

## Systematic Review

# *Schinus molle* L. Essential Oil: Chemotypes, Bioactive Compounds, and Pharmaceutical Insights: A Systematic Review

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## Abstract

*Schinus molle* L. Essential Oil (SMEO) displays a rich scientific literature, including preliminary studies on its antimicrobial, antioxidant, and anti-cancer properties. This review seeks to systematically analyze the influence of the chemotype diversity of SMEO on its biological and pharmaceutical applications, with a particular focus on antimicrobial, antioxidant, and anti-cancer activities, and to identify research gaps for effective pharmaceutical exploitation. The article selection process was carried out in June 2025 and focused on the PubMed, Scopus, and MDPI databases, producing 176 articles, of which 51 were selected for this review. The present systematic review included the articles published in English and Spanish, with no limitations on the year of publication; data from patent and symposium abstracts were excluded. A qualitative assessment of the selected articles was carried out, including a TRL (Technology Readiness Level) analysis. The results were summarized using hierarchical cluster analysis and a strategic patent search tree, and were processed into tables, graphs, and a heat map, which enabled discussions and proposals for new research trends to be developed. The chemical composition varies significantly depending on the production area, climatic conditions, and seasonality, but the presence of two prevalent chemotypes is evident,  $\alpha$ -phellandrene and sabinene, respectively. Data on antimicrobial, antioxidant, and anti-cancer activity were promising, and some formulation prototypes are available, pointing toward the potential development of pharmaceutical and veterinary products. The use of nanotechnology appears to be crucial for the potential pharmaceutical application of SMEO, but further studies are needed. Specifically, further investigation of the properties of SMEO or its components in wound healing applications could represent a new research trend. This review highlights the state of the art of pharmacological research on SMEO and suggests future research directions with a view to develop formulations suitable for safety and efficacy improvements.

**Keywords:**  $\alpha$ -phellandrene; essential oil; sabinene; *Schinus molle*; wound-healing



Academic Editor: Cunshan Zhou

Received: 28 October 2025

Revised: 8 December 2025

Accepted: 16 December 2025

Published: 6 January 2026

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## 1. Introduction

Research concerning the use of essential oils (EOs) in the pharmaceutical sector has very ancient roots but is still relevant today [1–3]. The scientific literature on the subject is truly extensive and several review articles summarize the potential pharmaceutical applications of specific OEs, such as Nutmeg (*Myristica fragrans*) essential oil (EO), Eucalyptus (*Eucalyptus* spp.) EO, Ginger (*Zingiber officinale*) EO [4–6], and some isolated compounds, such as 1,8-cineole, carvacrol, limonene, and bisabolol [7–10]. Among the most active research frontiers are studies relating to anti-cancer activity [11,12], pain treatment and anxiety [13–15], and other activities (antioxidant, antimicrobial, and anti-inflammatory, etc.), which are sometimes synergistic, and that can assist further therapeutic interventions, such as in the treatment of wounds [16]. Finally, antibiotic resistance represents an ever-increasing risk to world health, and here too, research into essential oils represents an important research line [17].

*Schinus molle* L. is a species native to the tropical zone of the American continent and belongs to the Anacardiaceae family. *S. molle* is a dioecious tree with aromatic leaves that often secrete sticky substances. The woody trunk has whitish latex. The flowers are panicle-like and unisexual, with an open corolla with five oval, oblong, downwardly oblique petals. The fruits are defined as red globose drupes with a sweet, pungent flavor and an epicarp that is dehiscent when dry. *S. molle* is native to the American tropics but is common as an ornamental and spice plant in several countries in the Mediterranean region and southern Europe [18]. The chemical composition of essential oils and their biological activity may vary depending on the geographical area, environmental conditions, climate change, and extraction techniques [19,20]. Understanding and defining the chemotypes of SMEO is fundamental because variations in chemical profiles directly influence the biological activities and therapeutic potentials of the oil. Chemotypes such as  $\alpha$ -phellandrene-rich and sabinene-rich oils have been shown to possess distinctive bioactivities, ranging from antimicrobial and anti-inflammatory to neuroprotective and anti-cancer effects. These chemotypical differences underscore the necessity of chemical standardization in pharmaceutical development, as reproducible efficacy and safety profiles depend on the consistent supply of specific chemotype variants.

The oldest data in relation to the chemical composition of SMEO are cited by Terhune et al. [21] and report  $\beta$ -phellandrene,  $\alpha$ -pinene, and carvacrol as the majority compounds, also mentioning, for the first time, the identification of  $\beta$ -spathulene in a natural product. Physiological chemical variability often leads producers selecting oils characterized by a certain chemotype. The chemotype concept has been widely discussed and defined in various scientific disciplines, ranging from organic chemistry to pharmacology. It refers to a category of chemical compounds that share a common basic chemical structure but can vary in some structural or functional aspects, which gives them different biological or pharmacological properties. It is known that the qualitative and quantitative composition of essential oils is not standard; this is why they usually have different quality, value, and prices on the market [22]. The bioactivity of a plant is contingent upon its unique chemical composition. For instance, the essential oil composition of two plants belonging to the same botanical species can exhibit variability. External factors can further influence this composition, leading to diverse biochemical characteristics. Research indicates that the presence of different chemotypes within a plant can modify the oil's activity and its subsequent biological effects. The chemical composition of an essential oil is subject to influence from hybridization, environmental conditions, and agricultural practices [23].

The concept of a “chemotype” has been widely discussed and defined in various scientific disciplines, ranging from organic chemistry to pharmacology. It refers, in general terms, to a category of chemical compounds that share a common basic chemical structure

but can vary in some structural or functional aspects, giving them distinct biological or pharmacological properties. Different chemotypes can have very different therapeutic properties, aromas, and biological effects. According to Castañeda et al. [24], chemotype is crucial in the identification and classification of secondary metabolites in plants, allowing us to understand variations in biological properties between different species or even within the same species under different environmental conditions. On the other hand, Baser and Buchbauer [22] emphasize the importance of chemotype in pharmacognosy, noting that the accurate identification of the chemotypes of medicinal plants is essential to ensure the efficacy and safety of phytotherapeutic treatments. In the field of medicinal chemistry, the concept of chemotypes has been used by Avellaneda-Tamayo et al. [25] to facilitate rational drug design, highlighting how small modifications in the chemical structure of a compound can give rise to chemotypes with significantly different pharmacological profiles. This is not only relevant in the development of new drugs, but also in the optimization of existing compounds to improve their therapeutic activity and reduce side effects. Research has highlighted the influence of environmental factors, such as climate and altitude, on the development of chemotypes. For example, Kokkini et al. [26] mentions that these factors, together with genetics, are determinants in the differentiation of chemotypes in species such as oregano (*Origanum vulgare*). Available toxicological evidence indicates that SMEO exhibits low acute toxicity, minimal dermal irritation, and no detectable mutagenic effects. Ferrero et al. (2007) [27] demonstrated the absence of adverse outcomes in acute and subacute toxicity assays in rodents, while Bras et al. (2011) [28] reported negligible skin irritation in standard dermal tests. Furthermore, Apollo Duarte et al. (2018) [29] found no genotoxicity in either Ames or micronucleus assays, and Opdyke (1975) [30] showed no irritating or sensitizing effects at concentrations of 4% on 25 human volunteers, above those typically used in topical formulations. Nonetheless, these studies remain limited in scope and design, and more comprehensive in vivo and clinical investigations are required to fully substantiate the safety of SMEO for food, pharmaceutical, and cosmetic applications. Its diverse biological activities and lack of harm to healthy cells suggest significant potential for various industries, warranting further research and application [31]. Based on these preliminary findings, the aim of this systematic review is to show the state-of-the-art pharmaceutical uses of SMEO, to provide a novel point of view and research strategies for plant-based pharmaceutical products.

Scientific output relating to SMEO has increased significantly since 2005 and has followed two main paths. One has explored its application as a biopesticide, and there are three review articles on this topic [32–34], while the other has collected a series of studies investigating its antioxidant, antimicrobial, and anti-cancer properties.

Previous articles often treat the essential oil as a homogeneous entity, overlooking the significant chemical variability driven by geographical and environmental factors. To address this gap, this study represents the first systematic review following PRISMA guidelines that correlates specific chemotypes (such as the alpha-phellandrene and sabinene rich profiles) with distinct biological activities. This chemotype-centered approach is crucial for standardizing SMEO for future pharmaceutical applications.

## 2. Research Strategy

This review followed the PRISMA 2020 methodology framework [35].

### 2.1. Information Sources

A systematic search was conducted in the following:  
PubMed, Scopus, and MDPI.

All databases were accessed between 1 and 30 June 2025.

Reference lists were screened to identify additional records.

Only English and Spanish publications were included; no publication year limits were applied. The gray literature was excluded, except for a structured patent search that was used to contextualize innovation claims.

## 2.2. Search Terms

The search was conducted using the following keywords, alone and in combination: “*Schinus molle* essential oil”, “pharmaceutical”, and “medicinal”. The search was restricted to titles and abstracts to avoid the inclusion of studies only mentioning the topic in discussion sections.

## 2.3. Eligibility Criteria

Inclusion criteria:

Studies reporting the chemical composition and/or biological activity of SMEO, peer-reviewed research articles, and English or Spanish language.

Exclusion criteria:

Conference abstracts, symposium papers, patents, reviews, and editorials studies without analytical or biological data.

## 2.4. Selection and Data Collection Process

Three reviewers independently screened titles/abstracts, extracted data, and removed duplicates. Discrepancies were resolved by discussion.

## 2.5. Data Items

Extracted data included the following:

- (a) Study country;
- (b) Plant part used;
- (c) Analytical and biological assay methods;
- (d) Main EO components;
- (e) Microorganisms tested;
- (f) Biological results;
- (g) Reference.

Data were tabulated into five thematic tables. A PRISMA flow diagram (Figure 1) summarizes the study selection process.

## 2.6. Synthesis Methods

Due to heterogeneity in outcomes, units, and methodologies, no meta-analysis was possible. Instead, the following was conducted:

Chemotype-based stratification was applied and a hierarchical clustering analysis (Ward’s linkage and Euclidean distance) was performed on 70 chemical fingerprints.

Heat-maps with dendrograms supported the interpretation of antimicrobial, antioxidant, and anti-cancer activities.

## 2.7. Sensitivity Analysis

Sensitivity evaluation included the following:

- (i) Excluding studies lacking valid controls.
- (ii) Restricting to studies reporting both composition and bioactivity.
- (iii) Confirming chemotype-based interpretations using only full-methodology studies.

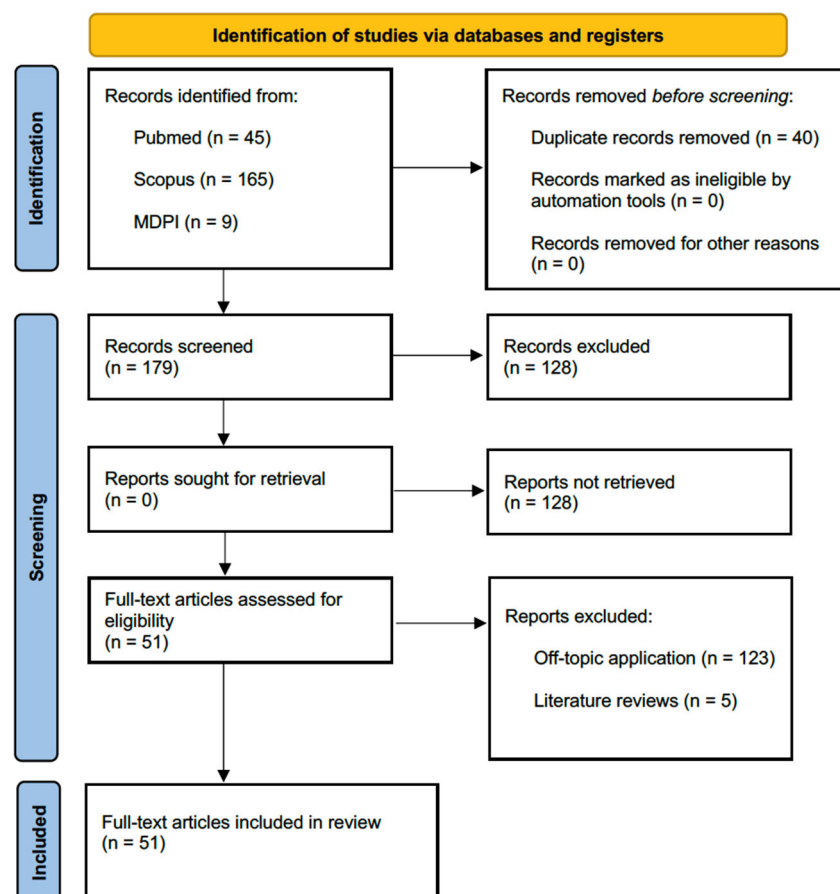


**Figure 1.** PRISMA flowchart illustrating the study selection process in the current review.

### 2.8. Risk of Bias and Reporting Bias

Selective reporting bias was reduced by multi-database searching, predefined eligibility criteria, and dual-language inclusion.

A reporting bias assessment via a funnel plot was not applicable. A patent landscape analysis supported the identification of selective disclosure trends.

### 2.9. Certainty Assessment

Certainty of evidence was evaluated narratively using a GRADE-inspired approach. Overall confidence was low–moderate for antimicrobial, low for antioxidant, and very low–low for anti-cancer evidence.

### 2.10. Protocol and Registration

No protocol was preregistered (e.g., PROSPERO). Criteria and procedures were predefined and aligned with PRISMA 2020 (Supplementary Materials). Future extensions will include preregistration. No protocol amendments were required.

## 3. Hierarchical Cluster Analysis

To identify grouping patterns among the studies reporting SMEOs based on their predominant compounds, the procedure proposed by Radice et al. [36] was applied with some modifications. A data matrix was constructed from the collected studies, based on the chemical composition reported in 70 independent SMEO analyses. Each row represented an individual study, and the columns corresponded to the identified chemical compounds. To reduce the dimensionality of the matrix and focus exclusively on the most representative metabolites, the first filter that was implemented only retained the three

compounds with the highest relative abundance in each study. The frequency of occurrence of each compound within the total set of studies was then calculated, and a second statistical filter was applied, using the 75th percentile ( $Q3 = 7$ ) of this distribution as the minimum threshold for inclusion. In this way, only those compounds whose frequency of occurrence was equal to or higher than this threshold was selected, which made it possible to delimit a subset of metabolites with high chemical representativeness and recurrent relevance in the composition of SMEO. Subsequently, Ward's method was applied in order to minimize intra-cluster variance, and the Euclidean distance was used as the dissimilarity metric [37]. The visual representation of the analysis was performed using a heat map with dendrograms in both dimensions (rows and columns), using the `clustermap` function of the Seaborn v0.12.2 package, running in Python v3.10.19, in a Jupyter Notebook environment under the Anaconda v2023.03 distribution. The Viridis palette, selected for its high visual perceptibility and compatibility with continuous representations [38], was used for color coding. Since the values used represented absolute proportions of chemical composition (expressed as percentages), no additional statistical transformations or matrix standardizations were necessary.

#### 4. Patent Search Strategy Tree for SMEO in Pharmaceutical Context

Finally, in order to explore industrial relevance, a preliminary search on public patent databases Espacnet and Google Patent and proprietary database (Orbit by Questel) was also conducted, focusing on patents related to the use of SMEO in pharmaceutical, medicinal, or therapeutic applications—particularly antimicrobial, anti-inflammatory, wound healing, or neuroprotective activities—and revealed no granted or published patents that comprehensively cover these criteria. A total of 346 hits were retrieved (1996–2024) using the following keywords: (“*Schinus molle*”) AND (“essential oil”) AND (“pharmaceutical” OR “medicinal” OR “therapeutic”) AND (“antimicrobial” OR “anti-inflammatory” OR “wound healing” OR “neuroprotective”); specific and direct references to *Schinus molle* for these therapeutic purposes were reported in the title (6 times) and/or in the abstract (16 times) and/or in claims (150 times), but essential oils were rarely reported. Detailed information regarding the patent search strategy is available as complementary data.

### 5. Results

#### 5.1. Chronological and Geographical Distribution of the Selected Studies

Based on the selection criteria, Figure 2 displays the timeline of the selected studies, revealing a timeframe stretching from 2008 to 2025. Notably, 2018, 2020, and 2024 stand out as the years with the highest number of publications (three each).

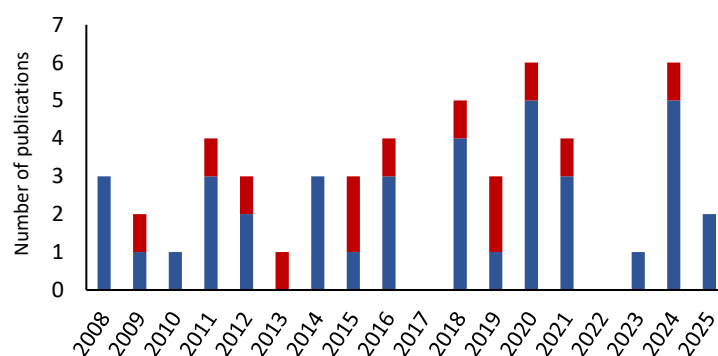


**Figure 2.** Number of publications relating to the chemical composition and biological activities of SMEO (blue columns) and to chemical composition only (red column) per year.

As shown in Figure 3, Brazil was the country where the highest number of articles were published (15), followed by Tunisia (6), Mexico, Algeria, and Argentina (5). Further studies, albeit in smaller numbers, were reported from other geographical areas in Africa, Central America, Europe, and Asia, testifying to the widespread distribution of the species.

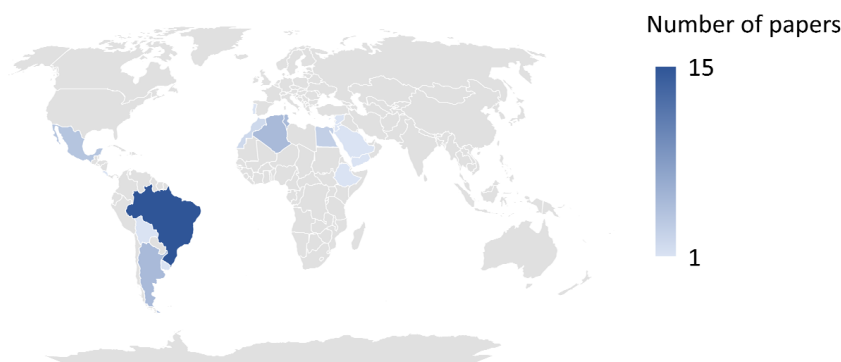


**Figure 3.** Geographical distribution of the articles examined.

### 5.2. Antimicrobial Activity of SMEO

The antimicrobial activity of EOs has been extensively researched in recent decades and is one of the most sought-after functionalities for potential applications in pharmaceuticals, cosmetics, and food [16,39,40]. In recent decades, pharmaceutical studies involving the antimicrobial activity of EOs and their components have focused on wound healing, dental surgery, and antibiotic resistance [10,41–44]. In many cases, EOs are microencapsulated, embedded in nanoemulsions, liposomes, and hydrogels or part of nanofiber-based wound dressings obtained by electrospinning techniques [45–50].

All of the techniques described above make it possible to compensate for the poor water solubility, rapid oxidation, and volatility of EOs, increasing their efficacy, bioavailability, and allowing controlled dosing and more targeted therapeutic action. Table 1 brings together data on the antimicrobial activity of SMEO.

**Table 1.** Main data concerning antimicrobial activity of SMEO.

| Country   | Part    | Extraction Method | Analytical Method | Main Compounds                                                                        | Method                         | Microorganism                                              | Results                                       | Positive Control           | Negative Control                      | References |
|-----------|---------|-------------------|-------------------|---------------------------------------------------------------------------------------|--------------------------------|------------------------------------------------------------|-----------------------------------------------|----------------------------|---------------------------------------|------------|
| Algeria   | L       | HD                | GC–FID and GC–MS  | $\alpha$ -phellandrene (12.70%)<br>germacrene D (10.15%)<br>limonene (11.90%)         | Violacein inhibition           | <i>C. violaceum</i>                                        | Violacein inhibition (%): 76.20               | n.r.                       | n.r.                                  | [31]       |
|           |         | HD                |                   |                                                                                       | Quorum-sensing inhibition zone |                                                            | Quorum-sensing inhibition zone (mm): 10.00    | n.r.                       | n.r.                                  |            |
| Algeria   | S       | HD                | n.r.              | n.r.                                                                                  | Disk diffusion                 | <i>S. aureus</i><br><i>E. coli</i>                         | Inhibition zone (mm): 20.00<br>16.30          | Chloramphenicol            | n.r.                                  | [51]       |
| Algeria   | L       | HD                | GC–MS             | $\alpha$ -phellandrene (26.50%)<br>Limonene (8.60%)<br>$\beta$ -phellandrene (12.40%) | Broth microdilution            | <i>E. coli</i><br><i>S. aureus</i><br><i>S. pyogenes</i>   | Inhibition halo (mm): 17.10<br>19.80<br>13.60 | Ampicillin (10 $\mu$ L/mL) | Absolute ethanol                      | [52]       |
| Argentina | F and L | SD                | GC–MS             | sabinene (34.74%)<br>germacrene D (7.00%)<br>terpinen-4-ol (5.50%)                    | Agar vapor diffusion           | <i>E. coli</i><br><i>P. aeruginosa</i><br><i>S. aureus</i> | Inhibition halo (mm): 18.50<br>11.30<br>29.50 | Gentamicin                 | Aqueous solution agar 0.15% + 5% DMSO | [53]       |

Table 1. Cont.

| Country   | Part        | Extraction Method | Analytical Method | Main Compounds                                                                   | Method                                       | Microorganism                                                                                                                                                                                                     | Results                                                                                       | Positive Control                 | Negative Control                            | References |
|-----------|-------------|-------------------|-------------------|----------------------------------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------|------------|
| Argentina | F and L     | SD                | GC–MS             | β-phellandrene (34.30%)<br>α-phellandrene (11.50%)<br>Camphene (7.90%)           | Anti-QS activity assay: macrodilution method | <i>E. coli</i><br><i>L. innocua</i><br><i>S. aureus</i>                                                                                                                                                           | Diameter of QS inhibition halos (mm): 5.000                                                   | n.r.                             | LB broth without adding the essential oils. | [54]       |
|           |             |                   |                   |                                                                                  | Anti-QS activity assays: disk diffusion      |                                                                                                                                                                                                                   | Diameter of antimicrobial halos (mm): 24.00                                                   | Paper disk with sterile LB broth | n.r.                                        |            |
|           |             |                   |                   |                                                                                  | Broth microdilution                          |                                                                                                                                                                                                                   | MIC (% v/v):<br>0.320<br>0.320<br>0.320                                                       | n.r.                             | n.r.                                        |            |
| Brazil    | L           | HD                | GC–FID and GC–MS  | 1,8-cineole (7.60%)<br>terpinen-4-ol (6.10%)<br>epi-α-cadinol (27.30%)           | Broth microdilution                          | <i>C. albicans</i>                                                                                                                                                                                                | MIC (mg/mL): 2.500                                                                            | n.r.                             | n.r.                                        | [55]       |
| Brazil    | L           | SD                | GC–MS             | β-pinene (25.23%)<br>epi-α-cadinol (21.29%)<br>α-pinene (18.72%)                 | Broth microdilution                          | <i>C. neoformans</i><br><i>P. brasiliensis</i><br><i>T. quinckeanum</i>                                                                                                                                           | MIC (μg/mL):<br>625.0<br>39.06<br>625.0                                                       | Vancomycin and gentamicin        | Broth sterility                             | [56]       |
| Brazil    | L, S        | HD                | n.r.              | n.r.                                                                             | n.r.                                         | <i>A. flavus</i><br><i>A. niger</i><br><i>A. fumigatus</i>                                                                                                                                                        | Inhibition of mycelial growth at 100 μg/mL (%):<br>91.18<br>70.10<br>37.12                    | Frownicide 500 SC®               | Solution with no essential oil              | [57]       |
| Brazil    | L           | HD                | GC–FID and GC–MS  | Spathulenol (26.93%)<br>β-caryophyllene (19.90%)<br>caryophyllene oxide (12.60%) | Broth microdilution                          | <i>C. albicans</i><br><i>C. glabrata</i><br><i>C. krusei</i><br><i>C. tropicalis</i><br><i>C. rugosa</i><br><i>C. orthopsilosis</i><br><i>C. metapsilosis</i><br><i>C. parapsilosis</i><br><i>C. parapsilosis</i> | MIC (μg/mL):<br>62.50<br>62.50<br>31.20<br>125.0<br>62.50<br>31.20<br>125.0<br>62.50<br>62.50 | Amphotericin B                   | n.r.                                        | [58]       |
| Cyprus    | F, L        | n.r.              | GC–FID and GC–MS  | Cis-sabinene hydrate (11.60%)<br>terpinen-4-ol (24.10%)                          | Disk diffusion                               | <i>E. coli</i><br><i>P. aeruginosa</i><br><i>S. aureus</i><br><i>S. maltophilia</i>                                                                                                                               | Inhibition halo (mm):<br>14.00<br>9.000<br>14.00<br>15.00                                     | Amikacin and Vancomycin          | Sterile medium                              | [59]       |
| Egypt     | L           | HD                | GC–MS             | α-phellandrene (29.87%)<br>β-phellandrene (21.08%)<br>elemol (13.00%)            | Microdilution                                | <i>A. flavus</i><br><i>A. ochraceus</i><br><i>A. niger</i><br><i>P. funiculosus</i><br><i>P. ochrochloron</i><br><i>C. albicans</i>                                                                               | MIC (μg/mL):<br>0.270<br>0.310<br>0.610<br>0.430<br>0.470<br>0.970                            | Fluconazole and ketoconazole     | n.r.                                        | [60]       |
| Egypt     | Wood branch | HD                | GC–MS             | α-elemol (14.79%)<br>β-Pinene (13.39%)<br>α-Phellandrene (10.41%)                | Disk diffusion                               | <i>S. aureus</i>                                                                                                                                                                                                  | Inhibition zone (mm): 15.00                                                                   | Tetracycline                     | DMSO                                        | [61]       |
| Ethiopia  | F, L        | HD                | GC–MS             | α-phellandrene (20.60%)<br>β-phellandrene (10.80%)<br>α-pinene (8.70%)           | Disk diffusion                               | <i>E. coli</i>                                                                                                                                                                                                    | Inhibition zone (mm): 7.500                                                                   | Amoxicillin                      | Petroleum ether and chloroform              | [62]       |

Table 1. Cont.

| Country  | Part  | Extraction Method | Analytical Method | Main Compounds                                                                           | Method                      | Microorganism                                                                                               | Results                                                            | Positive Control            | Negative Control        | References |
|----------|-------|-------------------|-------------------|------------------------------------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------------|-------------------------|------------|
| Mexico   | L     | HD                | n.r.              | n.r.                                                                                     | Antifungal assay            | <i>A. parasiticu</i>                                                                                        | Inhibition (%):<br>61.30                                           | Terravax Czapek             | Tween                   | [63]       |
| Mexico   | L     | HD                | GC–MS             | α-phellandrene *<br>(32.80%)<br>sylvestrene *<br>(22.30%)                                | Microdilution assays        | <i>S. aureus</i><br><i>S. pyogenes</i>                                                                      | MIC (μg/mL):<br>250.0<br>125.0                                     | Oxacillin and vancomycin    | n.r.                    | [64]       |
|          | F     |                   |                   | α-phellandrene **<br>(45.00%)<br>sylvestrene **<br>(34.30%)                              |                             | <i>S. pyogenes</i>                                                                                          | MIC (μg/mL):<br>250.0                                              |                             |                         |            |
| Mexico   | F     | HD                | GC–MS             | β-myrcene (39.70%)<br>δ-cadinene (7.80%)<br>α-phellandrene (7.10%)                       | Broth microdilution         | <i>S. pneumoniae</i>                                                                                        | MIC (μg/mL):<br>125.0                                              | Amoxicillin                 | n.r.                    | [65]       |
| Morocco  | F     | SD                | GC–FID and GC–MS  | β-myrcene (58.70%)<br>α-phellandrene (11.00%)<br>limonene (10.10%)                       | Broth microdilution         | <i>A. baumannii</i><br><i>Salmonella</i> sp.<br><i>S. aureus</i><br><i>P. aeruginosa</i>                    | MIC (μL/mL):<br>0.300<br>0.400<br>0.500<br>0.200                   | Ciprofloxacin               | n.r.                    | [66]       |
| Morocco  | F, L  | HD                | GC–MS             | α-phellandrene (9.60%)<br>germacrene D (3.55%)<br>carvacrol (3.20%)                      | Broth microdilution         | <i>S. aureus</i>                                                                                            | MIC (mg/mL):<br>0.250                                              | n.r.                        | Sterile distilled water | [67]       |
| Portugal | L     | HD                | GC–FID and GC–MS  | α-phellandrene (25.90%)<br>limonene (11.70%)<br>β-myrcene (11.10%)                       | Agar disk diffusion method  | <i>S. epidermidis</i><br><i>S. aureus</i>                                                                   | MIC (mg/mL):<br>63.00<br>125.0                                     | Tetracycline chloride       | DMSO in culture media   | [68]       |
|          | F     |                   |                   | β-myrcene (51.30%)<br>α-limonene (14.10%)<br>phellandrene (14.00%)                       |                             | <i>S. aureus</i><br><i>E. faecalis</i>                                                                      | MIC (mg/mL):<br>125.0<br>500.0                                     |                             |                         |            |
| Tunisia  | L     | HD                | GC–MS             | α-phellandrene (26.48%)<br>β-phellandrene (18.11%)<br>( <i>E</i> )-caryophyllene (5.63%) | Modified resazurin method   | <i>L. monocytogenes</i>                                                                                     | MIC (mg/mL):<br>28.00                                              | n.r.                        | n.r.                    | [69]       |
| Tunisia  | AP    | HD                | GC–MS             | Limonene (31.14%)<br>α-phellandrene (20.62%)<br>delta-cadinene (9.09%)                   | Microdilution method        | <i>E. faecalis</i>                                                                                          | Inhibition zone (mm):<br>12.00<br>29.00                            | n.r.                        | n.r.                    | [70]       |
| Tunisia  | F *** | HD                | GC–MS             | α-phellandrene (40.38%)<br>limonene + phellandrene (24.97%)<br>β-myrcene (18.67%)        | Paper-disk diffusion method | <i>E. coli</i><br><i>S. typhimurium</i><br><i>B. subtilis</i><br><i>B. cereus</i>                           | Inhibition zone (mm):<br>11.00<br>13.00<br>20.00<br>10.00          | Ampicilline                 | n.r.                    | [71]       |
| Tunisia  | F     | HD                | GC–FID and GC–MS  | α-phellandrene (38.80%)<br>β-phellandrene (29.30%)<br>β-pinene (15.60%)                  | Disk diffusion              | <i>P. aeruginosa</i><br><i>P. morgani</i><br><i>S. aureus</i><br><i>S. anatuma</i><br><i>S. enteritidis</i> | Inhibition zone (mm):<br>9.000<br>9.000<br>8.000<br>9.000<br>8.000 | Streptomycin and Netilmycin | Medium and DMSO (0.1%)  | [72]       |

AP = aerial parts; HD = hydrodistillation; SD = steam distillation; GC–FID = Gas Chromatography with Flame Ionization Detector; GC–MS = Gas Chromatography–Mass Spectrometry; F = fruits; L = leaves; S = stem; n.r. = not reported; \*—colorless fraction; \*\*—yellow fraction; \*\*\*—intermediate ripening stage. DMSO has been used as a solvent for the EOs.

Regarding the chemical composition of the EOs, it is known that antimicrobial activity results from the synergistic effect of various components. Notably, the selected studies show that  $\alpha$ -phellandrene is among the most commonly found in SMEOs. Several studies highlighted in this review consistently associate the  $\alpha$ -phellandrene chemotype of SMEO with significant antimicrobial, anti-inflammatory, and anti-cancer effects, which are pivotal for its therapeutic value. Conversely, sabinene-dominant chemotypes exhibit promising neuroprotective properties, including a reduction in neuroinflammatory markers and the improvement of memory functions in animal models. This chemotypic specificity in bioactivity suggests that future research and pharmaceutical formulations should prioritize chemotype authentication to maximize therapeutic outcomes.

However, a more in-depth analysis of the detected chemotypes and the main essential oil compounds is described in Section 5.6. Data on the antimicrobial activity of SMEO indicate wide-ranging activity against gram-positives, gram-negatives, and fungi, with particularly promising inhibition values against *C. violaceum*, *S. pneumoniae*, and *S. aureus*. Anyway, regarding antimicrobial activity, further studies are needed on SMEO and its main compounds.

### 5.3. Antioxidant Activity of SMEO

Along with antimicrobial, antioxidant activity is perhaps the most studied property of EOs and there is extensive scientific production in this regard [73–75].

As pointed out by de Sousa et al. [16], the hypothesized mechanisms of action focus on the inhibition of peroxidation and can be traced back to the ‘trapping activity’ of phenols, due to their phenolic H-atom capable of inactivating free radicals and their ability to enhance the termination phase of lipid peroxidation.

The antioxidant activity of SMEO is not merely due to radical scavenging but involves specific molecular mechanisms. The presence of monoterpenes and phenols allows for the donation of hydrogen atoms to free radicals (Hydrogen Atom Transfer—HAT), effectively terminating the lipid peroxidation chain reaction [76].

Moreover, the relationship between antioxidant activity and anti-inflammatory activity is considered essential in the development of various pre-clinical states, connected to an excessive presence of ROS (reactive oxygen species) that then develop into pathological conditions. In this sense, EOs seem to be able to inhibit the production of cytokines, control arachidonic metabolism, and promote pro-inflammatory gene expression [77].

In addition to possible applications in food and cosmetics, the antioxidant properties of OEs are being explored pharmacologically for their possible role in counteracting oxidative processes associated with chronic inflammation (oxidative stress), which is believed to be responsible for various disease states such as diabetes, neurodegenerative diseases, aging processes, and cancer [78]. Table 2 summarizes the data on the antioxidant activity of SMEO.

**Table 2.** Main data regarding antioxidant activity of SMEO.

| Country | Part | Extraction Method | Analytical Method | Main Compounds                                                                                       | Antioxidant Assay | Activity                                    | Positive Control                                                               | Negative Control | References |
|---------|------|-------------------|-------------------|------------------------------------------------------------------------------------------------------|-------------------|---------------------------------------------|--------------------------------------------------------------------------------|------------------|------------|
| Algeria | F    | HD                | GC-FID and GC-MS  | $\alpha$ -cadinol (25.10%)<br>$\delta$ -cadinene (13.00%)<br><i>epi</i> - $\alpha$ -muurolol (9.80%) | ABTS              | IC <sub>50</sub><br>(mg/mL):<br>0.700–5.000 | Trolox                                                                         | n.r.             | [79]       |
|         | L    |                   |                   | $\delta$ -cadinene (16.10%)<br>$\alpha$ -cadinol (12.90%)<br>germacrene-d (9.30%)                    | DPPH              | IC <sub>50</sub><br>(mg/mL):<br>6.900–8.600 | Tocopherol, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) |                  |            |

Table 2. Cont.

| Country    | Part   | Extraction Method | Analytical Method | Main Compounds                                                                                                                                                              | Antioxidant Assay                                                  | Activity                                                                         | Positive Control                         | Negative Control           | References |
|------------|--------|-------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------|----------------------------|------------|
| Algeria    | L      | HD                | GC–FID and GC–MS  | camphene (31.82%)<br>limonene (14.71%)<br><i>p</i> -cymene (9.25%)                                                                                                          | $\beta$ -Carotene-linoleic acid<br>DPPH<br>ABTS<br>Metal chelating | Inhibition (%):<br>25.20<br>15.60<br>29.20<br>31.40                              | BHA (butylated hydroxy-anisole) and EDTA | n.r.                       | [31]       |
| Algeria    | S      | HD                | n.r.              | n.r.                                                                                                                                                                        | DPPH                                                               | IC <sub>50</sub> (mg/L): 0.410                                                   | Ascorbic acid                            | n.r.                       | [51]       |
| Argentina  | F      | HD                | GC–MS             | elemol (12.90%)<br>$\alpha$ -pinene (12.10%)<br>$\beta$ -pinene (9.90%)                                                                                                     | DPPH                                                               | Inhibition (%): 18.30                                                            | n.r.                                     | Milli-Q water              | [80]       |
| Argentina  | L      | HD                | GC–MS             | sabinene (60.00%)<br>$\beta$ -pinene (16.50%)<br>$\alpha$ -pinene (8.80%)                                                                                                   | DPPH                                                               | IC <sub>50</sub> (mg/L): 37.93                                                   | Quercetin                                | n.r.                       | [81]       |
| Brazil     | F, L   | HD                | GC–FID and GC–MS  | <i>epi</i> - $\alpha$ -cadinol (27.30%)<br>1,8-cineole (7.60%)<br>terpinen-4-ol (6.10%)                                                                                     | DPPH                                                               | IC <sub>50</sub> ( $\mu$ g/mL) > 100.0                                           | butylated hydroxy-toluene (BHT)          | n.r.                       | [55]       |
| Costa Rica | L      | HD                | GC–FID and GC–MS  | $\beta$ -pinene (31.10%)<br>$\alpha$ -pinene (22.70%)<br>$\gamma$ -cadinene (6.00%)                                                                                         | DPPH                                                               | IC <sub>50</sub> ( $\mu$ g/mL): 36.30                                            | butylated hydroxy-toluene, BHT           | n.r.                       | [82]       |
| Egypt      | L      | HD                | GC–MS             | $\alpha$ -elemol (14.80%)<br>$\beta$ -pinene (13.40%)<br>myrcene (12.20%)                                                                                                   | DPPH                                                               | IC <sub>50</sub> ( $\mu$ g/mL): 12.66                                            | Tannic acid and (+)-catechin             | DPPH solution in methanol  | [61]       |
| Egypt      | F, L   | HD                | GC–MS             | $\alpha$ -phellandrene (29.87%)<br>$\beta$ -phellandrene (21.00%)<br>elemol (13.00%)                                                                                        | DPPH<br>$\beta$ -Carotene-linoleic acid                            | IC <sub>50</sub> (mg/L): 8.900<br>IC <sub>50</sub> (mg/L): 6.600                 | Butylated hydroxy-toluene (BHT)          | n.r.                       | [60]       |
| México     | F<br>L | HD                | GC–MS             | $\alpha$ -phellandrene (39.00%)<br>sylvestrene (36.40%)<br>$\rho$ -cymene (5.10%)<br>$\alpha$ -phellandrene (45.00%)<br>sylvestrene (34.30%)<br>germacrene D (3.80%)        | DPPH                                                               | EC <sub>50</sub> ( $\mu$ g/mL) > 250.0<br>EC <sub>50</sub> ( $\mu$ g/mL) > 250.0 | Quercetin, rutin, and pyrocatechol       | n.r.                       | [64]       |
| Morocco    | F      | SD                | GC–FID and GC–MS  | $\beta$ -myrcene (58.70%)<br>$\alpha$ -phellandrene (11.00%)<br>limonene (10.10%)                                                                                           | DPPH<br>ABTS<br>FRAP<br>$\beta$ -carotene                          | mg TE/g of EO:<br>74.00<br>5.270<br>7.440<br>15.61                               | Trolox                                   | Stock solution and ethanol | [66]       |
| Morocco    | F, L   | HD                | GC–MS             | $\alpha$ -phellandrene (9.60%)<br>germacrene d (3.55%)<br>carvacrol (3.20%)                                                                                                 | $\beta$ -carotene bleaching                                        | Dose- and time-dependent antioxidant activity comparable to that of BHT          | Butylated hydroxy-toluene (BHT)          | Ascorbin acid              | [67]       |
| Portugal   | F<br>L | HD                | GC–FID and GC–MS  | $\beta$ -myrcene (51.30%)<br>$\alpha$ -phellandrene (14.10%)<br>limonene (14.00%)<br>$\alpha$ -phellandrene (25.90%)<br>limonene (11.70%)<br>$\beta$ -phellandrene (10.50%) | $\beta$ -carotene/linoleic acid method                             | Inhibition (%):<br>Leaf EO—57.00<br>Fruit EO—19.00                               | Ascorbic acid                            | Stock solution and ethanol | [68]       |

Table 2. Cont.

| Country | Part | Extraction Method | Analytical Method | Main Compounds                                                                                              | Antioxidant Assay | Activity                       | Positive Control               | Negative Control | References |
|---------|------|-------------------|-------------------|-------------------------------------------------------------------------------------------------------------|-------------------|--------------------------------|--------------------------------|------------------|------------|
| Tunisia | F    | SD                | GC-MS             | $\alpha$ -phellandrene (46.52%)<br>$\beta$ -phellandrene (20.81%)<br>$\alpha$ -terpineol (8.38%)            | ABTS              | IC <sub>50</sub> (mg/L): 257.0 | Ascorbic acid                  | n.r.             | [83]       |
| Tunisia | F    | HD                | GC-MS             | $\alpha$ -phellandrene (40.38%)<br>limonene+<br>$\beta$ -phellandrene (24.90%)<br>$\beta$ -myrcene (11.54%) | DPPH              | Inhibition (%): 29.00          | Butylated hydroxy-toluene, BHT | n.r.             | [71]       |

AP = aerial parts; HD = hydrodistillation; SD = steam distillation; GC-FID = Gas Chromatography with Flame Ionization Detector; GC-MS = Gas Chromatography–Mass Spectrometry; F = fruits; L = leaves; S = stem; n.r. = not reported.

Concerning the chemical composition, studies on the antioxidant activity of SMEO again show a certain prevalence of the presence of  $\alpha$ -phellandrene, although it is less marked than in Table 1. The most commonly used test is the DPPH, followed by the ABTS method and  $\beta$ -carotene-linoleic acid. Although these preliminary assays are very popular in the early stages of research into the bioactivities of EOs, their interpretation in the field of application remains controversial. The antioxidant activity of essential oil components is influenced by their lipophilicity and the methodological characteristics of preliminary assays. The DPPH and ABTS methods have the advantage of being relatively inexpensive and easy to perform, but the carotene bleaching assay seems to be more recommended in simulating the lipid peroxidation processes to which the reaction mechanisms of the OEs seem to respond [16,42]. While substantial antimicrobial effects have been observed across diverse geographic sources and chemotypes, the variability in chemical composition poses challenges for consistent pharmaceutical applications. Differences in extraction methods, environmental factors, and genetic variability lead to heterogeneous chemotypes, affecting the reproducibility of results. This variability, if unmanaged, complicates comparisons across studies and may hinder the regulatory approval of SMEO-based products. Hence, establishing rigorous chemotype characterization and standardization protocols emerges as an essential step for advancing SMEO from preclinical research to clinical and pharmaceutical use.

Considering this perspective, although preliminary data on antioxidant activity are abundant, variable, and promising, it would be appropriate to test this biological activity again in more challenging assays.

#### 5.4. Anti-Cancer Activity of SMEO

Research into the anti-cancer properties of EOs and their pure components is a relatively new and emerging area of cancer research, justified by the fact that natural or plant-derived products are already on the market and new studies are underway [84,85]. The amount of data on anti-cancer properties and mechanisms of OEs is high and corroborated by in vitro and in vivo research. New research trends are mainly directed towards the application of nanotechnology and synergistic treatment between EOs and conventional anti-cancer drugs. In addition, there are extensive studies on the potential anti-cancer effect of isolated compounds (such as eugenol and carvacrol, etc.), which are single molecules that may represent the chemotype of certain essential oils. In such cases, the results can be attributed to a single chemical entity, thereby minimizing issues associated with the chemical variability of essential oils. This approach disregards the potential synergistic effect of the various components of the EO and lends itself to the development of simpler formu-

lations (e.g., nanoparticles and nanoemulsion, etc.), which allows greater reproducibility of results [86–88]. Nevertheless, clinical trials are still scarce and the need to standardize and stabilize EOs slows down the development of potential drugs [89]. At the same time, beyond their direct therapeutic effect on cancers, essential oils are also being studied for their potential in managing symptoms in patients undergoing cancer therapy [90]. Table 3 brings together the data on the anti-cancer activity of SMEO.

**Table 3.** Main data regarding anti-cancer activity of SMEO.

| Country      | Part    | Extraction Method | Analytical Method | Main Compounds                                                                                                                                     | Anti-Cancer Assay                                                                       | Activity (µg/mL)                                                                                    | Positive Control | Negative Control    | References |
|--------------|---------|-------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------------|---------------------|------------|
| Brazil       | F, L    | HD                | GC–FID and GC–MS  | 1,8- <i>epi</i> - $\alpha$ -cadinol (27.30%)<br>cineole (7.60%)<br>terpinen-4-ol (6.10%)                                                           | HT-29<br>MCF7<br>NCI-ADR/RES<br>NCI-H460<br>K562<br>OVCAR-3<br>PC-3<br>UACC-62<br>786-0 | IC <sub>50</sub> :<br>26.43<br>31.68<br>3.400<br>50.69<br>0.890<br>26.05<br>27.20<br>28.66<br>30.44 | Doxorubicin      | n.r.                | [55]       |
| Costa Rica   | L       | HD                | GC–FID and GC–MS  | $\beta$ -pinene (31.10%)<br>$\alpha$ -pinene (22.70%)<br>$\gamma$ -cadinene (6.00%)                                                                | C2C12<br>ECV-304<br>EMT6<br>Hep3B<br>HepG2<br>J774<br>K562                              | LD <sub>50</sub> :<br>116.1<br>118.8<br>75.70<br>211.2<br>108.9<br>252.8<br>78.70                   | Limonene         | n.r.                | [82]       |
| Egypt        | F, L    | HD                | GC–MS             | $\alpha$ -phellandrene (29.87%)<br>$\beta$ -phellandrene (21.08%)<br>elemol (13.00%)                                                               | MCF-7<br>HeLa<br>Jurkat<br>HT-29<br>T24<br>HEK-293                                      | IC <sub>50</sub> :<br>41.30<br>119.5<br>14.85<br>18.35<br>>300.0<br>>300.0                          | Taxol            | Vinblastine sulfate | [60]       |
| Egypt        | F<br>Fl | HD                | GC–FID and GC–MS  | $\alpha$ -phellandrene (25.60%)<br>limonene (20.90%)<br>myrcene (16.80%)<br>$\rho$ -cymene (25.55%)<br>myrcene (6.13%)<br>$\alpha$ -pinene (5.41%) | HCT116<br>HepG-2<br>HCT116                                                              | IC <sub>50</sub> (µg):<br>1.150<br>0.950<br>IC <sub>50</sub> (µg):<br>0–98                          | Doxorubicin      | n.r.                | [91]       |
| Jordan       | L       | HD                | GC–MS             | $\alpha$ -phellandrene (48.01%)<br>$\beta$ -phellandrene (33.89%)<br>$\alpha$ -thujene (4.58%)                                                     | HCT116<br>Caco-2<br>MCF7<br>T47D                                                        | IC <sub>50</sub> :<br>43.29<br>21.14<br>30.95<br>36.81                                              | Doxorubicin      | n.r.                | [18]       |
| Saudi Arabia | F       | HD                | GC–MS             | $\alpha$ -phellandrene (26.24%)<br>myrcene (21.57%)<br>$\gamma$ -gurjunene (7.51%)                                                                 | HepG2                                                                                   | IC <sub>50</sub> :<br>11.90                                                                         | Doxorubicin      | n.r.                | [92]       |
| Tunisia      | F       | SD                | GC–MS             | $\alpha$ -phellandrene (46.52%)<br>$\beta$ -phellandrene (20.81%)<br>$\alpha$ -terpineol (8.38%)                                                   | MCF-7                                                                                   | IC <sub>50</sub> :<br>54.00                                                                         | Tamoxifen        | n.r.                | [83]       |

HD = hydrodistillation; SD = steam distillation; GC–FID = Gas Chromatography with Flame ionization Detector; GC–MS = Gas Chromatography–Mass Spectrometry; F = fruits; Fl = flowers; L = leaves; S = stem; n.r. = not reported.

As shown in Table 3, the data from the anti-cancer activity studies also show a relative prevalence of the  $\alpha$ -phellandrene chemotype in the composition of the oils. Here, again, a wide range of tests on different cell lines is shown, with the IC<sub>50</sub> values obtained by Simionatto et al. (2011) [55] on K652 cells standing out among the results of 0.89 µg/mL.

Regarding the mechanism of action, particularly for the alpha-phellandrene chemotype, recent studies suggest a reactive oxygen species (ROS)-mediated pathway. The accumulation of intracellular ROS triggers the loss of mitochondrial membrane potential ( $\Delta\psi_m$ ), leading to the release of cytochrome c and the subsequent activation of the caspase cascade (intrinsic apoptosis), rather than a direct non-oxidative mitochondrial interaction [93].

#### 5.5. Other Bioactivities and Preliminary Formulation Studies

Table 4 summarizes the results of additional biological activity studies alternative to those described in the previous tables. This research includes a smaller number of studies compared to those related to antimicrobial, antioxidant, or anti-cancer activity but are still useful to have an overall view of the state-of-the-art regarding research on SMEO.

**Table 4.** Additional data concerning the biological activity of SMEO.

| Country | Part | Extraction Method | Analytical Method | Main Compounds                                                                   | Method                                                                                        | Biological Activity                                                                                                                                          | Positive Control                                                                  | Negative Control                                         | References |
|---------|------|-------------------|-------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------|------------|
| Algeria | L    | HD                | GC-FID and GC-MS  | camphene (31.82%)<br>limonene (14.71%)<br><i>p</i> -cymene (9.25%)               | Human Red Blood Cell (HRBC) membrane stabilization<br><br>Egg albumin denaturation techniques | % Inhibition of denaturation (at 200 µg/mL): 63.80<br>(Diclofenac sodium 75.30)<br><br>% Egg albumin (at 200 µg/mL): 37.60<br>(Diclofenac sodium 64.30)      | diclofenac sodium                                                                 | n.r.                                                     | [31]       |
| Brazil  | L    | HD                | GC-FID and GC-MS  | spathulenol (26.93%)<br>β-caryophyllene (19.90%)<br>caryophyllene oxide (12.69%) | Antileishmanial Assays (Promastigote forms of <i>Leishmania</i> )                             | Antileishmanial Activity<br>IC <sub>50</sub> (µg/mL): 21.45                                                                                                  | Promastigote forms incubated with Amphotericin B (Concentrations: 0.0027–1.56 µM) | Promastigote forms RPMI 1640 medium containing 0.1% DMSO | [94]       |
| Brazil  | L    | HD                | GC-MS             | <i>epi</i> -α-cadinol (22.85%) and<br>γ-cadinene (9.66%)<br>spathulenol (7.62%)  | Platelet aggregation assays                                                                   | Antiplatelet activity<br>Inhibition (%) at 5 mg/mL: 80.00<br>Inhibition (%) at 40 mg/mL: 48.00<br>(low concentration oil, greater the antiplatelet activity) | Aspirin                                                                           | Buffer                                                   | [95]       |
| Brazil  | L    | HD                | GC-MS             | α-pinene (23.49%)<br>sabinene (11.36%)<br>bicyclogermacrene (10.13%)             | Interleukins Secretions                                                                       | Immune response activation                                                                                                                                   | n.r.                                                                              | Phosphate buffer pH 7.4                                  | [29]       |
| Tunisia | AP   | HD                | GC-MS             | DL-limonene (31.14%)<br>α-phellandrene (20.62%)<br>Delta-cadinene (9.09%)        | Nitrite quantification                                                                        | Anti-inflammatory activity<br>Suppression of nitric oxide production, (% at 62.5 µg/mL): 51.41                                                               | n.r.                                                                              | n.r.                                                     | [70]       |
| Syria   | L    | HD                | n.r.              | n.r.                                                                             | Cholesterol esterase inhibitory activity                                                      | Cholesterol esterase inhibitory activity (%): 8.410                                                                                                          | Sodium fluoride                                                                   | n.r.                                                     | [96]       |

AP = aerial parts; HD = hydrodistillation; SD = steam distillation; GC-FID = Gas Chromatography with Flame Ionization Detector; GC-MS = Gas Chromatography–Mass Spectrometry; L = leaves; n.r. = not reported.

Data on the biological activity of SMEO are abundant but only three studies investigate the potential pharmaceutical or veterinary applications by including the EO as an ingredient in formulations. Table 5 summarizes the existing data.

Table 5. SMEO preliminary formulation studies.

| Country | Part | Extraction Method | Analytical Method | Main Compounds                                                                              | Formulation                                   | Biological Activity                                                                                                                                                                                                                                  | Positive Control | Negative Control                    | References |
|---------|------|-------------------|-------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-------------------------------------|------------|
| Brazil  | L    | HD                | GC-FID and GC-MS  | caryophyllene oxide (15.3%)<br>cubenol (12.7%)<br>spathulenol (11.70%)                      | Chitosan-based buccal delivery system         | Antimicrobial activity                                                                                                                                                                                                                               | n.r.             | n.r.                                | [97]       |
| Mexico  | L    | n.r.              | n.r.              | n.r.                                                                                        | Chitosan nanoparticles by ionotropic gelation | Antimicrobial activity                                                                                                                                                                                                                               | Gentamicin       | n.r.                                | [98]       |
| Cyprus  | L    | HD                | GC-FID and GC-MS  | $\alpha$ pinene (17.12%)<br>$\alpha$ -phelandrene (13.22%)<br>$\beta$ -phelandrene (11.98%) | Essential oil-loaded PVA/GA hydrogel          | Wound healing application<br>Inhibition zone at 0.2 mL<br><i>S. molle</i> EO (mm):<br><i>S. aureus</i> —10.20<br><i>B. subtilis</i> —9.300<br>Moisture retention capacity (%):<br>93.12<br>Water vapor transmission rate (g/m <sup>2</sup> h): 32.73 | Erythromycin     | PVA/GA hydrogel membrane without EO | [99]       |

HD = hydrodistillation; GC-FID = Gas Chromatography with Flame Ionization Detector; GC-MS = Gas Chromatography–Mass Spectrometry; L = leaves; n.r. = not reported.

The studies reported in Table 5 are promising for the development of a new prototype of pharmaceutical formulations based on SMEO. As reported by Alves et al. [98], a chitosan-based buccal gel for veterinary application has been developed and showed a promising antimicrobial activity against *Staphylococcus* spp. and *Streptococcus* spp. (MIC = 750 µg/mL), *Corynebacterium* spp. (MIC = 1000 µg/mL), and *Pseudomonas* spp. (MIC = 1250 µg/mL). These findings open a potential development route for a new plant-based treatment of periodontal disease in pets. Barrera-Ruiz et al. [98] compared the antimicrobial properties of chitosan nanoparticles with several encapsulated EOs and their respective EOs in pure form. Data concerning pure SMEO showed antimicrobial activity against *Enterococcus* sp. (vancomycin resistant) (CI<sub>50</sub> = 414 µg/mL) but the microencapsulated form of the same EO was able to inhibit the proliferation of *S. aureus* (35.0% inhibition versus 19.2% performed by gentamicin), *Enterococcus* sp. (vancomycin resistant) (35.0% inhibition), and *K. pneumoniae* (50.0% inhibition), proposing that chitosan nanoparticles appear to enhance the antimicrobial effect. Finally, as reported by Omoyeni et al. [99], the essential oil-loaded PVA/GA hydrogel based on SMEO presented promising antimicrobial activity with inhibition zones of 10.2 and 9.3 mm, (at 0.2 mL) for *S. aureus* and *B. subtilis*, respectively. The same gel formulation showed also promising data concerning the moisture retention capacity (93.12%) and water vapor transmission rate (32.73 g/m<sup>2</sup>h). These preliminary results seem to point to the first application strategy that enables the valorization of SMEO in the production environment.

Based on the available formulation prototypes, the pharmaceutical development of SMEO is currently oriented predominantly toward topical delivery. The hydrogels, polymeric membranes, and chitosan-based systems described in the selected studies were specifically designed for wound healing, skin antimicrobial action, or surface-level veterinary applications, all of which align with topical administration. Although one study explored a chitosan-based buccal delivery system for veterinary use, no evidence supports SMEO nanostructures for oral systemic or transdermal systemic routes. Therefore, current research trends indicate that SMEO-based nanostructures are being developed primarily

for topical use, with potential expansion into transdermal delivery only after additional permeability and safety data become available.

#### 5.6. SMEO Chemotypes. A Focus on Their Main Biological Activity and Potential Application

Figure 4 presents a heat map combined with hierarchical clustering analysis, which allowed the integration of the relative composition values of the essential oils collected to identify relationships between the studies in terms of their majority compounds. This analysis showed clear differences in the relative proportion of the selected metabolites, which is evidence of a marked chemical variability between the studies considered. However, certain compounds such as  $\alpha$ -phellandrene and sabinene stood out for their high frequency and relative abundance. Other relevant compounds are  $\alpha$ -pinene,  $\beta$ -pinene,  $\beta$ -phellandrene, limonene, and myrcene.

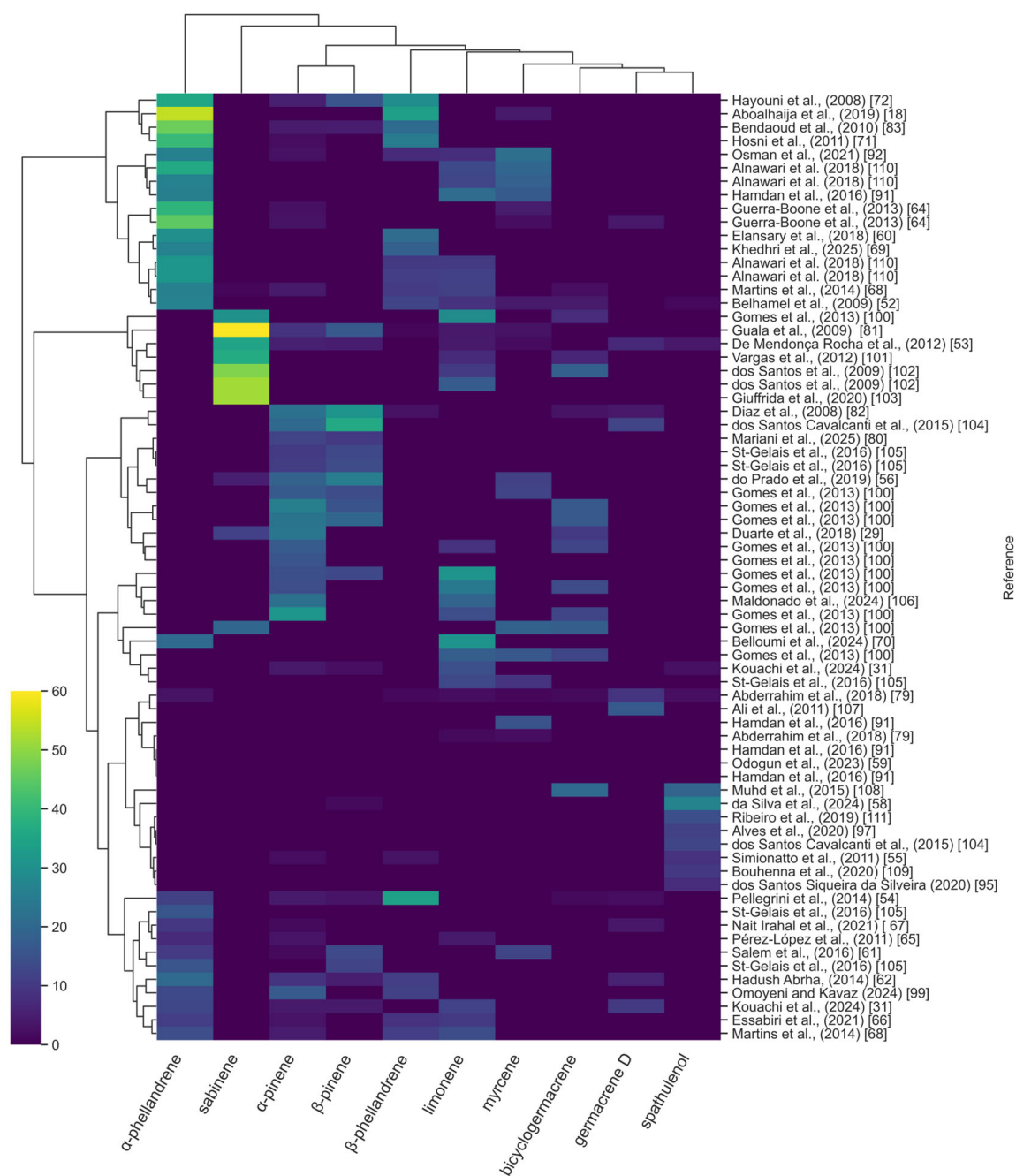


**Figure 4.** Dendrogram and heatmap of *S. molle* EO similarities by using Ward's method [18,29,31,52–56,58–62,64–72,79–83,91,92,95,97,99–111].

For the purpose of this review, chemotypes were categorized based on the dominant compounds identified in the chromatographic profiles. A compound was considered a 'chemotype marker' if it represented the highest percentage in the composition, typically exceeding a threshold of 15% of the total oil. In cases where two compounds were co-dominant, mixed chemotypes (e.g.,  $\alpha$ -phellandrene/limonene) were defined. Among the compounds analyzed,  $\alpha$ -phellandrene stood out as a major component with a high presence in the chemical profiles of SMEOs. This finding is consistent with that reported by Radice et al. [112], who identified  $\alpha$ -phellandrene as a key structural marker in essential oils with antimicrobial, anti-cancer, and antinociceptive activities, in addition to other biological activities that confirm SMEO's potential as a biopesticide. Additional findings regarding pure  $\alpha$ -phellandrene's potential in wound healing treatment have been reported by Salas-Oropeza et al. [113] and de Christo Scherer et al. [114]. These studies hypothesize a dual synergistic action conducted by  $\alpha$ -phellandrene, expressed by antimicrobial and anti-inflammatory activity.  $\alpha$ -Phellandrene appears to be able to non-stimulate fibroblast cell proliferation and inhibit the pro-inflammatory cytokines in a dose-dependent manner. A study performed by Pinheiro-Neto et al. [115] showed that  $\alpha$ -phellandrene could be a potential compound with antinociceptive and antineoplastic properties in cellular and animal models, at doses between 25 and 50 mg/kg, paving the way for new research into pharmaceutical formulations for the treatment of oncological pain. A study by Susanto et al. [116] further investigated the synergistic effect of  $\alpha$ -PA and 5-FU, reporting a reduction in HT-29 cell viability and subsequent apoptosis. The research suggested the activation of the mitochondria-dependent pathway and the extrinsic apoptosis pathway as potential mechanisms. Older studies [117–119] also report preliminary data on the anti-cancer action of  $\alpha$ -phellandrene against human liver tumor cells (J5) and the ability to stimulate the immune responses and induced cell apoptosis in a murine WEHI-3 leukemia model. Gonçalves et al. [120] also proposed that  $\alpha$ -phellandrene could be used as an adjuvant in hemorrhagic cystitis induced by treatment with ifosfamide, a common chemotherapy drug.  $\alpha$ -Phellandrene seems to be able to reduce urothelial damage due to its anti-inflammatory properties, showing a reduction in malondialdehyde, nitrite/nitrate, and myeloperoxidase, the tissue markers involved in bladder tissue damage. A study conducted in the same year by Siqueira et al. [121] further supported the anti-inflammatory activity of  $\alpha$ -phellandrene, providing evidence in relation to its ability to show neutrophil migration modulation and mast cell stabilization in animal models. Finally, a study proposed by Kumar et al. [122] using the rotenone-induced Parkinson's disease model links the antioxidant properties of  $\alpha$ -phellandrene to the possibility of modulating neurotransmitter levels and, therefore, it acts as a neuroprotector. These findings open up a further potential use of  $\alpha$ -phellandrene and OEs rich in this compound as potential agents to slow the progression or alleviate the symptoms of Parkinson's disease. Regarding topical application, in vitro searches on ethosomal gel formulation showed anti-inflammatory activity and good skin permeation, focusing on the potential of  $\alpha$ -phellandrene- and  $\alpha$ -phellandrene-rich EOs as an alternative transdermal delivery system formulation [123]. Finally, as reported by Kang et al. [124],  $\alpha$ -phellandrene appears to increase the cutaneous presence of cyclic adenosine monophosphate (cAMP), promoting the increase in growth factors that enable the proliferation of dermal papillae cells (DPCs). These preliminary results therefore project the potential use of an SMEO with an alpha-phellandrene chemotype in the formulation of cosmetic products for hair growth.

In the dendrogram,  $\alpha$ -phellandrene shows a distribution that tends to be divided into two groups: one in the upper part, characterized by high concentrations, and another in the lower section with lower values. This division suggests the possible existence of at least

two chemotypes defined by the relative abundance of  $\alpha$ -phellandrene, which reinforces its importance both from a taxonomic and functional point of view.

Another compound that forms a clearly defined group is sabinene, which, although it does not have as high a frequency of occurrence as  $\alpha$ -phellandrene, stands out for showing significantly higher concentration values in a specific set of studies, indicating a dominant presence of this monoterpene in certain samples. This distribution suggests that sabinene may act as a marker compound for a particular chemical profile within SMEO. This observation suggests the importance of considering not only the frequency of occurrence, but also the relative magnitude of metabolites in the identification and characterization of possible chemotypes. Concerning the potential application of SMEOs rich in sabinene, some preliminary in vivo and in vitro data concerning this compound can lead future investigation on the whole essential oil. The compound sabinene seems to be able to enhance memory function in mice treated with lipopolysaccharide, which can induce neuroinflammation. This monoterpene may reduce some biochemical markers of neuroinflammation, such as TNF- $\alpha$  and IL-6, showing neuronal cell damage activity and oxidative stress protection [125]. Additionally, the anti-ischemic stroke properties of sabinene have been investigated by Ozah et al. (2025) [126], reducing acetylcholinesterase activity and promoting astrocyte-neurotrophic support due to antioxidant and anti-inflammatory effects. The antiepileptic efficacy of sabinene has also been investigated by Alumona et al. (2025) [127] in an animal model; the mentioned terpene may reduce pentylenetetrazol-induced seizures, enhancing the scientific preliminary evidence about the neuroprotective activity of sabinene. Previous studies on sabinene have also reported preliminary preventive action (in vitro) against skeletal muscle atrophy and promising antibacterial action (in silico) against *S. typhimurium* [128,129]. Recent studies performed by Quian et al. (2025) [130] focused on the potential anti-cancer effect of sabinene. According to in vivo and in vitro studies, sabinene can inhibit cell proliferation and induce apoptosis in hepatocellular carcinoma cells.

Regarding limonene, this molecule has been reported as a potential antihyperperic terpene [131].

Based on the references previously reported, Table 6 summarizes the reported chemotypes and their most-supported potential biological effects.

In addition, a second group of metabolites including  $\alpha$ -pinene,  $\beta$ -pinene,  $\beta$ -phellandrene, and limonene were identified, which show more dispersed patterns within the heat map, with relatively lower concentrations than  $\alpha$ -phellandrene and sabinene but with a high frequency rate in the studies analyzed. The observed variability could reflect ecological, genetic, or methodological differences, as well as the influence of soil and climatic conditions or the phenological stage of collection of the plant material [31]. Nevertheless, their recurrent presence and moderate-to-high relative abundance reinforce their value as possible auxiliary metabolites in the definition of chemotypes. This hierarchical structure reveals the coexistence of different recurrent chemical profiles between studies, pointing to the existence of intraspecific variability in the essential oils obtained from *S. molle*.

The variability observed in other components also opens possibilities for the selection of genotypes with optimized chemical profiles for specific applications, whether pharmaceutical, agricultural, or industrial. Finally, it is worth mentioning that the variability of the composition of SMEO is also linked to the time of year in which the plant material is taken for distillation. As reported by Pereira et al. [132], samples collected in different areas of the Rio de Janeiro state in Brazil show the prevalence of bicyclogermacrene and sabinene during summer, autumn, and spring, ranging, respectively, between 34.34% and 21.06% and 45.4% and 26.54%. In the winter period, the data reported the prevalence of myrcene and sabinene (21.97% and 27.32%), respectively. A further study by Volpini-Klein et al. [133] reported that samples taken in the autumn had a higher content of sesquiterpenes and sam-

ples taken in the spring were richer in monoterpenes. In contrast, the data from the winter and summer seasons showed no significant differences in composition. In summary, the prevalent compounds obtained from the leaves and fruits of *S. molle* are sabinene, myrcene, epi- $\alpha$ -cadinol, germacrene-D, and bicyclgermacrene. The same study also indicated that there is significant variation in the content of essential oils using different extraction methods, such as hydrodistillation, steam distillation, and fractional hydrodistillation.

**Table 6.** Reported chemotypes and their most-supported potential biological effects.

| Chemotype              | Dominant Terpenes                            | Most-Supported Potential Biological Effect                       | Key Evidence Type                                                                                                                                                                       |
|------------------------|----------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| $\alpha$ -phellandrene | $\beta$ -phellandrene, limonene, and myrcene | Antimicrobial                                                    | Antimicrobial assay                                                                                                                                                                     |
|                        |                                              | Antinociceptive                                                  | Formalin test, glutamate test, and carrageenan-induced hyperalgesia assay                                                                                                               |
|                        |                                              | Anti-inflammatory                                                | Inhibition of pro-inflammatory cytokine production                                                                                                                                      |
|                        |                                              | Anti-cancer                                                      | Immune response promotion and cytotoxic activity in in vivo and in vitro models                                                                                                         |
|                        |                                              | Neuroprotector                                                   | Rotenone-induced Parkinson's disease model                                                                                                                                              |
|                        |                                              | Wound healing treatment                                          | Wound contraction model                                                                                                                                                                 |
| sabinene               | myrcene                                      | Neuroprotector, anti-ischemic stroke, and antiepileptic activity | Acetylcholinesterase assay, assays for molybdenum-containing enzymes and pro-inflammatory cytokines, TNF- $\alpha$ and IL-6 quantification, and pentylenetetrazol-induced seizure assay |
|                        |                                              | Skeletal muscle atrophy prevention                               | Intracellular ROS assay and cell atrophy and muscle atrophy assay                                                                                                                       |
|                        |                                              | Anti-cancer                                                      | Apoptotic biomarker quantifications in in vivo and in vitro models                                                                                                                      |

The data on the main compounds identified above justify further research into the SMEO variants rich in the described chemotypes, with the aim of verifying the preliminary data and observing whether there are positive or negative synergistic effects between the studies on the individual compounds and the essential oil as such. Any confirmation of biological activity would lead to a further formulation development phase. All these data reinforce the need for further research to select and standardize the production of specific chemotypes in order to develop pharmaceutical formulations and obtain reproducible efficacy results.

#### 5.7. Patent Landscape and Industrial Relevance

Based on the above-mentioned patent search strategy tree, the vast majority of relevant and frequently cited patents (e.g., WO2016/162343, EP3280497, US20180078491, US11045669, and FR3034664) are centered on hydroalcoholic extracts of the aerial parts of *Schinus molle*, mainly leaves. These patents focus on compositions enriched in polyphenols like quercitrin and miquelianin, with applications mostly in cosmetics and skin protection.

Regarding patents directly related to the SMEO, the data indicates very limited presence. Few or no patents specifically claim or emphasize “*Schinus molle* essential oil” for pharmaceutical or therapeutic uses, especially with antimicrobial, anti-inflammatory, wound healing, or neuroprotective properties.

The Brazilian patent family BR102016028710 mentions pharmaceutical compositions containing the essential oil of *Schinus molle* for ectoparasite treatment in veterinary use

(fleas and ticks), including topical formulations like powders, shampoos, and sprays. This is one notably explicit patent family utilizing the essential oil form.

The older US patent US5512284 also claims a pharmaceutical composition containing SMEO, emphasizing its bactericidal properties against pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* for topical use. Most patents mentioning the essential oil either relate to formulations or veterinary applications, not the full scope of pharmaceutical/therapeutic uses covered by hydroalcoholic extract patents.

This highlights a significant opportunity for novel research and potential industrial development based on SMEO.

The few patents that do mention essential oils often refer to generic formulations or delivery systems without exclusive coverage of SMEO. This lack of specific patent protection underscores the scientific and applicative value of experimental research on *Schinus molle* and its principal constituents (such as  $\alpha$ -phellandrene and sabinene). Moreover, the scarcity of patents dedicated to SMEO opens promising avenues for intellectual property development and the valorization of pharmaceutical and cosmetic products, leveraging its well-documented antimicrobial, anti-inflammatory, and potentially neuroprotective properties.

## 6. Discussion

### 6.1. From Fundamental to Applied Research. A Technology Readiness Level (TRL) Approach

The articles selected in this review article show a significant presence of preliminary studies on the antimicrobial, antioxidant, and anti-cancer activity of SMEO. Nevertheless, the transition from basic to applied research requires a careful analysis of those scientific-technical and regulatory aspects that enable the development of marketable products in competitive settings. The first aspect to be assessed is the standardization of production and process aspects, which were partially addressed in the studies performed by Volpini-Klein et al. [133] and Ribeiro et al. [111]. The first technical-scientific issue is the inherent variability of essential oils, which must be harmonized to productions that guarantee a specific chemotype, allowing for a reproducible chemical composition within a given range. Essential oils, like other products of natural origin, have a high degree of variability as they are closely related to genetic, environmental, and climatic factors (e.g., altitude, exposure to light, growth stage, anatomical part of the plant, and soil characteristics, etc.) that influence their chemical composition and, in fact, their organoleptic characteristics and biological activity. Genetic factors characterize the intrinsic variability of secondary metabolism and the plant's ability to adapt to its environment. Similarly, all the stages related to the harvesting, processing, and storage of oils are decisive for the relative standardization of the final product [22,134]. The second technical-scientific aspect that requires further study concerns the development of pharmaceutical formulations that enable the biological activities of SMEO. The preliminary studies shown in Table 5 represent the new frontier of research that should be prioritized, expanding the activities of the studies and flanking them with stability and compatibility assays and possible controlled-release studies. Research on wound healing activity could be particularly interesting in light of the recent publications [48,135–137]. All the cited studies support the application of essential oils within polymer-based wound dressings, nanofibers loaded with essential oils (obtained by electrospinning) or chitosan/essential oil/ZnO nanobiocomposites. The antimicrobial, antioxidant, and anti-inflammatory activity of the EOs appear to act synergistically with the other components of the biomaterials, enhancing angiogenesis and collagen synthesis. The overall effect results in an acceleration of the healing process.

The effect of the EOs seems to involve the inhibition of plasminogen activator-1 (PAI-1), type I collagen formation, and the regulation of certain growth factors (IGF-1, FGF-2, and VEGF) involved with insulin-like growth factor 1, fibroblast growth, and

vascular endothelial tissue reproduction, respectively. These mechanisms explain cellular repair and wound resolution [49].

The Technology Readiness Level (TRL) approach was proposed by Arnouts et al. [138] and Héder [139] to classify the stages of development of a product or process, with the aim of defining the priorities and strategic choices needed to move from the preliminary study phases to products suitable for commercialization. Identifying the TRLs of an applied research process aids the definition of necessary funding and subsequent activities. The TRL classification includes nine levels of technological readiness (TRL1 to TRL9) which define the results obtained at the various stages of productive development, from preliminary results to the realization of a prototype suitable for a competitive environment. The results highlighted in this systematic review work are in the TRL 1–TRL 4 range associated with laboratory-scale development, considering the first experiments related to pharmaceutical formulations and the desired pathway for the valorization of SMEO. Future research should focus from TRL 5 to TRL 7, on the pilot-scale validation of preliminary results (TRL 5–TRL 7) and then flow towards the full development of the technology and final products (TRL8–TRL9).

### 6.2. Pharmaceutical Translational Potential and Challenges

The therapeutic promise of SMEO is widely documented at the *in vitro* and some *in vivo* levels, yet its translation into clinically approved phytopharmaceuticals remains limited. Primary challenges include the intrinsic chemical variability among chemotypes, which impacts dose standardization and therapeutic predictability. Moreover, the volatile nature and chemical instability of essential oils necessitate the development of advanced formulations—such as nanoemulsions, hydrogels, and polymer-based delivery systems—to ensure effective bioavailability and controlled release. Although promising bioactivities exist, particularly in wound healing, antimicrobial resistance mitigation, and oncology-supportive therapies, clinical trials and pharmacokinetic studies are lacking. Regulatory frameworks further require the validated standardization of chemotype-specific oils and thorough quality control to ensure patient safety. Future translational research should thus focus on chemotype-guided standardization, formulation technologies enhancing stability and delivery, and early phase clinical validation to bridge existing gaps between the bench and bedside.

### 6.3. Critical Assessments of the Papers Reviewed

The systematic review process also includes a critical appraisal of the selected articles. Identifying the state-of-the-art research related to the article's topic allows us to identify any gaps in previous research and, therefore, propose new studies that can fill them. At the same time, good practices or well-established results emerging from selected articles allow us to avoid repeating those types of studies and advance toward complementary research, with a view to scaling new TRLs.

The article evaluation was based on the following criteria: (a) Does the article clearly define the scientific problem of the research? (b) Are the plant material selection and transformation procedures adequately described, and do they allow for the reproducibility of the experiments? (c) Are the materials and methods used for analytical procedures and biological activity tests comprehensively described? (d) Is the chemical characterization of the SMEO samples clearly described? (e) Are the biological activity data adequately described and discussed, facilitating the planning of further studies? (f) Are the obtained data useful for a subsequent research phase and are they scalable following the TRL approach?

The selected articles meet the requirements of points (a), (b), and (c), and the information regarding the botanical parts of the plant used to extract the EOs is particu-

larly complete and precise, indicating the clear prevalence of the leaves and fruits. Furthermore, the extraction methods are clearly described, and the studies by Pereira de Menezes Filho et al. [57] and Volpini-Klein et al. [133] are particularly useful in relation to the seasonal and geographical variability of SMEO. The rich presence of data relating to the extraction process is essential for subsequent large-scale standardization of distillation, facilitating subsequent developments in applied research, potential cost analysis, and the appropriate sizing of plants in the event of production expansion. Essential oil composition (point d) was reported in almost all of the selected studies, enabling the development of hierarchical cluster analysis and the subsequent identification of the main chemotypes. This information is also crucial for future research as it allows targeted studies to replicate or refute the preliminary biological activity data obtained on individual molecules on chemotyped oils, especially in the case of alpha-phellandrene and sabinene, the two main chemotypes.

The data set relating to biological activity (point e) is correctly described and methodologically sound. The method description is sufficiently consistent and reproducible, although it should be noted that information regarding the positive control and, especially, the negative control of some tests is not always present. The few formulation studies in Table 5 provide detailed information on the formulation prototypes and are of great interest for indicating future research trends. The use of nanotechnology appears to be crucial for stabilizing SMEO and enhancing the preliminary biological activities identified in this review.

Finally, an assessment of point (f) identifies current research at a TRL between 1 and 4, indicating that scientific research into the pharmaceutical potential of SMEO requires a clear shift toward larger-scale trials and an applied research approach. Further studies focusing on seasonality, production, and extraction processes with larger-capacity facilities are recommended, seeking to obtain data for supply chain development and the optimization of oil production. At the same time, especially regarding antimicrobial and antioxidant activity, preliminary data on the oil as such are abundant and allow for further research on formulation development. The simultaneous presence of preliminary evidence regarding antioxidant, antimicrobial, and anti-inflammatory activity suggests intensifying studies in the field of wound healing and topical formulations. Regarding studies on tumor activity, further research on chemotyped oils or the major components of SMEO is recommended, along with intensifying research on animal models.

In conclusion, preliminary data on the development of SMEO-based pharmaceuticals provide some insights into future formulation developments, despite the need to address some gaps regarding product standardization and biological activity. Future research should, however, focus on higher TRLs to test the potential of SMEO in more competitive environments.

## 7. Research Needs and Future Trends

The pharmaceutical application of essential oils presents a complex challenge due to their intrinsic variability and the resulting difficulty in ensuring reproducible biological activity. At the same time, most essential oils exhibit multiple and synergistic properties (e.g., antioxidant and antimicrobial) that can be effective in specific formulations, also considering potential synergies with synthetic active ingredients [140–142]. Preliminary data on SMEO indicate potential use in pharmaceutical or veterinary formulations. However, further research is needed to provide complementary results to those identified in this review, with a view to developing applied research scalable to formulation models. Advancing *Schinus molle* essential oil into clinical practice necessitates integrative efforts combining chemotype-specific characterization with pharmaceutical technology innova-

tion. Prioritizing chemotypes such as  $\alpha$ -phellandrene-rich variants for targeted indications, standardizing production protocols, and investing in novel delivery platforms will be key to overcoming current translational barriers. Such multidisciplinary approaches can convert promising preclinical data into standardized, efficacious, and safe phytopharmaceutical products, unlocking the full therapeutic potential of this botanical resource.

From this work, it is evident that future new emerging research trends point to the following approaches: (1) the development of research aimed at optimizing production and extraction processes, with the aim of consolidating the production chain of chemotyped oils; (2) in light of these preliminary data on SMEO and the prevalent compounds, conduct new research aimed at confirming or deepening the biological activity data with chemotyped oils; (3) the intensification of research aimed at formulation development, with particular emphasis on wound healing and topical antimicrobial applications; and (4) the implementation of further toxicity studies on SMEO.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/pr14020180/s1>; Table S1: PRISMA 2020 for Abstracts Checklist [143]; Table S2: PRISMA 2020 checklist.

**Author Contributions:** Conceptualization, S.M., M.R. and L.S.; Funding Acquisition, S.M. and S.R.-N.; Methodology, S.M., M.R., S.R.-N. and A.D.; Software, R.A.-N.; Writing—Original Draft Preparation, M.R., M.A.E.E. and L.H.V.-C.; Writing—Review and Editing, M.L.P.F., M.R. and I.G.; Supervision, S.M. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was supported by the Universidad Estatal Amazónica, Ecuador Republic, from University of Ferrara, Italy (project FAR 2024 2S.M) and by the project RTI 05-22, “Cooperative Open Innovation Model in the Northern Chilean Patagonia”, funded by the University of Los Lagos, Chile.

**Data Availability Statement:** The original contributions presented in this study are included in the article/Supplementary Materials. Further inquiries can be directed to the corresponding author.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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