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Chemo-profiling of methanolic and ether oleoresins of *Salvia coccinea* and *in vitro* pesticidal evaluation with *in silico* molecular docking and ADME/Tox studies

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ABSTRACT

The objective of the present study was to examine the chemical compositions of *Salvia coccinea* oleoresins prepared in methanol and petroleum ether. GC-MS analysis of *Salvia coccinea* methanolic oleoresin (SCMO) and *Salvia coccinea* ether oleoresin (SCEO) resulted in the identification of 15 and 12 constituents, comprising 84.7 and 81.2% of the total composition, respectively. Both SCMO and SCEO varied in their chemical composition in terms of quantity, namely, oleic acid (22.3-25.9%), palmitic acid (8.9-8.4%), stigmasta-3,5-dien-7-one (3.4-11.8%), stigmasterol acetate (3.5-5.3%), neophytadiene (4.8-1.7%), phytol (1.6-7.8%) and phthalic acid (2.1-3.1%). In addition to the qualitative differences between SCMO and SCEO concomitantly, both oleoresins were examined for their pesticidal activities. Oleoresins demonstrated significant nematicidal activity against *Meloidogyne incognita*, insecticidal activity against *Lipaphis erysimi*, antifungal activity against *Curvularia lunata*, and antibacterial activity against *Staphylococcus aureus*. For nematicidal activity, SCMO and SCEO exhibited a high mortality of 65.66±1.69 and 54.33±1.24 and egg hatching inhibition of 26.33±1.20and 33.33±1.24 at 200 µg/mL. Similarly, SCMO and SCEO exhibited excellent insecticidal activity with 94.87±1.44 % and 86.75±1.85 % mortality at 1000 µg/mL. However, both oleoresins exhibited moderate antifungal and antibacterial activities compared to standards. Due to the quantitative difference in chemical composition and the presence of several phytoconstituents that were absent in SCEO, SCMO displayed stronger pesticidal effects than SCEO. To estimate the binding energy and structure-activity relationships between chemical constituents and pesticidal activities, *in silico* molecular docking and ADME/Tox studies have also been performed using a web-based online tool. On the basis of the present study, it is inferred that the herb *Salvia coccinea* might be a good source of phytochemicals and can be used for the development of herbal-based pesticides/formulations after proper clinical trials.

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1. Introduction

Organic molecules derived from plants have a variety of applications in medicine and other industrial processes as a source of environmentally benign chemicals such as starch isolated from mandua grains (Eleusine coracana; family Poaceae) and have been reported to be used for medicinal and industrial purposes [1,2]. Due to the widespread and excessive use of synthetic pesticides, pest management is currently experiencing substantial economic and environmental issues. The biodegradability, non-target toxicity, and lasting impacts of synthetic pesticides have become major concerns. Pesticides include a variety of substances such as herbicides, insecticides, nematicides, molluscicides, rodenticides, bactericides, piscicides, avicides, animal repellents, antimicrobials, fungicides, disinfectants and sanitisers [3]. The excessive use of synthetic pesticides has resulted in resistance problems besides other issues. According to epidemiological research, carbamates and organophosphates can cause cancer, mutation, teratogenicity, or allergies. These harmful substances are likely to cause a variety of diseases in humans, including cancer, skin conditions, hypertension, and renal diseases due to their long-term

accumulation in fruits and vegetables [4]. Medicinal plants are a major depository of secondary metabolites that might be a source of new organic pesticides. Natural pesticides are less harmful to human health, are more environment friendly, less expensive, and are easier to use in integrated pest control compared to synthetic ones [5]. The development of herbal-based pesticides such as essential oils, extracts, and pure chemicals, and their formulations, is underway to offset the negative effects of synthetic pesticides [6]. Several significant medications have been extracted and found in plants, and plant extracts have been used as an essential source of bioactive chemicals for numerous drug development projects [7]. The Lamiaceae species are mainly used for food preservation, flavouring, and medical uses, because of their curative and preventive qualities. Each species has a particular and intricate combination of bioactive secondary metabolites with important anti-inflammatory, antibacterial, antioxidant, antimicrobial, antiviral, and anticancer activities [8,9].

Salvia (Sage) is the largest genera of the Lamiaceae family with approximately 1,000 species. It is used mainly for its decorative, fragrant, and culinary properties [10]. Sage has a long history of being used to treat illnesses and promote health, as evidenced by the word "*Salvia*" in its Latin name, which means "to cure". In the food, pharmaceutical, and perfume industries, *Salvia* species are typically used for their essential oils [10]. In traditional medicine, many of them have been used as antihydrotics, tonics, antirheumatoid agents, anti-microbials, antispasmodics, antiseptics, astringents, digestives, anti-inflammatories, carminatives, and agents with antimutagenic activity for ages [11]. *Salvia multiorrhiza* has been used for a very long time in traditional Chinese medicine to treat hepatic and cardiovascular conditions. According to several studies, *Salvia* has been reported to be one of the best sources of natural antioxidants due to polyphenolic compounds [12,13]. The petroleum ether extract of *Salvia tebesana* Bunge has been reported to be a strong antiproliferative agent [14]. Essential oils and plant extracts of *Salvia officinalis* L., *Salvia syriaca*, *Salvia argentea*, and *Salvia sclarea* have been shown to have cytotoxic effects as well as antimicrobial, antifungal, insecticidal, and larvicidal capabilities against a variety of insects [15,16].

Salvia coccinea is medium in size (60-80 cm height). It is grown as an attractive plant, which is also known as banderilla (Texas sage, scarlet sage, crimson sage, tropical sage, and blood sage) [11,17]. It grows naturally in shaded, high-altitude, hilly, or rocky areas. It can be found growing in disturbed areas in the Nairobi and Elgon districts and is widely distributed throughout Southern Africa. The species is rare and has frequently escaped cultivation. Furthermore, it can be found in Singapore, the western Himalayas, tropical and subtropical areas of Asia, Africa, and Europe [18]. Terpenoids, polyphenols, anthocyanins, essential oils, and *β*-sitosterol have been identified as phytoconstituents of *S. coccinea* in previous investigations. Linolenic, linoleic, and oleic acids have been reported in their seed oils and extracts, along with their importance as chemotaxonomic indicators for the cosmetic, dietary supplement, and pharmaceutical industries [17]. *S. coccinea* has been reported as an abundant source of antioxidant polyphenols with medicinal potential [11,16]. Essential oils of *S. cryptantha* and *S. multicaulis* have been reported to exhibit antibacterial and antioxidant activities [19]. Biosynthesised silver nanoparticles (ScAgNP) from *Salvia coccinea* leaf extract have been reported to exhibit cytotoxic, antioxidant, and anti-inflammatory potential in monocytic THP-1 cells. Our research group has also reported the essential oil composition of the aerial part of *Salvia reflexa* and its antioxidant, antifungal, and antifeeding activities [20,21]. In continuation of our research on the Lamiaceae family, the objective of the present study was to investigate the phytochemical analysis of the methanolic and ether oleoresins of *Salvia coccinea* and its pesticidal evaluation, namely, nematicidal, antimicrobial, and insecticidal activity. Structure-activity relationships (SARs) between major compounds of EOs with possible pesticidal activities have been studied by *in silico* molecular docking and ADME/Tox studies. To our knowledge, there are no reports on the chemical composition and *in vitro* pesticidal effects of methanol and ether oleoresin of *S. coccinea* collected from Uttarakhand, India. Thus, it is being reported for the first time.

2. Experimental

2.1. Collection of plant material

The fresh aerial plant material of *Salvia coccinea* was collected from Pilot Baba Ashram, Bhowali, Uttarakhand, India (29.3596° N, 79.4815 ° E) located at a height of 2312 m, in July 2020. The plant was identified and verified as *Salvia coccinea* by Dr. Dharmendra Singh Rawat (Plant Taxonomist), Department of Biological Sciences, College of Basic Sciences and Humanities, Govind Ballabh Pant University of Agriculture and Technology, Pantnagar. The verified sample has been deposited with the voucher specimen number GBPUH-1019/08-10-2020.

2.2. Preparation of oleoresins

Using the cold percolation method, the oleoresins were prepared from finely ground shade-dried leaves by gradually soaking them in methanol and periodically shaking the mixture for seven days. The filtrate obtained was further fractionated in petroleum ether through liquid-liquid extraction. The ether and methanol oleoresins were then further evaporated at 45-60 °C in a rotary evaporator under vacuum at 45-60 °C until dryness.

2.3. GC-MS analysis and identification of chemical compounds

The methanol and ether oleoresins were analysed using a GC-MS-QP 2010 Ultra equipped with a 5MS DB-5 silica capillary column (30 m × 0.25 mm and 0.25 m thickness) and a mass spectrometer (5971 Å) as a detector. Parameters for the analysis were programmed as follows: carrier gas He; column flow rate: 1.21 mL/min; column injection temperature: 260 °C, injection mode: split, pressure: 69 KPa, split ratio: 1:10, interphase temperature: 270 °C, and scan range: 50-600 Da. The temperature was first set to 50 °C for 2 minutes, increased to 210 °C (at a rate of 3 °C/min), lowered for 2 minutes, and then increased to 240 °C (at a rate of 8 °C/min) and isothermal for 11 minutes. With an injection volume of 0.1 µL and a split mode of 1:100, MS was taken under EI condition (70 eV). The identification of the constituents of the oleoresins was based on the fragmentation pattern of the mass spectra with those of authentic samples of the Kovatt indices and the MS library (NIST14.lib, FFNSC2.lib and WILEY8.LIB) by comparing the spectra with data from the literature [22].

2.4. Nematicidal activity

2.4.1. Nematode population collection

The *Meloidogyne incognita* population was reared on capsicum at the Centre for Vegetable Research Center, Govind Ballabh Pant University of Agriculture and Technology, Pantnagar, in a glasshouse maintained at 25±2 °C. Capsicum (*Capsicum annuum*) was taken as the infected plant with root knots. From the roots of sickly capsicum, mature egg masses selected by hand were taken and cultured in distilled water at 25 °C in a growth chamber. Juveniles that had just emerged (J_2) were collected and stored at 5 °C until needed [23].

2.4.2. In vitro mortality assay on second stage larvae (J_2) of *M. incognita*

An *in vitro* mortality assay was performed against second-stage larvae (J_2) of *M. incognita*. The galled roots were cut into small pieces of 2 cm and thoroughly cleaned under running water to remove the second stage larvae (J_2) from the egg masses and the dirt attached to them. The small pieces of roots placed in sodium hypochlorite (2%) solution were stirred for two minutes to separate the organic matter from the eggs. The eggs were sieved over a 38 µm-pore, collected, and cleaned after the solution was put through a series of sieves. To collect 2nd stage juveniles from the hatched eggs after 48 hrs, the egg suspension was first incubated at 28±1 °C. A total of 100 juveniles were taken in Petri dishes containing different concentrations (25-200 µg/mL) of oleoresin. Observations of three replicates were taken at the time intervals of 24, 48, and 72 h using a stereobinocular microscope. The juveniles placed in tween-20 (1%) were taken as control. All treatments were arranged in a CRD (completely randomised design) manner. To check the aliveness (mortality) of the larvae, they were transferred to water. None of the immobile larvae recovered their mobility, which confirmed the death of the larvae. The percentage of nematode mortality was calculated using Abbott's formula.

$$\% \text{ Nematode mortality} = 100 \times \frac{Nc\text{-}Nt}{Nc} \quad (1)$$

where Nt = number of viable nematodes after treatment and Nc = number of viable nematodes in the water control.

2.4.3. In vitro egg hatchability test of *M. incognita*

The *in vitro* egg hatchability experiment was carried out to evaluate the effectiveness of SCMO and SCEO against *M. incognita*. Two *M. incognita* egg masses were suspended in a 25-200 µg/mL mixture of SCMO and SCEO in gridded Petri dishes. The control group consisted of egg masses dissolved in a tween-20 solution (1.0%). Treatments were kept at a constant temperature of 27±1 °C in a bio-oxygen demand (BOD) incubator with all treatments set in triplicate and in a completely random order. To record the findings on egg hatchability at intervals of 24, 48, and 72 h, respectively, the number of eggs hatched was counted under a microscope with a magnification of 40×.

2.5. Insecticidal activity using the toxicity bioassay method

Lipaphis erysimi were directly collected from a mustard field at the Norman E. Borlogue Research Centre, Govind Ballabh Pant University of Agriculture and Technology, Pantnagar and acclimatised in the laboratory of the Department of Entomology, College of Agriculture, Govind Ballabh Pant University of Agriculture and Technology, Pantnagar, until the emergence of the third instar larvae. *L. erysimi* of the mustard plant were reared in a muslin-walled box in the growth chamber of the glass house at 25±1 °C and relative humidity (RH) of 65±5%.

According to protocols practised previously, the experiment was evaluated in a Petri plate using the contact toxicity method [24]. Fresh and clean mustard leaves were collected, along with aphids (*L. erysimi*) on them from the field. Each leaf disc (4×4 sq. cm) of the fresh mustard plant was placed upside down on a 1 cm layer of agar solution (1 % agar solution using 1 g of agar in 100 mL of boiled distilled water) in a Petri dish. A ventilation hole was made in the middle of the Petri plate to maintain moisture in the leaf. Adult aphids were separated from the leaves with the help of a camel brush after 2 hours and collected in a box. Mustard leaves were soaked for 30 seconds at various concentrations (50-1000 µg/mL) of oleoresins and a solution of 1% tween-20 (1.0 mL of tween-20 in 99.0 mL of distilled water) before drying. Three replications of each concentration of oleoresins were taken along with control (1% tween-20). 15 adult aphids were starved for 3-4 hours before being placed on agar-layered Petri plates. Observations were taken at the time intervals of 24, 48 and 72 h after the nymph release. The numbers of dead aphids were counted and calculated using Abott's formula. The LC_{50} values of oleoresins were calculated using the Statistical Package for the Social Sciences (SPSS) 16.0 software package after probit analysis of the mortality data. Triplicate results of the studies were statistically analysed as mean±SD using one-way ANOVA (significant at $p < 0.05$).

2.6. Antifungal activity

The phytopathogenic fungi, namely *Curvularia lunata,* were obtained from the Department of Plant Pathology, College of Agriculture, Govind Ballabh Pant University of Agriculture and Technology, Pantnagar. Fungal colonies were asceptically transferred to Petri plates containing the medium and incubated for one week at 25±2 °C until the fungi were revived and grown on potato dextrose agar (PDA) medium. 39 g of PDA was mixed in boiling distilled water (1000 mL) and thoroughly stirred. After adding 500 mg of chloramphenicol to the medium, 200 mL of the medium was transferred to each 500 mL conical flask and plugged with non-absorbent cotton plugs. For sterilisation, the medium was autoclaved for 30 min (15 lbs psi at 121.6 °C).

To perform antifungal activity, PDA plates were prepared by heating solidified PDA at 450 °C and pouring 20 mL each in sterilised Petri plates in a laminar flow. PDA plates containing different concentrations of oleoresins (25-200 µg/mL) were inoculated with the test fungus disc (Diameter = 5 mm) and incubated for seven days at 26±2 °C and 68±2% RH until the control plates reached full growth. Observations of three replicates for five different concentrations of oleoresins were noted after approximately 7 days. The typical standard fungicide used was carbendazim. The percentage inhibition was calculated using the formula [25-27].

$$\text{Percent inhibition} = \frac{X\text{-}Y}{X} \times 100 \quad (2)$$

where, X = Radial growth in control and Y = Radial growth in treatment.

2.7. Antibacterial activity

The reported protocol was used to study antibacterial activity [28,29]. It was evaluated against representative Gram-positive bacteria (*Staphylococcus aureus*). Nutrient agar (NA), nutrient broth (NB), and agar-agar were obtained from Hi medium and stored at 4 °C until use. 28 g of Muller-Hinton agar was added to 1000 mL of distilled water along with 10 g of agar-agar powder to prepare the media solution. The mixture was autoclaved for sterilisation at 120 °C and 15-20 lbs. Similarly, inoculation of bacterial culture was prepared using 2.6 g of nutrient broth in 200 ml of distilled water and autoclaved at 128 °C and 15-20 lbs. In laminar flow, nutritional agar medium (20 mL) was placed into the sterilised Petri plates and left undisturbed until solidified. For sterile testing, incubate the solidified Petri plates overnight at 37 °C.

Pure cultures of Gram-positive bacteria were prepared in a test tube containing 5 mL of sterile nutrient broth. Incubate the bacterial tube overnight at 37 °C. 1% tween 20 solution (1.0 mL tween 20 in 99.0 mL of distilled water) was mixed with different amount (25-250 µg/mL) of SCMO and SCEO to form uniform solution. 5 mm of sterilised paper disk (Whatman no. 1) were cut and dipped in different concentration of SCMO and SCEO.

After some time, the paper disk was placed on the plate again and incubated for 24 h at 37 °C for the growth of bacterial colonies. Tween 20 (1%) and amikacin (standard) were used as a positive control and a negative control. The zone of inhibition was measured in millimetres after 24 hours and compared to a standard. To calculate the zone of inhibition, we used Equation (3),

$$\text{Zone of inhibition} = \frac{(\text{Diameter of inhibition zone} - \text{Diameter of disk})}{2} \quad (3)$$

2.8. Statistical analysis

Each treatment was repeated three times and the experimental data were expressed as mean±standard deviation. ANOVA was used to analyse the experimental data for nematicidal, insecticidal, antifungal, and antibacterial activities at a significance level of 1% ($p < 0.01$). At each level of significance, a substantial difference was discovered between the data examined. The pooled data were subjected to a three-factor analysis using SPSS.16 software.

2.9. Molecular docking studies

Molecular docking is a method for predicting the activity and affinity of small molecules with macromolecules like proteins in different orientations to understand the host-guest relationship at a minimum energy level. Molecular docking is a virtually developed crucial approach to determine the binding energy and learn about the numerous ligand-protein interactions through software like Autodock 4.2.6 (The Scripps Research Institute, USA). Gasteiger charges were calculated and registered as a pdbqt file using AutodockTools (ADT ver.1.5.7) [30]. Different 3D complex structures for the target proteins for different pests were data mined from the Protein Data Bank (PDB), *viz*. acetylcholonisterase protein (PDB ID: 1C2O) for *M. incognita* [31]. PDB ID: 3HNR, melanin biosynthesizing enzyme trihydroxy naphthalene reductase from *Curvularia lunata* [32], while PDB ID: 4TZK, mycobacterium tuberculosis enoyl reductase enzyme for *Staphylococcus aureus* [33], PDB ID: 5F3Y for *Lipaphis erysimi* have been taken directly from PDB (www.rscb.org/pdb) as no previous literature was found. Thus, it is being reported for the first time. The main identified compounds, such as oleic acid, palmitic acid, stigmasta-3,5-dien-7-one, neophytadiene, stigmasterol acetate, and phytol from SCMO and SCEO, were used as ligands (guest molecules) obtained from PubChem (3D structures). To examine the chemical interactions of complicated structures, 3D structures of ligands and proteins were created using BIOVIA Discovery Studio 2019. By introducing Kollmann charges and polar hydrogens in the proteins, all water molecules were eliminated. Using the graphical user interface program (AutoDock Tools), the pdbqt files were prepared for protein and ligands and a grid map was created using a grid box called AutoGrid (grid space of 0.375 Å and the grid size was set to 40×40×40 points). Cluster analysis was used to assess docked results with an RMS (root mean square) tolerance of 2.0. The dock score used to express the binding affinity of the test ligands (compounds) with the receptors (protein) indicates the estimated binding free energy B.E. (kcal/mol) in negative terms, which is reported as the enzyme inhibition constant (Ki) value. Higher calculated binding free energy values in negative terms or lower enzyme inhibition constant values suggest higher ligand receptor binding affinities [30].

2.10. In-silico ADME/Tox studies

A computer-based drug design method called ADME/Tox analysis is a virtual and preliminary stage of drug discovery. Absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox) studies are carried out during the drug discovery, lead optimization, and preclinical development phases. To predict the pharmacokinetic characteristics and the safety profile of the discovered drugs/phytoconstituents, ADME/Tox profiling was used using web-based software (SwissADME and pkCSM) to reduce the time and cost of expensive experiments compared to traditional methods [34,35]. The main compounds identified as oleic acid, palmitic acid, stigmasta-3,5-dien-7-one, neophytadiene, stigmasterol acetate, and phytol from SCMO and SCEO were studied for their *in silico* potential.

3. Results and discussion

3.1. Comparative chemical composition of oleoresins

The average yields of SCMO and SCEO were found to be 2.3 and 1.3 %, respectively. GC/MS analysis revealed the presence of more than 15 compounds that contributed 84.6% of the total oleoresin composition in SCEO and more than 12 constituents that contributed 81.2% of the total oil in SCMO. The main components of SCMO were oleic acid (22.3 %), stigmasta-4-en-3-one (17.6 %), palmitic acid (8.9%), neophytadiene (4.8%), tridecane (4.2 %), dodecane (3.5 %), stigmasterol acetate (3.5 %), stigmasta-3,5-dien-7-one (3.4 %), linoleic acid (3.3 %), stigmast-5-en-3-ol, oleate (2.8 %), pentadecane (2.3 %), methyl stearate (2.2%) and phthalic acid (2.1 %). The remaining constituents of oleoresin were in minor and trace amounts.

The main phytoconstituents of SCEO were oleic acid (25.9 %), stigmasta-3,5-dien-7-one (11.8 %), palmitic acid (8.4 %), phytol (7.8 %), linalool (5.4 %), stigmasterol acetate (5.3 %), α-cedrol (4.2 %), β-sitosterol (3.2 %), phthalic acid (3.1 %), squalene (2.8 %), neophytadiene (1.7 %), and limonene (1.6 %). The remaining constituents of oleoresin were in minor and trace amounts. Compounds such as dodecane, tridecane, pentadecane, methyl palmitate, linoleic acid, methyl stearate, and stigmast-5-en-3-ol, oleate were not found in SCEO, while linalool, α-cedrol, limonene, squalene and β-sitosterol were not found in SCMO. The literature survey did not reveal no report on the chemical composition of SCMO and SCEO. So, it could be assumed as the first report on the chemical composition of SCMO and SCEO. The detailed comparative chemical composition profiling and Venn diagram of SCMO and SCEO are presented in Table 1 and Figure 1.

Oleic acid has been reported to be a substantial component in the hexane extract of *S. fruticosa* and the seed oil of *S. candidissima* in the previous study [36]. Linolenic acid (18:3, 33.1%), linoleic acid (18:2, 25.2%), oleic acid (18:1, 13.3%) and stearic acid (18:0, 12.5%) have been reported as the main fatty acids in *S. coccinea* seed oil [17]. Similarly, oleic acid, palmitoleic acid, stearic acid, and linoleic acid have been reported in the hexane extract of *S. fruticosa* [37]. Linoleic acid (18:2; 24.3-69.2%), linolenic acid (18:3; 0.6-40.8%), oleic acid (18:1; 8.3-31.0%), palmitic acid (16:0; 3.8-21.0%) and stearic acid (18:0; 1.8-5.2%) have been reported as the main component in the hexane extract of nine *Salvia* seeds (*Salvia syriaca*, *Salvia potentilli* folia, *Salvia candidissima* ssp. *occidentalis, Salvia macrochlamys, Salvia poculata, Salvia tomentosa, Salvia recognita, Salvia virgata,* and *Salvia ceratophylla*) [36]. Similarly, linoleic acid has been reported in the majority of the seed oils of *S. albimaculata* (37.2%), *S. cedronella* (49.2%), *S. cryptantha* (61.1%), *S. forskahlei* (60.8%), *S. fruticosa* (47.6%), *S. virgata* (44.5%), *S. tchihatcheffii* (44.2%), *S. hypergeia* (43.7%), *S. tomentosa* (41.0%) and *S. halophila* (31.4%) [36]. Tricosanoic acid (C23:0), stearic acid (C18:0); heneicosanoic acid (C21:0); *cis*-10-heptadecanoic acid (C17:1); and palmitic acid (C16:0) have been reported as the major components in the petroleum ether extract of *S. poculata* whereas α-linolenic acid has been reported as the major component in the ether extract of clary sage seeds (*S. sclarea* L.), followed by oleic and linoleic acids, respectively [17,38,39].

Table 1. Comparative chemical composition of SCMO and SCEO *.

Sample no	Compound	Kovat indices	Oleoresin		Method of identification
			SCEO	SCMO	
1	Dodecane	1200	-	3.5	M^+ = 57, *m/z* = 98, 85, 71, 43, 41 (100%)
2	Tridecane	1300	-	4.2	M^+ = 57, *m/z* = 99, 85, 71, 43, 41 (100%)
3	Pentadecane	1500	-	2.3	M^+ = 57, *m/z* = 99, 85, 71, 43, 41 (100%)
4	Linalool	1620	5.4	-	M^+ = 71, *m/z* = 115, 95, 67, 55, 41 (100%)
5	α-Cedrol	1600	4.2	-	M^+ = 43, *m/z* = 148, 130, 105, 91, 57, 41 (100%)
6	Limonene	1029	1.6	-	M^+ = 43, *m/z* = 151, 123, 109, 95, 81, 57, 41 (100%)
7	Phytol	1943	7.8	1.6	M^+ = 68, *m/z* = 109, 95, 82, 57, 41 (100%)
8	Neophytadiene	-	1.7	4.8	M^+ = 68, *m/z* = 123, 109, 95, 82, 55, 41 (100%)
9	Methyl palmitate	1921	-	2.1	M^+ = 74, *m/z* = 143, 87, 57, 41 (100%)
10	Palmitic acid	-	8.4	8.9	M^+ = 73, *m/z* = 129, 98, 85, 60, 43 (100%)
11	Linoleic acid	2133	-	3.3	M^+ = 67, *m/z* = 123, 109, 95, 81, 55, 41 (100%)
12	Methyl stearate	2125	-	2.2	M^+ = 74, *m/z* = 143, 101, 87, 69, 41 (100%)
13	Oleic acid	2142	25.9	22.3	M^+ = 55, *m/z* = 97, 81, 69, 41 (100%)
14	Phthalic acid	1590	3.1	2.1	M^+ = 149, *m/z* = 167, 113, 84, 71, 57, 41 (100%)
15	Squalene	-	2.8	-	M^+ = 69, *m/z* = 137, 121, 95, 81, 41 (100%)
16	Stigmasterol acetate	-	5.3	3.5	M^+ = 68, *m/z* = 123, 109, 95, 82, 55, 41 (100%)
17	Stigmast-5-en-3-ol, oleate	-	-	2.8	M^+ = 43, *m/z* = 119, 105, 69, 57, 41 (100%)
18	β-Sitosterol	-	3.2	-	M^+ = 43, *m/z* = 213, 145, 95, 81, 57, 41 (100%)
19	Stigmasta-3,5-dien-7-one	-	11.8	3.4	M^+ = 43, *m/z* = 174, 161, 81, 57, 41 (100%)
20	Stigmasta-4-en-3-one	-	-	17.6	M^+ = 124, *m/z* = 229, 149, 95, 57, 41 (100%)

* SCMO = *Salvia coccinea* methanolic oleoresin, SCEO = *Salvia coccinea* ether oleoresin, t = trace < 0.1%.

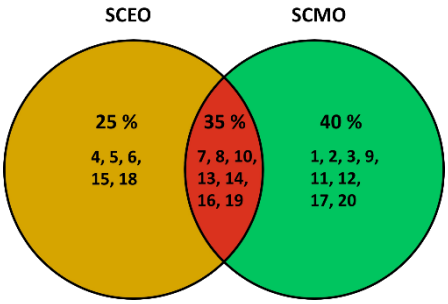


Figure 1. Venn diagram of the oleoresin composition of SCMO and SCEO.

Palmitic acid (25.8 %), phytol (24.0 %), *E*-caryophyllene (12.4 %), and caryophyllene oxide (10.7 %) have also been reported in *Salvia reflexa* from our laboratory [20]. In the present study, linoleic acid was found to be present in SCMO but was missing in SCEO. However, oleic acid, stigmasta-3,5-dien-7-one, palmitic acid, stigmasterol acetate, phthalic acid, neophytadiene, and phytol were identified in both oleoresins. The extensive variations between *Salvia* species may be caused by the extraction method, the season, the stage of development, and the unique habitat from which the plant was taken. Moreover, the composition of oleoresins varies greatly with respect to the geographical proximity. According to the published literature, the marker components in the *Salvia* species plant extract include oleic acid and palmitic acid. The methanolic and ether oleoresin of *Salvia coccinea* has never been studied before. Therefore, a comparison with the previously reported data was not possible. However, our findings generally agree with those of published reports on other *Salvia* species.

3.2. Nematicidal activity

The nematicidal activity of SCMO and SCEO (25-200 µg/mL) was investigated by monitoring the hatching of the eggs and the juvenile mortality of larvae of the second stage (J_2) of *M. incognita*. As the concentration increased, juvenile mortality increased, while egg hatching decreased. Nematodes are extremely poisonous to the solvent methanol. Therefore, all methanolic samples were evaporated until dryness to remove the traces of methanol. The powdered extract solubilised in water and Tween-20 was tested against nematodes with water as the negative control. Similarly, ether extracts were also used in powder form. The % mortality of SCMO (60.33±0.47%, 62.33±0.47% and 65.66±1.69%, respectively) and SCEO (40.33±1.24%, 51.33±0.81% and 54.33±1.24%, respectively) was shown to be effective at the highest concentration (200 µg/mL) when exposed for 24, 48, and 72 hours, as shown in Table 2. At 200 µg/mL, SCMO (6.00±0.57%, 9.66±0.33% and 26.33±1.20%) and SCEO (9.33±0.94%, 11.33±1.33% and 33.33±1.24%) showed a significant inhibitory effect of egg hatching against *M. incognita* when exposed for 24, 48, and 72 hours, as shown in Table 3. The LC_{50} and IC_{50} values for SCMO and SCEO have been mentioned in Tables 2 and 3. LC_{50} and IC_{50} values for SCMO were observed to be 120.98 µg/mL and 20.04 µg/mL, respectively. For SCEO, these values were 206.41 µg/mL and 29.71 µg/mL, respectively.

In the present study, oleic acid and palmitic acid have been identified as the main compounds in SCMO and SCEO. No data exist on the nematicidal activity of SCMO and SCEO to compare with the experimental results of the present investigation. In previous studies, *Salvia officinalis* has also been reported to exhibit nematicidal activity against *M. incognita* [40]. Palmitic acid (C16:0) and oleic acid (C18:19c), isolated from the stem and root of *Mucuna aterrima*, have been reported to exhibit nematicidal activity against *M. incognita* due to the presence of double bonds in oleic acid at the, α- and β-position of the carbonyl group. Palmitic acid has been reported to cause significantly higher mortality in second-stage juveniles of *M. incognita* compared to oleic acid [41]. Linoleic acid isolated from the stem and root of *Mucuna aterrima*, have been reported to exhibit good nematicidal activity against *M. incognita* [42]. Linoleic acid (100±0.00) has been reported to exhibit better nematicidal activity compared to palmitic acid (68.00±0.7) and oleic acid (85.00±4.0) against the cyst nematode *Heterodera zeae* [43].

Table 2. Nematicidal activity of SCMO against *M. incognita* *.

SCMO	(%) Juvenile (J_2) mortality			(%) Eggs hatching		
(µg/mL)	24 h	48 h	72 h	24 h	48 h	72 h
25	21.33±0.94 b	25.00±0.81 b	27.33±0.94 b	29.66±0.88 d	42.33±0.88 e	78.00±1.15 d
50	34.66±0.47 c	39.66±1.24 c	40.66±1.20 c	20.66±0.33 c	35.33±0.88 d	63.66±0.88 c
100	45.66±1.69 d	48.66±2.49 d	53.00±2.16 d	13.33±0.88 b	20.00±1.15 c	48.00±1.15 c
150	54.66±1.24 e	58.33±2.05 e	62.66±1.69 e	9.33±0.66 ab	13.33±0.88 b	38.33±2.02 b
200	60.33±0.47 f	62.33±0.47 f	65.66±1.69 e	6.00±0.57 a	9.66±0.33 a	26.33±1.20 a
Control (1% Tween 20)	0.00±0.00 a	0.66±0.00 a	2.33±0.33 a	56.00±3.21 e	80.00±1.15 f	107.33±3.71 e
LC_{50}/IC_{50} (µg/mL)	120.98 µg/mL			20.04 µg /mL		

* SCMO = *Salvia coccinea* methanolic oleoresin, SCEO = *Salvia coccinea* ether oleoresin, Within a column, mean values (a, b, c, d, e, f) followed by the same letter are not significantly different according to Tukey's and Duncan's test ($p < 0.05$).

Table 3. Nematicidal activity of SCEO against *M. incognita* *.

SCEO	(%) Juvenile (J_2) mortality			(%) Eggs hatching		
(µg/mL)	24 h	48 h	72 h	24 h	48 h	72 h
25	11.33±0.94 b	15.33±0.57 e	27.00±1.41 b	41.66±0.88 d	44.66±3.29 c	70.00±1.63 e
50	20.66±0.94 c	34.33±1.88 d	41.33±1.69 c	34.00±1.33 c	38.66±0.88 bc	60.66±0.94 d
100	28.66±0.47 d	37.66±1.76 cd	39.66±1.52 c	28.00±0.81 b	32.33±0.47 b	54.66±0.47 c
150	36.33±1.24 e	41.33±0.81 e	44.33±1.69 c	10.66±0.94 a	16.66±0.85 a	43.33±0.47 b
200	40.33±1.24 f	51.33±0.81 f	54.33±1.24 d	9.33±0.94 a	11.33±1.33 a	33.33±1.24 a
Control (1% Tween 20)	0.00±0.00 a	0.66±0.00 a	2.33±0.33 a	42.33±2.05 d	73.33±1.15 d	107.33±3.71 f
LC_{50}/IC_{50} (µg/mL)	206.41 µg/mL			29.71 µg /mL		

* SCMO = *Salvia coccinea* methanolic oleoresin, SCEO = *Salvia coccinea* ether oleoresin, Within a column, mean values (a, b, c, d, e, f) followed by the same letter are not significantly different according to Tukey's and Duncan's test ($p < 0.05$).

Table 4. Insecticidal activity of SCMO and SCEO against nymph of *Lipaphis erysimi* *.

Concentration	Mortality % (mean±SD)					
(µg/mL)	SCMO			SCEO		
	24 h	48 h	72 h	24 h	48 h	72 h
50	23.71±1.11 e	36.75±2.96 e	42.09±3.86 d	7.90±0.37 e	20.94±3.70 e	31.41±2.57 d
100	39.59±1.85 d	52.56±2.22 d	55.12±1.87 c	23.71±1.11 d	28.84±3.33 d	36.75±2.96 d
250	55.34±2.59 c	60.47±1.85 c	63.03±1.60 c	39.52±1.85 c	50.00±3.84 c	52.56±2.22 c
500	68.37±1.48 b	76.28±1.11 b	81.62±2.12 b	52.56±2.22 b	63.03±2.60 b	65.59±1.29 b
1000	84.18±0.74 a	86.75±2.12 a	94.87±1.44 a	76.28±1.11 a	81.62±1.12 a	86.75±1.85 a
Control	00.00±0.00 f	00.00±0.00 f	00.00±0.00 e	00.00±0.00 f	00.00±0.00 f	00.00±0.00 e
LC_{50} (µg/mL)	153.67 µg/mL			410.36 µg/mL		

* SCMO = *Salvia coccinea* methanolic oleoresin, SCEO = *Salvia coccinea* ether oleoresin, Within a column, the mean values (a, b, c, d, e, f) followed by the same letter are not significantly different according to the Tukey's and Duncan's test ($p < 0.05$).

The EOs of *Tagetes* species herbs containing neophytadiene has been reported to exhibit nematicidal activity [44]. SCMO and SCEO also possess the neophytadiene component and hence might be responsible for the nematicidal activity or synergistic effect of other constituents. Similarly, the main compounds such as oleic acid, palmitic acid, stigmasta-3,5-dien-7-one, linoleic acid present in SCMO and SCEO could be responsible for the good nematicidal activity against *M. incognita*. Due to the non-toxic properties and environmental friendliness of plant extracts, SCMO and SCEO can be used effectively to develop ecofriendly herbal formulations to manage pest nematodes without posing a threat to the environment.

3.3. Insecticidal activity

Lipaphis erysimi, commonly known as mustard aphid, is a serious damaging pest. The results reported in Table 4 showed that there was significant mortality in adults with *L. erysimi* when exposed to different concentrations (50-1000 µg/mL) of SCMO and SCEO. The results showed varying mortality percentages at different dose levels, where the percent mortality increased with increasing dose levels. At a higher dose (1000 µg/mL), SCMO exhibited 94.87±1.44% mortality in 72 h, while SCEO exhibited 86.75±1.85% mortality. The ANOVA showed a significant difference among the concentrations of oleoresins, including the control. The toxicity and minimum median lethal concentration (LC_{50}) of SCMO and SCEO were found to be 153.67 µg/mL and 410.36 µg/mL, respectively. These experimental observations were found to be in total agreement with the insecticidal activity against *Aphis craccivora* in the n-hexane fraction of *Triadica sebifera* (LC_{50} = 196.61 mg/L) containing neophytadiene [45]. *Salvia officinalis essential oil* has been reported to show a strong repellent effect (95.0±5.77%) against *Aphis fabae* at the highest concentration of 0.16 µL/cm² at 24 hours [46]. The findings of the t-test revealed that SCMO and SCEO had a stronger repellent effect compared to the control, which could be due to the presence of various combinations of fatty acids and the synergistic interaction of the major/minor constituents of oleoresins. *Oenocarpus bataua* and *Attalea speciosa oils* have been reported to consist of fatty acids such as oleic acid and palmitic acid and exhibited a mortality rate of 100% against *L. erysimi* at concentrations of 10, 25, 50 and 100% [47]. In the present study, SCMO exhibited better insecticidal activity compared to SCEO, possibly due to the synergistic interaction of fatty acids observed in the insecticidal activity of neem oil against *Aphis craccivora,* which has been reported to consist of linoleic acid, oleic, and palmitic acid as the main components [48].

3.4. Antifungal activity

In the present study, SCMO and SCEO exhibited antifungal activity against phytopathogenic fungi at various doses (25-200 µg/mL) (Table 5), revealing a percent suppression of mycelial growth of the tested fungus. The antifungal potential of SCMO and SCEO against *C. lunata* was 19.27±0.25 % and 15.19±0.67 % at 25 µg/mL whereas 68.36±0.48 and 65.02±0.48 µg/mL, respectively, at the highest dose of 200 µg/mL. The antifungal activity of the *S. coccinea* methanolic extract against different species of Candida (*C. albicans, C. parapsilosis, C. tropicalis, C. krusei* and *C. glabrata*) has been reported to show a minimum inhibitory concentration (MIC) of 125 µg/mL which was found to be in accordance with the results of the present study [49]. The methanolic extract of *S. africanalutea*, *S. cryptantha*, *S. officinalis*, *S. tomentosa*, and *S. verticillata* has been reported to show effective antifungal properties against *Monilia laxa*, *Fusarium oxysporum,* and *Aspergillus niger* [50].

Table 5. Antifungal activity of SCMO and SCEO against *C. lunata* *.

Concentration (µg/mL)	% Mycelial growth inhibition				
	25	50	100	150	200
SCMO	19.27±0.25 [a]	23.91±0.37 [b]	40.42±0.93 [c]	52.09±0.25 [d]	68.36±0.48 [e]
SCEO	15.19±0.67 [a]	22.80±0.37 [b]	37.83±0.47 [c]	50.24±0.38 [d]	65.02±0.48 [e]
Carbendazim (standard)	100.00±0.00	100.00±0.00	100.00±0.00	100.00±0.00	100.00±0.00

* SCMO = *Salvia coccinea* methanolic oleoresin, SCEO = *Salvia coccinea* ether oleoresin, Within a column, the mean values (a, b, c, d, e, f) followed by the same letter are not significantly different according to the Tukey's and Duncan's test ($p < 0.05$).

Table 6. Antibacterial activity of SCMO and SCEO against *S. aureus*.

Concentration (µg/mL)	Zone of inhibition (ZOI) in mm±SD		
	SCMO *S. aureus*	SCEO *S. aureus*	Standard Amikacin
25	5.93±0.25 [a]	2.60±0.25 [a]	15.33±0.33 [a]
50	10.58±0.37 [b]	5.39±0.84 [b]	18.66±0.66 [a]
100	16.35±0.63 [c]	10.42±0.17 [c]	20.66±0.33 [a]
150	19.13±0.38 [d]	13.94±1.02 [d]	27.00±0.57 [a]
200	22.06±0.15 [e]	19.10±1.12 [e]	31.66±0.33 [a]
Control	0.00±0.00 [f]	0.00±0.00 [f]	

* SCMO = *Salvia coccinea* methanolic oleoresin, SCEO = *Salvia coccinea* ether oleoresin, Within a column, the mean values (a, b, c, d, e, f) followed by the same letter are not significantly different according to the Tukey's and Duncan's test ($p < 0.05$).

Table 7. Molecular docking analysis of the main compounds of SCMO and SCEO against target proteins from various biological activities *.

Compounds	ΔGb	Ki	I. E.	B.E.	R.M.S.D.	Residual Interactions		
						Van der Waals	Pi-alkyl	Pi-sigma
PDB ID: IC2O								
Oleic acid	-4.69	363.71	-9.46	-4.77	93.37	GLY441, GLU199, GLY119, SER122, ASP72, GLY80, SER200, SER81	TYR121, HIS440, TYR334, ILE439, TRP84, TRP432	PHE330
Palmitic acid	-5.85	308.71	-9.26	-9.53	96.03	TYR70, GLY80, ASP72, ASN85, SER81, GLY441, GLU199, GLY118, SER200, GLY119	TRP84, PHE330, TYR334, TRP432, HIS440	-
PDB ID: 5F3Y								
Oleic acid	-1.26	118.62	-6.04	-1.55	105.94	ARG356, ASP372, ARG364, GLU376, LEU380	ALA375, LEU360, VAL379, ARG534, TRP385, PHE535, LYS538	-
Palmitic acid	-2.50	14.70	-6.97	-6.52	107.85	ARG356, GLU376	LEU380, TRP385, PHE535, VAL379, LYS538, LEU360, VAL363, ARG364, ALA375	-
PDB ID: 3HNR								
Oleic acid	-2.78	9.23	-7.55	-7.32	22.75	GLU251, ILE316, LYS155, ARG134, ALA224, SER223	ALA252, LEU225, PHE315, VAL163, ILE151	-
Palmitic acid	-2.23	23.24	-6.70	-6.61	21.45	ARG134, SER223, LYS155, ILE316	LEU225, ALA252, PHE315, ILE151, VAL163	-
PDB ID: 4TZK								
Oleic acid	-4.99	219.54	-9.76	-10.46	94.69	ILE439, GLY80, SER81, ASP72, GLU199, TYR121, GLY118, SER200, GLY119, PHE331, GLY117	TYR442, TRP432, TRP84, PHE330, HIS440, TYR334	-
Palmitic acid	-2.53	14.01	-7.00	-5.95	70.80	ARG174, MET175, LEU171, PRO48, ARG47	GLU299, PHE300	-

* Free binding energy, ΔG; Estimated inhibition constant, Ki; Residual interactions represent amino acid interactions forming hydrogen bonds with the ligand through Van der Waals, alkyl, and pi-alkyl interactions.

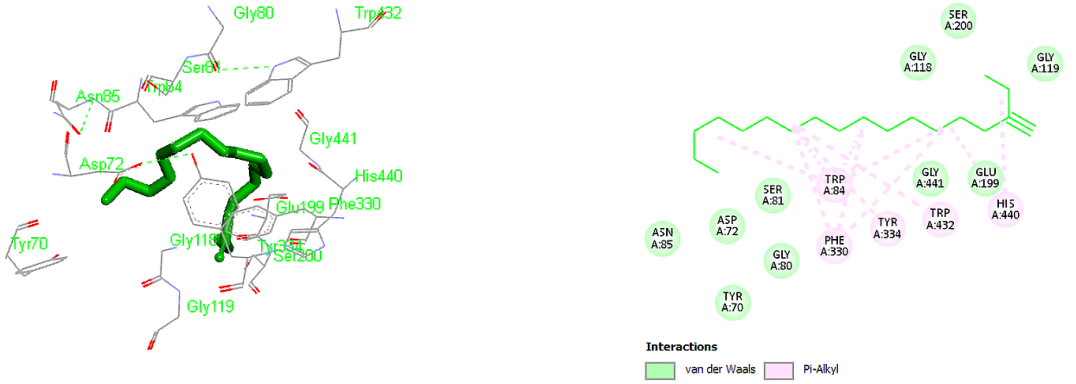
Similarly, the brain lipid of red shrimp (*Metapenaeus brevicornis*) consists of oleic acid and has been reported to be active against the fungal pathogen *Curvularia lunata* [51]. *Salvia reflexa* EO has been reported to exhibit significant antifungal activity (100% at 100 ppm) against *C. lunata* with palmitic acid (25.80%), phytol (24.0 %) as the main component [20]. SCMO and SCEO have been found to exhibit almost similar antifungal potential. The acetone extract of *Foeniculum vulgare* containing oleic acid, palmitic acid, and linoleic acid as the main constituents has been reported to exhibit good antifungal activity [52]. The EO of *Salvia sharifii* has been reported to exhibit significant antifungal activity against *Aspergillus niger, Aspergillus flavus,* and *Candida glabrata* [53]. The aforementioned constituents have also been identified in SCMO and SCEO that could be responsible for the antifungal activity against *C. lunata*.

3.5. Antibacterial activity

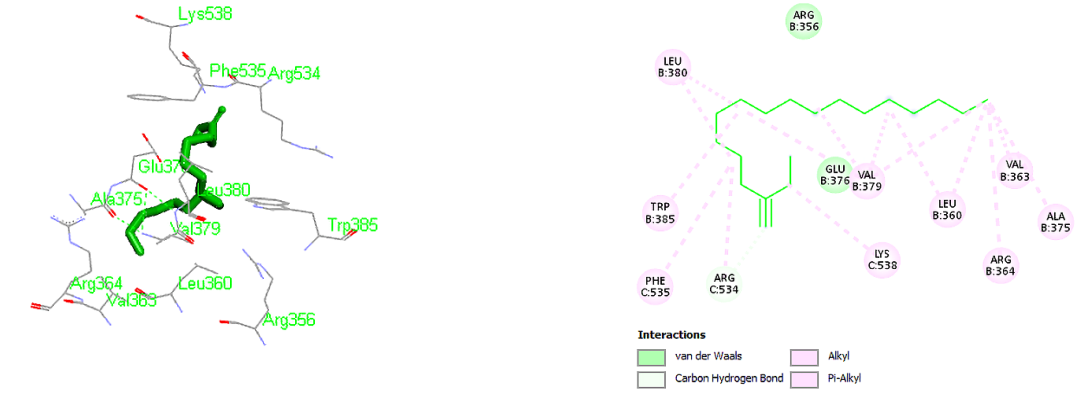
The antibacterial potential against the pathogenic bacterial strain *S. aureus* has been studied and expressed in terms of zone of inhibition (ZOI) in millimetres. At 25 µg/mL, SCMO and SCEO exhibited minimum antibacterial activity and followed the order: Amikacin (ZOI = 15.33±0.33) > SCMO (ZOI = 5.93±0.25) > SCEO (ZOI = 2.60±0.25).

At 200 µg/mL, SCMO and SCEO exhibited maximum antibacterial activity and followed this order: Amikacin (ZOI = 31.66±0.33) > SCMO (ZOI = 22.06±0.15) > SCEO (ZOI = 19.10±1.12). Similarly, the methanolic extract of *S. cryptantha* and *S. multicaulis* demonstrated strong anti-bacterial activity. *S. multicaulis* exhibited significant anti-bacterial activity against *S. aureus* with 10.00±0.16 mm zone of inhibition at 100 µg/mL, which was determined to be consistent with the experimental findings of the present investigation (Table 6) [54]. The methanolic extract of *Salvia leriifolia* and *Salvia pisidica* has been reported to exhibit substantial antibacterial activity against *S. aureus* at various concentrations [55,56]. It has been reported that the methanol extracts of the seaweeds of *Ulva lactuca* consist of neophytadiene which might be responsible for the antibacterial activity against *E. coli, K. pneumonia, S. typhi* and *S. aureus* [57]. However, no reports are available on the antibacterial activity of SCMO and SCEO and are being reported for the first time. The main compounds such as oleic acid, palmitic acid, linoleic acid, and neophytadiene present in SCMO and SCEO might be responsible for the antibacterial activity against *S. aureus*.

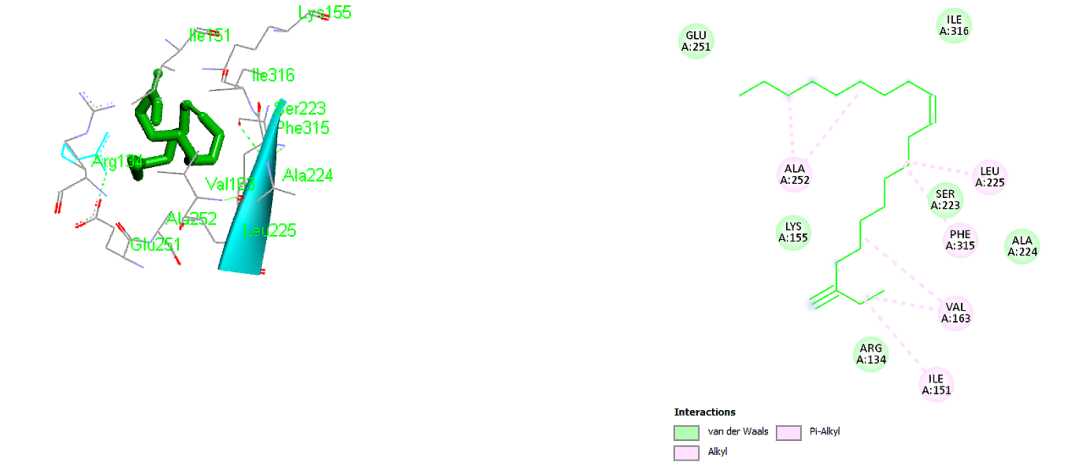
Palmitic acid with 1C2O



Palmitic acid with 5F3Y



Oleic acid with 3HNR



Oleic acid with 4TZK

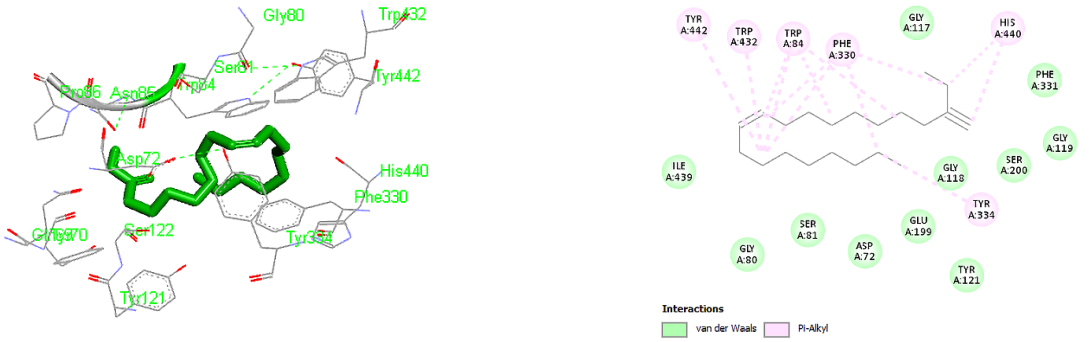


Figure 2. Schematic representation of 3D and 2D interactions of major compounds of SCMO and SCEO docked into the active site of targeted proteins involved in various biological activities illustrating interactions with amino acid residues in the binding site based on the lowest binding energies. 1. Palmitic acid with 1C2O (ache in nematicidal activity) 2. Palmitic acid with 5f3y (protein in *Lipaphis erysimi*) 3. Oleic with 3hnr (Antifungal protein) 4. Oleic acid with 4tzk (Antibacterial protein).

Table 8. ADME/Tox analysis of major compounds of SCMO and SCEO *.

Major compounds	Oleic acid	Palmitic acid	Stigmasta-3,5-dien-7-one	Neophytadiene	Stigmasterol acetate	Phytol
Drug likeness						
Lipinski rule	Yes	Yes	Yes	Yes	Yes	Yes
Bioavailability score	0.85	0.85	0.55	0.55	0.55	0.55
Absorption						
Water solubility (log mol/L)	-5.924	-5.562	-6.75	-8.559	-6.859	-7.535
$CaCO_2$ Permeability (log Papp in 10^{-6} cm/s)	1.563	1.558	1.317	1.425	1.203	1.399
Human intestinal absorption (% Absorbed)	91.82	92.00	97.54	92.85	97.08	90.643
Skin Permeability (log Kp)	-1.725	-2.717	-2.651	-2.518	-2.792	-2.631
P-glycoprotein substrate	No	No	No	No	No	No
Distribution						
VDss (log L/kg)	-0.558	-0.543	0.051	0.692	0.051	0.385
Fraction unbound (human) (Fu)	0.052	0.101	0	0	0	0
BBB permeability (log BB)	-0.168	-0.111	0.739	0.983	0.739	0.793
CNS permeability (log PS)	-1.654	-1.816	-1.765	-1.299	-1.765	-1.527
Metabolism						
CYP2D6 substrate	No	No	No	No	No	No
CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes	Yes
CYP1A2 inhibitor	Yes	No	No	Yes	No	Yes
CYP2C19 inhibitor	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No
Excretion						
Total Clearance	1.884	1.763	0.539	1.764	0.539	1.686
Renal OCT2 Substrate	No	No	No	No	No	No
Toxicity						
Hepatotoxicity	0.55	0.52	0.79	0.79	0.71	0.79
Carcinogenicity	0.64	0.63	0.60	0.73	0.52	0.76
Immunotoxicity	0.99	0.99	0.98	0.99	0.99	0.99
Mutagenicity	1.00	1.00	0.96	0.98	0.98	0.97
Cytotoxicity	0.71	0.74	0.75	0.81	0.78	0.85

* Lipinski rule of five; molecular weight < 500 Da, number of H donor bonds ≤ 5, number of H acceptor bonds ≤ 10, number of rotatable bonds < 10, lipophilicity (octanol/water partition coefficient, log P) < 5 and total polar surface area < 140 $Å^2$; Yes represents not more than one violation; skin permeability is expressed as Log Kp; P-gpI = P-glycoprotein inhibitor; Human intestinal absorption (HIA); BBB (blood-brain barrier) permeability is expressed as log BB (log BB > -1.0 is moderately cross blood-brain barrier); VDss (Volume of distribution should be less than 0.45; Cytochromes (Cyp) of the P450 family (CYP2D6 and CYP3A4 substrate, CYP1A2, CYP2C19, CYP2D6, CYP2C9 and CYP3A4 inhibitors); toxicity measured in probability values varying from 0.00 to 1.00.

3.6. Molecular docking analysis

In medicinal chemistry and drug discovery, molecular docking is used to predict how two molecules will interact. By exploring the optimum confirmation of the ligand-protein complex and its relative orientation, docking was found to be helpful for drug design. The enzyme's active site was docked with the major bioactive compounds of methanol and ether oleoresin of *S. coccinea*. The Gibbs free energy (ΔG), the intermolecular energy (I.E.), the binding energy (B.E.) for each bioactive compound against different protein targets, the inhibition constant, Ki, root mean square deviation (R.M.S.D.) and the residual interactions were listed in Table 7. Palmitic acid exhibited the lowest binding energy of -9.53 kcal/mol (PDB ID: 1C2O) and -6.52 kcal/mol (PDB ID: 5F3Y). The lowest binding energy against 3HNR was exhibited by oleic acid (B.E. = -7.32 kcal/mol). Similarly, oleic acid exhibited the lowest binding energy of -10.46 kcal/mol against 4TZK. Thus, the higher effectivity of oleic acid to be used as a potent bactericide can be inferred. There is no consistent pattern found in the lowest binding energy values of the main compounds that allows any component to be considered responsible for the results, instead it is the synergistic/addition effect of other main/minor compounds, which suggests that *S. coccinea* is a bioactive mixture that could be responsible for the significant results observed in *in vitro* studies [41,47,51]. The strongest ligand-protein interactions, determined by the lowest binding energies, are represented in Figure 2 in three-dimensional and two-dimensional docked conformations along with the residual interactions that form hydrogen bonds, which demonstrate the strength and catalytic activity of the binding complex. These interactions showed the strength and catalytic activity of the binding complex.

3.7. ADME/Tox studies analysis

To assess a drug for safety and efficacy, which is essential for regulatory approval, drug developers can use ADME features. Absorption was predicted from % of human intestinal absorption (HIA), lipophilicity, and water solubility of the compound. Drug likeness prediction was done using the Lipinski rule of five. The major compounds of methanol and ether oleoresin of *S. coccinea* did not violate more than one rule of Lipinski to exhibit drug-like behaviour and thus would be considerable for absorption (Table 8) [58]. The logarithmic Kp values of all major compounds were found within the range of -1.72 to -2.79 cm/s, inferring low skin permeability. The distribution was also predicted for oleic acid, palmitic acid, stigmasta-3,5-dien-7-one, neophytadiene, stigmasterol acetate, and phytol which showed high GI absorption and no permeability of the BBB. None of the compounds were found to be substrates of the permeability glycoprotein (P-gp). Metabolism was predicted based on inhibitor interactions, that is, cytochromes from the P450 family (CYP1A2, CYP2C19, CYP2D6, CYP2C9 and CYP3A4 inhibitors) involving the mechanism where different drugs compete for the same enzyme binding site and inhibition of cytochromes could lead to drug efficacy or toxicity (Table 8). Excretion and toxicity were predicted using the online tool Protox II based on the Web, where LD_{50} values and toxicological parameters (hepato-

toxicity, carcinogenicity, mutagenicity and cytotoxicity) were predicted for the main compounds that did not show toxicity [59,60]. Based on the ADME/Tox study, we can conclude that the main compounds of methanol and ether oleoresin of *S. coccinea* and their combinations can be considered effective and efficacious against the therapeutic target and showed a good pharmacokinetic profile.

4. Conclusions

SCMO and SCEO obtained from *S. coccinea* were found to be rich in fatty acids and terpenoids. The nematicidal, insecticidal, antifungal, and antibacterial activities were statistically evaluated and showed a significant relationship with oleoresins. In higher concentrations, insecticidal activity showed complete mortality of mustard aphids. *In vitro* antifungal and antibacterial activity has been observed in both oleoresins. SCMO and SCEO exhibited good nematicidal activity against *M. incognita*. The methanol and petroleum ether oleoresins of *S. coccinea* exhibited significant pesticidal activities that are being reported for the first time. Although the fatty acid composition obtained in oleoresins has previously shown pesticidal activity, the significant results in the present study could be due to the synergistic effect of the major or minor phytoconstituents. Furthermore, it has been supported by *in silico* molecular docking and ADME/Tox studies. This herb can be explored for the development of environmentally benign natural pesticides, aside from its academic importance for the generation of databases. However, more studies are needed to isolate and identify the components of *Salvia coccinea* responsible for endowing the species with its pesticidal activity. The extract and oleoresins or essential oils of *Salvia* species can be used to prepare formulations for the development of green pesticides. The activity-guided separation and identification of active constituents from extracts may be further helpful as a lead molecule in the development programme of the pesticide industry.

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Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered to.
Sample availability: Samples of the compounds are available from the author.

CRediT authorship contribution statement

Conceptualization: Kirti Nagarkoti; Methodology: Kirti Nagarkoti; Software: Avneesh Rawat; Validation: Tanuja Kabdal; Formal Analysis: Ravendra Kumar; Investigation: Dharmendra Singh Rawat; Resources: Ravi Mohan Srivastava, Satya Kumar; Data Curation: Kirti Nagarkoti; Writing - Original Draft: Kirti Nagarkoti, Avneesh Rawat; Writing - Review and Editing: Om Prakash; Visualization: Om Prakash; Funding acquisition: Kirti Nagarkoti; Supervision: Om Prakash; Project Administration: Om Prakash.

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