of EOs penetrate the cell wall and damage cell membranes by altering permeability and seal and affect morphology, growth, reproductive functions and viability of microorganisms [105]. An injured plasma membrane may result in a leakage of cellular components, including nucleic acids and proteins, and cellular collapse until death, representing the mode of action underlying the biostatic and biocidal EOs effects [106]. EOs also may induce decreased Succinate dehydrogenase (SDH) and nicotinamide adenine dinucleotide hydride (NADH) oxidase activities and cause extreme changes in ultra-structures by penetrating and dissolving the mitochondrial membranes [107]. The exposure of *Escherichia coli* and *Staphylococcus aureus* to *Salvia sclarea* EO caused cell plasmalemma disintegration with a massive leakage of cellular material and reduction of the intracellular ATP, as well as nuclear DNA content [108]. Among all components of the sage volatile blends, the monoterpene alcohol linalool has been shown to have the strongest antifungal activity, while 1,8-cineole was only moderate, and linalyl acetate was lower [109–111]. The antifungal in vitro activity of linalool has been attributed to leakage of intracellular material that dramatically affects radial mycelial growth and conidial production and germination of treated pathogens with severity according to dose [112]. Ultrastructural studies carried out on *Botrytis cinerea* exposed to 1,8-cineole revealed detrimental effects on cell organelles [113]. The volatile bicyclic sesquiterpene  $\beta$ -caryophyllene showed inhibitory effects against bacteria via suppression of DNA replication [114]. Sage EOs are assayed both in vitro and in vivo on a wide range of plant pathogens, giving encouraging indications about their fungicidal activity measured as MIC and MIF and disease control efficacy, also in comparison with synthetic molecules (Table 2).

**Table 2.** Sage essential oils with antimicrobial activity on phytopathogens, main active components, susceptible microorganisms and bioassay to test the control efficacy.

Sage Species ( <i>Salvia</i> spp.)	Major Components	Target Phytopatogens	Efficacy on Bioassay	Reference
<i>S. aucheri</i> var. <i>aucheri</i>		<i>Alternaria alternata</i> , <i>Penicillium italicum</i> , <i>Fusarium equiseti</i>	In vitro mycelial growth inhibition	[115]
<i>S. cryptantha</i> , <i>S. officinalis</i> , <i>S. tomentosa</i>	Eucalyptol, Camphor, $\alpha$ -pinetene, $\beta$ -thujone, borneol, camphor, 3-thujonene	<i>Botrytis cinerea</i> , <i>Monilia laxa</i> , <i>Aspergillus niger</i> , <i>Penicillium</i> sp.	In vivo on apple	[70]
<i>S. cryptantha</i> , <i>S. officinalis</i> , <i>S. tomentosa</i>		<i>Fusarium oxysporum</i> f.sp. <i>radicis-lycopersici</i>	In vitro mycelial growth inhibition	[69]
<i>S. desoleana</i>	1,8-cineole	<i>A. niger</i> , <i>A. ochraceus</i> , <i>A. versicolor</i> , <i>A. flavus</i> , <i>A. terreus</i> , <i>A. alternata</i> , <i>Penicillium ochrocholon</i> , <i>P. funiculosum</i> , <i>Cladosporium cladosporoides</i> , <i>Trichoderma viride</i> , <i>Fusarium tricinctum</i> , <i>Phomopsis helianthi</i>	In vitro determination of MIC and MFC	[116]

Table 2. Cont.

Sage Species ( <i>Salvia</i> spp.)	Major Components	Target Phytopatogens	Efficacy on Bioassay	Reference
<i>S. fruticosa</i>		<i>A. niger</i> , <i>A. oryza</i> , <i>Mucor pusillus</i> , <i>F. oxysporum</i>	In vitro mycelial growth inhibition	[117]
<i>S. fruticosa</i>	1,8-Cineole, Camphor	<i>Bipolaris/Drechslera sorociniana</i> , <i>Fusarium subglutinans</i> , <i>F. verticillioides</i> , <i>F. oxysporum</i> , <i>F. tricinctum</i> , <i>F. sporotrichioides</i> , <i>F. equiseti</i> , <i>F. incarnatum</i> , <i>F. proliferatum</i> , <i>Macrophomina phaseolina</i>	In vitro determination of MIC and MFC	[118]
<i>S. fruticosa</i>	Eucalyptol, Camphor	<i>B. cinerea</i> , <i>Fusarium solani</i> var. <i>coeruleum</i> , <i>Clavibacter michiganensis</i> subsp. <i>michiganensis</i>	In vitro mycelial growth inhibition	[119]
<i>S. fruticosa</i>	Hispidulin, salvigenin, cirsimaritin, carnosic acid, carnosol, and 12-methoxycarnosic acid	<i>Aspergillus tubingensis</i> , <i>B. cinerea</i> , <i>P. digitatum</i>	In vitro determination of MIC and MFC	[65]
<i>S. fruticosa</i>	1,8-cineole, $\alpha$ -thujone, $\beta$ -thujone, camphor, (E) caryophyllene	<i>F. oxysporum</i> f.sp. <i>dianthi</i> , <i>F. proliferatum</i> , <i>Rhizoctonia solani</i> , <i>Sclerotium sclerotiorum</i> , <i>F. solani</i> f. sp. <i>cucurbitae</i>	In vitro mycelial growth inhibition	[120]
<i>S. hydrangea</i>		<i>A. alternata</i> , <i>A. solani</i> , <i>Aspergillus</i> sp., <i>Botrytis</i> sp., <i>Colletotrichum</i> sp., <i>Drechslera</i> sp., <i>Fusarium acuminatum</i> , <i>F. chlamydosporum</i> , <i>F. culmorum</i> , <i>F. equiseti</i> , <i>F. graminearum</i> , <i>F. incarnatum</i> , <i>F. nivale</i> , <i>F. oxysporum</i> , <i>F. proliferatum</i> , <i>F. sambucinum</i> , <i>F. scirpi</i> , <i>F. semitectum</i> , <i>F. solani</i> , <i>F. tabacinum</i> , <i>F. verticillioides</i> , <i>Nigrospora</i> sp., <i>Penicillium jensenii</i> , <i>Phoma</i> sp., <i>Pythium ultimum</i> , <i>Phytophthora capsici</i> , <i>Rhizoctonia solani</i> , <i>S. sclerotiorum</i> , <i>Sclerotinia</i> sp., <i>Trichothecium</i> sp., <i>Verticillium albo-atrum</i> , <i>V. dahliae</i> , <i>V.tenerum</i>	In vitro microbial growth inhibition	[121]
<i>S. lavendulifolia</i> , <i>S. sclarea</i>		<i>B. cinerea</i> , <i>C. gloeosporioides</i> , <i>F. oxysporum</i> , <i>P. ultimum</i> , <i>R. solani</i>	In vitro mycelial growth inhibition	[66]
<i>S. officinalis</i>		<i>F. graminearum</i> , <i>F. verticilloides</i> , <i>F. subglutinans</i> , <i>F. oxysporum</i> , <i>F. avenaceum</i> , <i>Diaporthe phaseolarum</i> var. <i>caulivora</i> , <i>Phomopsis viticola</i> , <i>Helminthosporium sativum</i> , <i>Colletotrichum coccodes</i> , <i>Thanatephorus cucumeris</i>	In vitro mycelial growth inhibition	[122]
<i>S. officinalis</i>		<i>A. alternata</i> , <i>Colletotrichum destructivum</i> , <i>Phytophthora parasitica</i>	In vitro determination of MIC and MFC	[123]
<i>S. officinalis</i>	Monoterpene	<i>Colletotrichum acutatum</i> , <i>B. cinerea</i> , <i>Clavibacter michiganensis</i> , <i>Xanthomonas campestris</i> , <i>Pseudomonas savastanoi</i> , <i>P. syringae</i> pv. <i>phaseolicola</i>	In vitro determination of MIC and MFC	[124]
<i>S. officinalis</i>	$\alpha$ -p-thujone, 1,8-cineole and camphor	<i>B. cinerea</i>	In vitro mycelial growth inhibition	[125]
<i>S. officinalis</i>		<i>R.solani</i> , <i>Streptomyces scabies</i>	In vivo on potato	[126]

Table 2. Cont.

Sage Species ( <i>Salvia</i> spp.)	Major Components	Target Phytopatogens	Efficacy on Bioassay	Reference
<i>S. officinalis</i>	Camphor, $\alpha$ -thujone, 1,8-cineole, viridiflorol, $\beta$ -thujone, $\beta$ -caryophyllene, 2,2-diphenyl-1-picrylhydrazyl radical-scavenging, linoleic acid peroxidation, ferric reducing assays	<i>B. cinerea</i> , <i>R. solani</i> , <i>F. oxysporum</i> , <i>A. alternata</i>	In vitro determination of MIC and MFC	[127]
<i>S. officinalis</i>		<i>F. oxysporum</i> , <i>B. cinerea</i>	In vitro mycelial growth inhibition	[128]
<i>S. officinalis</i>		<i>Verticillium fungicola</i> var. <i>fungicola</i> , <i>Cladobotryum</i> sp.	In vitro determination of MIC and MFC	[129]
<i>S. officinalis</i>		<i>F. oxysporum</i> f. sp. <i>cicer</i> , <i>Alternaria porri</i>	In vitro mycelial growth inhibition	[130]
<i>S. officinalis</i>	Camphor, camphene, eucalyptol	<i>Fusarium graminearum</i>	In vitro determination of MIC and MFC	[131]
<i>S. officinalis</i>	1,8-cineole, $\beta$ -thujone, L-camphor	<i>Verticillium dahliae</i>	In vitro mycelial growth inhibition	[132]
<i>S. officinalis</i>		<i>Xanthomonas campestris</i> pv. <i>phaseoli</i> , <i>Clavibacter michiganensis</i> subsp. <i>michiganensis</i> , <i>Pseudomonas tolaasii</i>	In vitro determination of MIC and MFC	[133]
<i>S. officinalis</i>	Thujone, camphor	<i>Rhizopus stolonifer</i>	In vitro mycelial growth inhibition	[134]
<i>S. officinalis</i>	Camphor, $\alpha$ -thujone	<i>V. fungicola</i> , <i>Trichoderma harzianum</i>	In vitro mycelial growth inhibition	[102]
<i>S. officinalis</i>		<i>A. alternata</i>	In vitro and in vivo on tomato	[125]
<i>S. officinalis</i>		<i>S. sclerotiorum</i>	In vitro and in vivo on lettuce	[78]
<i>S. officinalis</i>		<i>C. cinerea</i>	In vivo on tomato	[135]
<i>S. officinalis</i>	Cis-thujone, camphor	<i>P. italicum</i> , <i>Aspergillus</i> sp., <i>Cladosporium cladosporioides</i> , <i>Fusarium moniliforme</i>	In vitro determination of MIC and MFC	[103]
<i>S. officinalis</i>		<i>Phytophthora capsici</i>	In vitro and in vivo on zucchini	[136]
<i>S. officinalis</i>		<i>Colletotrichum nymphaeae</i>	In vitro and in vivo on strawberry	[137]
<i>S. officinalis</i>		<i>Aspergillus niger</i>	In vitro and in vivo on tomato paste	[138]
<i>S. officinalis</i>		<i>B. cinerea</i> , <i>P. expansum</i>	In vivo on apples	[139]
<i>S. officinalis</i>		<i>Monilinia laxa</i> , <i>B. cinerea</i> ,	In vivo on apricot, peach and almond	[140]
<i>S. officinalis</i>		<i>F. oxysporum</i> f. sp. <i>lycopersici</i> , <i>R. solani</i> , <i>S. minor</i>	In vitro mycelial growth inhibition	[52]
<i>S. officinalis</i>		<i>Alternaria dauci</i> , <i>A. radicina</i> , <i>C. lindemuthianum</i> , <i>Ascochyta rabiei</i>	In vitro mycelial growth inhibition	[141]
<i>S. officinalis</i> , <i>S. tomentosa</i>		<i>A. rabiei</i>	In vitro mycelial growth inhibition	[142]



Table 2. Cont.

Sage Species ( <i>Salvia</i> spp.)	Major Components	Target Phytopatogens	Efficacy on Bioassay	Reference
<i>S. pomifera</i> sp. <i>calycina</i>	$\alpha$ -thujone, $\beta$ -thujone	<i>Mycogone perniciosa</i>	In vitro determination of MIC and MFC	[100]
<i>S. pomifera</i> subsp. <i>calycina</i>	$\alpha$ -thujone, $\beta$ thujone, myrcene	<i>F. oxysporum</i> f. sp. <i>dianthus</i> , <i>F. solani</i> f.sp. <i>cucurbitae</i> , <i>F. proliferatum</i> , <i>S. sclerotiorum</i> , <i>R. solani</i> , <i>V. dahliae</i> , <i>P. expansum</i>	In vitro mycelial growth inhibition	[99]
<i>S. pomifera</i> subsp. <i>calycina</i>	$\alpha$ -thujone, $\beta$ -thujone, myrcene	<i>F. oxysporum</i> f.sp. <i>dianthy</i> , <i>F. solani</i> f.sp. <i>cucurbitae</i> , <i>F. proliferatum</i> , <i>S. sclerotium</i> , <i>R. solani</i> , <i>V. dalhie</i> , <i>P. expansum</i>	In vitro mycelial growth inhibition	[100]
<i>S. reflexa</i>	Phenols, diterpenes, fatty acids, Palmitic acid, phytol (E)caryophyllene, caryophyllene oxide, hexahydrofarnesylacetone, phytol isomer, $\beta$ -asarone, $\alpha$ -copaene, $\delta$ -cadinene	<i>Curvularia lunata</i> , <i>Helmenusathosporium maydis</i>	In vitro mycelial growth inhibition	[143]
<i>S. sclarea</i>	Linalyl acetate, linalool, $\alpha$ -terpineol, $\alpha$ -pinene, 1.8-cineole, limonene, $\beta$ -caryophyllene, $\beta$ -terpineol	<i>A. alternata</i> , <i>C. cladosporioides</i> , <i>C. fulvum</i> , <i>F. tricinctum</i> , <i>F. sporotrichoides</i> , <i>Phoma macdonaldii</i> , <i>Phomopsis helianthi</i> , <i>Trichoderma viride</i>	In vitro determination of MIC and MFC	[98]
<i>S. sclarea</i>	Linalyl acetate, linalool, geranyl acetate, R-terpineol,	<i>F. oxysporum</i> f. sp. <i>dianthi</i> , <i>S.sclerotiorum</i> , <i>Sclerotium cepivorum</i>	In vitro determination of MIC and MFC	[144]
<i>S. sclarea</i>	Linalool, linalyl acetate, geranyl acetate, $\beta$ -ocimene, caryophylleneoxide	<i>F. oxysporum</i> , <i>B. cinerea</i> , <i>R. solani</i> , <i>A. solani</i>	In vitro determination of MIC and MFC	[109]
<i>S. sclarea</i>	Caryophyllene oxide, sclareol, spathulenol, 1H-naphtho, pyran, $\beta$ -caryophyllene	<i>Epicoccum nigrum</i> , <i>Colletotrichum coccodes</i>	In vitro mycelial growth inhibition	[90]
<i>S. officinalis</i> , <i>S. sclarea</i>		<i>Pantoea agglomerans</i> , <i>Erwinia chrysanthemy</i>	In vitro inhibition measurement	[145]

MIC: Minimal inhibitory concentration; MFC: Minimum fungicidal concentration.

Volatility of active molecules from sage EOs benefits fumigating applications against soil-borne [120] and storage pathogens [146]. *S. officinalis* EO proved to be a potential alternative method to conventional fungicides for the control of Sclerotinia rot in lettuce [78].

Aromatic waters obtained from distillation after oil separation were also found to be active against two fungal pathogens, *Rhizoctonia solani* and *Sclerotinia minor* [147]. However, this product shaped up to be an extract.

Also, about EOs, formulation techniques have been developed especially in order to enhance the efficacy in practical application. Due to the higher hydrophobicity of compounds, innovative preparations have been developed to improve EOs aqueous dispersions, for example by absorbing them in a swelling matrix of semisynthetic copolymers [135,148], nanocapsule suspensions [149], microencapsulation within alginate [150] or solid lipid nanoparticles [151]. Kodadová et al. [152] have formulated *S. officinalis* EO monoterpenes into a chitosan-based hydrogel, while nanoemulsions containing *Salvia multicaulis* Vahl EO, have recently been pinpointed to enhance the safe control of food-borne bacteria [153].

### 3. Sage Essential Oils: Experimental Part of the Case Study

The case study concerns the evaluation of the bactericidal and fungicide effect of EOs extracted from seven species of sage, most of which are not well known. In detail, the sage species investigated were: *Salvia africana* L., *S. rutilans* Carrière, *S. munzii* Epling, *S. mellifera* Greene, *S. greggii* A. Gray, *S. officinalis* “Icterina” L. and *S. officinalis* L., the bacteria tested were: *Xanthomonas campestris* pv. *campestris* and *Pectobacterium carotovorum* subsp. *carotovorum*, both phytopathogens, while the fungi tested were: *Alternaria alternata*, *Botrytis cinerea*, *Sclerotinia minor*, *Fusarium oxysporum*, *F. sambucinum*, *F. semitectum*, *F. solani* and *Rhizoctonia solani*, all phytopathogenics.

Plant cultivation took place between 2005 and 2006 at “Improsta” farm, in the Campania Region, Southern Italy.

At the balsamic stage, the leaves were taken, and the essential oils were obtained by hydrodistillation. The oils extracted were stored at 4 °C until the tests for evaluation of their antibacterial and antifungal activity were run.

The EOs extracted were also analysed for their main constituents by GC and GC/MS [42].

To evaluate the ability of EOs to inhibit the growth of bacterial and fungal plant pathogens, in vitro plate tests were performed. For each essential oil, plugs (5 mm diameter) were removed from the edge of the growing mycelia or bacterial suspensions ( $10^8$  CFU mL<sup>-1</sup>) and were incubated overnight at 25 °C in sterile double distilled water (SDDW) containing 1% essential oil emulsion; for controls, plugs or bacterial suspensions were incubated in SDDW only. After incubation, plugs were transferred in the centre of potato dextrose agar (PDA) Petri plates (60 mm diameter) and incubated at 25 °C, while bacterial suspensions were incubated on nutrient agar (NA) Petri plates (60 mm diameter) at 28 °C. For each essential oil, treatments and incubation were performed in triplicate.

The diameter of the mycelia was measured daily until fungi reached the edge of the control plates, and data were expressed as % growth reduction (or, sometimes, growth increment) with respect to control; for bacteria, presence or absence of growth was evaluated after 48 h.

The EOs of the different species of sage showed different bactericidal and fungicide effects and a different composition for their main constituents. Both bacteria and phytopathogenic fungi showed different susceptibility depending on the bacterial or fungal species and depending on the essential oil used.

The bactericidal effect was generally more pronounced against *Pectobacterium carotovorum* subsp. *carotovorum*, with four out of seven essential oils, except for *Xanthomonas campestris* pv. *campestris*, on which only two EOs were found to be active (Table 3).

**Table 3.** Antibacterial activity of essential oils of *Salvia* spp. used in this study.

<i>Salvia</i> spp.	<i>Xanthomonas campestris</i> pv. <i>campestris</i>	<i>Pectobacterium carotovorum</i> subsp. <i>carotovorum</i>
<i>S. africana</i>	0	-
<i>S. rutilans</i>	-	-
<i>S. munzii</i>	0	0
<i>S. mellifera</i>	+/-	-
<i>S. greggii</i>	+/-	0
<i>S. officinalis</i> “Icterina”	0	0
<i>S. officinalis</i>	-	-

Legend: 0 = no inhibition; - = total inhibition; +/- = partial inhibition.

The fungicide effect of EOs was very different, depending on the fungal species. The EOs of some species of sage have been able to completely inhibit the growth of certain fungal species, such as *S. greggii* and *S. officinalis*, that completely inhibited the development of three phytopathogenic fungi:

*S. munzii*, that completely inhibited two fungal species, and *S. rutilans*, that completely inhibited one of the eight species of fungi tested (see Table 4). Some EOs were found to be less active, such as *S. africana*, *S. mellifera* and *S. officinalis* “Icterina”, as shown in Table 4. Some fungi were found, in general, to be very resistant to the tested EOs, such as *Fusarium sambucinum*, while other fungi were found to be more sensitive, such as the two “soil-borne” *Sclerotinia minor* and *Rhizoctonia solani* (see Table 4).

However, the EOs have also been able to increase the development of some fungal colonies, such as in the case of *S. africana* for *S. minor* and *R. solani*. It is possible to speculate that some constituents of the oils are used as a nutrient source. The different EOs were also analysed for their composition. The results are shown in Table 5. This Case Study was presented here to show how different Mediterranean species of sage may have interesting potential to provide EOs with antifungal and antibacterial properties. The research was carried out to screen new environmentally compatible suppressive means of eight fungal and two bacterial phytopathogens, which cause economically important diseases on several agrarian species worldwide. In this view, the assayed samples have displayed differential phytochemical profiles that suggest species-specific effects, likely to which the inhibitive activity could be associated. In agreement with the previous studies listed in the Table 2, the most active EOs contain thujone (cis\*trans), 1,8-cineole, camphor,  $\alpha$ -pinene and lower traces of geraniol. These compounds supported the activities of sage-sourced EOs against a plethora of fungi [118,120]. Moreover, among their major components,  $\delta$ -cadinene was also found in these samples, noticed in *Salvia reflexa* essential oil producing in vitro mycelia growth inhibition of *Curvularia lunata* and *Helmenusathosporium maydis*. On the other hand, the *S. africana* essential oil profile markedly differentiated from each other with the presence of p-cymene,  $\gamma$ -terpinene and epizonareme among the most abundant components, which to our knowledge have not been reported as antimicrobial effector constituents of sage EOs to determine detrimental effects against plant pathogens. This circumstance may explain the reduced bioactivity shown by the sample from *S. Africana* with respect to the other.

The methodology used in this study to assess the antifungal potential of EOs by submerging fungal plugs into an EOs emulsion has been developed previously [141] and could also be applied to MIC determination if repeated at different effective concentrations. The relevance of sage material to derive suitable antifungal EOs may have a friendly impact on developing sustainable protocols for practical application in plant disease management, where the availability of alternative tools to synthetic fungicides are urgent. Furthermore, the possibility to submit the residual biomasses of the sage plants to the distillation process also opens the way to a circular economy scheme.

**Table 4.** Antifungal activity of essential oils of *Salvia* spp. used in this study. The numbers indicate % reduction (values with –) or increase (values with +) of the diameter of the colonies treated with essential oils with respect to not treated (control).

<i>Salvia</i> spp.	<i>Alternaria alternata</i>	<i>Botrytis cinerea</i>	<i>Sclerotinia minor</i>	<i>Fusarium oxysporum</i>	<i>Fusarium sambucinum</i>	<i>Fusarium semitectum</i>	<i>Fusarium solani</i>	<i>Rhizoctonia solani</i>
<i>S. africana</i>	0	–31.2	+50.0	+3	–5.4	–12.5	–20.0	+20.0
<i>S. rutilans</i>	–55.5	–50.0	–100.0	–5.6	+8.1	–21.9	–4.0	+20.0
<i>S. munzii</i>	0	0	+33.3	–22.7	–9.9	–100.0	–40.0	–100.0
<i>S. mellifera</i>	–11.1	–50.0	–33.3	–14.1	+8.1	–35.5	–40.0	–24.0
<i>S. greggii</i>	–100.0	–50.0	–100.0	–18.5	+3.6	–25.0	–32.0	–100.0
<i>S. officinalis</i> “Icterina”	–33.3	–50.0	–50.0	–7.3	–1	–21.9	+8.0	+8.0
<i>S. officinalis</i>	–100.0	–100.0	–100.0	0	0	–50.0	0	–50.0

Some molecules have been found in many essential oils, such as canphor and  $\delta$ -cadinene, while other molecules have been found in interesting quantities only in a single species, such as p-menthadiene, isobornyl acetate,  $\gamma$ -terpinene, epizonareme and (Z)- $\beta$ -ocimene, as shown in Table 5.

Some of these molecules are already known to have bactericidal activity, such as camphor [154]; however, biocidal effects of an essential oil can be due to a synergistic action of the many active molecules which the oil contains.

**Table 5.** Main constituents of essential oils (% on total oil, *w/w*) extracted from *Salvia* spp. species used in this study.

Molecules	<i>S. mellifera</i>	<i>S. africana</i>	<i>S. rutilans</i>	<i>S. munzii</i>	<i>S. greggii</i>	<i>S. officinalis</i> "Icterina"	<i>S. officinalis</i>
Thujone ( <i>cis</i> * <i>trans</i> )			38.7	33.3	43.4	34.6	37.9
1,8-Cineole	38.8					4.6	4.2
Camphor	12.2		4.7	27.2	4.2	7.5	13.9
$\delta$ -Cadinene		3.8	11.5	8.9	14.0		
$\alpha$ -Pinene	9.2						4.4
<i>p</i> -Menthadiene	2.3						
Limonene	2.2						1.4
Isobornyl acetate						5.0	
Camphene						4.6	4.1
<i>p</i> -Cymene		17.7					1.2
$\gamma$ -Terpinene		12.9					
Epizonareme		11.3					
Cubebol							
Geranyl acetate			6.9		8.7		
Geraniol		2.3	6.5	4.0	3.4		
( <i>Z</i> )- $\beta$ -Ocimene				5.7			

#### 4. Conclusions and Future Remarks

The use of essential oils of *Salvia* spp. to control plant disease, can be a valid eco-friendly strategy to control plant diseases, but it is very important to improve their performance by applying nanotechnologies.

Nanotechnologies represent a great challenge for the future. An emerging direction is to apply the nanotechnologies [155,156] to plant defence.

The adoption of this technology in food and agrochemical industries is emerging, addressing new nanoformulations of biopesticides [157,158]. Formulations of nanobiopesticide and nanoherbicides as a "smart delivery system" are currently studied and produced from the perspective of an eco-friendly approach, by reducing herbicide inputs and providing more effective control on where and when an active ingredient is released.

In this regard, Jampílek, and Král'ová [156] showed state-of-the-art and future opportunities for nanobiopesticides in agriculture, with particular regards to pesticide-effective organic or inorganic (poly)materials of natural origin, EOs loaded in various matrices and green-synthesised metal or metal oxide nanoparticles (NPs).

In particular, novel strategies related to both the encapsulation of vegetable oils, related methods of preparation, applications as antimicrobials and insecticide/pesticide/pest repellents, have been studied and developed [157]. Recently, de Matos et al. [158] gave an updated overview on analytical methods and challenges of essential oils in nanostructured systems. This represents a new frontier in the area of interest.

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