OPEN ACCESS

Edited by:
Mijat Božović,
University of Montenegro,
Montenegro

Reviewed by:
Vanja Milija Tadic,
Institute for Medicinal Plant Research,
Serbia
Nicholas John Sadgrove,
Royal Botanic Gardens, Kew,
United Kingdom

*Correspondence:
Marek Bunse
marek.bunse@wala.de
Rolf Daniels
rolf.daniels@uni-tuebingen.de
Carsten Gründemann
Carsten.gruendemann@unibas.ch
Jörg Heilmann
Joerg.Heilmann@chemie.uni-regensburg.de
Dietmar R. Kammerer
dietmar.kammerer@wala.de
Michael Keusgen
keusgen@staff.uni-marburg.de
Ulrike Lindequist
lindequi@uni-greifswald.de
Matthias F. Melzig
Matthias.melzig@fu-berlin.de
Gertrud E. Morlock
gertrud.morlock@uni-giessen.de
Hartwig Schulz
hs.consulting.map@t-online.de
Ralf Schweiggert
ralf.schweiggert@hs-gm.de
Meinhard Simon
m.simon@icbm.de
Florian C. Stintzing
florian.stintzing@wala.de
Michael Wink
wink@uni-hd.de

Essential Oils as Multicomponent Mixtures and Their Potential for Human Health and Well-Being

Marek Bunse[1]*, Rolf Daniels[2]*, Carsten Gründemann[3]*, Jörg Heilmann[4]*, Dietmar R. Kammerer[1]*, Michael Keusgen[5]*, Ulrike Lindequist[6]*, Matthias F. Melzig[7]*, Gertrud E. Morlock[8]*, Hartwig Schulz[9]*, Ralf Schweiggert[10]*, Meinhard Simon[11]*, Florian C. Stintzing[1]* and Michael Wink[12]*

[1]Department of Analytical Development and Research, WALA Heilmittel GmbH, Bad Boll, Germany, [2]Department of Pharmaceutical Technology, University of Tübingen, Tübingen, Germany, [3]Translational Complementary Medicine, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland, [4]Department of Pharmaceutical Biology, University of Regensburg, Regensburg, Germany, [5]Institute of Pharmaceutical Chemistry, Philipps-Universität Marburg, Marburg, Germany, [6]Institute of Pharmacy, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany, [7]Institute of Pharmacy, Freie Universität Berlin, Berlin, Germany, [8]Institute of Nutritional Science, Chair of Food Science and TransMIT Center for Effect-Directed Analysis, Justus Liebig University Giessen, Giessen, Germany, [9]Consulting & Project Management for Medicinal & Aromatic Plants, Stahnsdorf, Germany, [10]Institute of Beverage Research, Chair of Analysis and Technology of Plant-Based Foods, Geisenheim University, Geisenheim, Germany, [11]Institute for Chemistry and Biology of the Marine Environment, University of Oldenburg, Oldenburg, Germany, [12]Institute of Pharmacy and Molecular Biotechnology, Heidelberg University, Heidelberg, Germany

Essential oils (EOs) and their individual volatile organic constituents have been an inherent part of our civilization for thousands of years. They are widely used as fragrances in perfumes and cosmetics and contribute to a healthy diet, but also act as active ingredients of pharmaceutical products. Their antibacterial, antiviral, and anti-inflammatory properties have qualified EOs early on for both, the causal and symptomatic therapy of a number of diseases, but also for prevention. Obtained from natural, mostly plant materials, EOs constitute a typical example of a multicomponent mixture (more than one constituent substances, MOCS) with up to several hundreds of individual compounds, which in a sophisticated composition make up the property of a particular complete EO. The integrative use of EOs as MOCS will play a major role in human and veterinary medicine now and in the future and is already widely used in some cases, *e.g.*, in aromatherapy for the treatment of psychosomatic complaints, for inhalation in the treatment of respiratory diseases, or topically administered to manage adverse skin diseases. The diversity of molecules with different functionalities exhibits a broad range of multiple physical and chemical properties, which are the base of their multi-target activity as opposed to single isolated compounds. Whether and how such a broad-spectrum effect is reflected in natural mixtures and which kind of pharmacological potential they provide will be considered in the context of ONE Health in more detail in this review.

Keywords: essentail oils, multicomponent mixtures, integrative medicine, phytotherapy, antibiotic resistance

HISTORY OF PHYTOTHERAPY

Aromatic plants have long been used in traditional medicine for their protective and therapeutic properties, in foods to impart flavor, but also as anti-inflammatory, antioxidant and antimicrobial agents (Freitas and Cattelan, 2018).

In Europe, phytotherapy is the best-known field of natural medicine today. One of the first and most detailed pharmacognostic guides on plants but also animals and their compounds such as essential oils or fatty acids is Dioscorides' 'De Materia Medica' (first century) (Staub et al., 2016). In mediaeval times (5th–15th century) herbs and extracts prepared therefrom were used for the treatment of various diseases, especially in monasteries, but also by healers, mostly women, who knew the potential of such preparations and later (since 13th century) by monks and pharmacists (Dufault et al., 2001). In the age of the plague (14th century), numerous epidemics of bubonic plague and other infectious diseases killed about 25% of the European population, which in consequence led to massive restrictions and regression in all areas of life. Despite basic knowledge of herbalism, nursing and medicine, the health system of mediaeval times could not prevent the consequences of the pandemic. At that time, living and working conditions as well as famines due to social structures and failed harvests were responsible for the fact that people were not able to live under adequate hygienic conditions, let alone to secure nutrition.

With the discovery of America and the sea route to India at the end of the 15th century (Renaissance), Europeans discovered plants that were previously unknown to them (e.g., cacao, chili pepper, sunflower), as well as options to treat further kinds of ailments. Thanks to printing, medicinal plants could be depicted and not only described, thus, they were more broadly recognized and knowledge could be shared to a greater extent. The most popular herbaria of this period are the "Herbarium Vivae Eicones" (1530) by Otto Brunfels, the "De Historia Stirpium" (1542) by Leonhart Fuchs, the "Herbarium" (1597) by John Gerard, the "English physician" (1649) by Nicholas Culpeper, and the "Theatrum botanicum" (1669) by John Parkinson (Makarska-Białokoz, 2020). A real breakthrough in the history of herbal medicine was initiated by Paracelsus, and especially his most famous phrase in relation to toxicology "Poison is in everything, and no thing is without poison; the dose makes it either a poison or a remedy" (Philippus Theophrastus Aureolus Bombastus von Hohenheim, 1493–1541; Holzinger, 2013). He studied the signature of plants, developed methods for extracting "therapeutic essences" from medicinal plants, and therefore is regarded as the father of phytochemistry and pharmacognosy.

Beginning in the 18th and 19th centuries, people have been increasingly concerned by the chemical knowledge of herbs and their constituents as well as their possible effects on health. Since then, it had been believed that individual specific chemical compounds are responsible for the healing properties of a medicinal plant and that effective preparations should consist of standardized, easily dosable substances or extracts. For this reason, individual constituents began to be increasingly isolated from plants. At that time, morphine isolated from opium poppy was considered a breakthrough in the study of medicinal plants

by the pharmacist Friedrich Wilhelm Adam Sertürner (Sertürner, 1806). Worldwide, many further important compounds were isolated from plants, such as strychnine, quinine, caffeine, salicin, cocaine, and digitalin, to name a few (Barnes, 2007). The era of scientific research on the chemical profile, the pharmacological and toxicological properties of plant extracts had dawned. Favored by the development of novel chromatographic and microscopic methods, herbs became the sources of medicines in the 20th century. Until 1930, herbal medicines were very popular and only gradually replaced by preparations obtained from chemical synthesis, the basis of synthetic drugs (Ferreira et al., 2014; Jamshidi-Kia et al., 2018; Makarska-Białokoz, 2020).

The trend of isolating single compounds was countered by the development of scientifically based rational phytotherapy. Distinct cultivation and processing methods were the basis of new guidelines, such as the World Health Organization (WHO) Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants or the European Medicines Agency (EMA) Guideline on Quality of Herbal Medicinal Products (CPMP/QWP/2819/00), herbal medicines of tested quality were developed from then on (Sahoo et al., 2010; Fürst and Zündorf, 2015). Today it seems to become more important than ever to develop effective and clinically proven, but also affordable medicines including traditional, long-established plant preparations. Furthermore, medicinal plants continue to hold great promise providing anti-inflammatory, antibacterial, antifungal, antiviral, anticancer, and antiparasitic compounds as leads. Thanks to their evolutionary development, plants possess a quite comprehensive arsenal of defense, protection, distribution and attraction strategies (Wink, 2003; Sakkas and Papadopoulou, 2017) based on bioactive and potentially pharmacologically active specialized metabolites. Given this considerable potential, medicinal plant extracts and their complex pharmacological and physiological effects are still highly underexplored, and the awareness of the need for more sound scientific studies is growing to better understand the rationale and the underlying principles of traditional therapeutic uses.

INHERENT COMPLEXITY

The basis of the diverse biological properties of medicinal plants and extracts therefrom is the interplay of complex secondary constituents such as alkaloids, terpenes, flavonoids, tannins, etc., as well as non-coding small RNA species, such as microRNA (Xie et al., 2016), which explain their diverse pharmacological and therapeutic properties both as individual compounds and as complex mixtures (MOCS; Wink, 2015). The latter are preparations used in phytotherapy, but which may also be applied as adjunctive therapy to a single compound of either synthetic or natural origin in the context of integrative medicine. Individual constituents in natural MOCS are often present at lower levels, compared to the amounts used in therapy with isolated individual components (Rasoanaivo et al., 2011; Gorlenko et al., 2020). Interestingly, a neat substance at the

same level as present in natural plant source mixtures, usually does not reach the same pharmacological effects on a quantitative and qualitative scale. This means that the same chemical constituent may exhibit a clear biological activity when forming part of a natural mixture (*e.g.*, a plant extract), whereas the isolated compound may not. Thus, natural compounds present in combination may enhance each other (synergism), complement each other (additive effect), or attenuate each other (antagonism) (Chou, 2006; Hemaiswarya et al., 2008; Połeć et al., 2022). This complex interplay of substances responsible for such effects may not only exhibit positive effects, but may also compensate for, attenuate or cancel out possible undesirable effects of other components (Caesar and Cech, 2019). The recent combination of planar chromatography with multiplex biological effect detection can straightforwardly differentiate such effects on the same plate (Ronzheimer et al., 2022; Schreiner et al., 2022). In addition, unlike isolated individual substances, MOCS often exhibit a broad spectrum of action (*i.e.*, they are multi-target drugs), since the diversity of molecular structures (multi-component), with their specific functional moieties and their respective chemical and physiological properties do not only have one common target, *i.e.* the "multi components result in multi targets" theory (Nahrstedt and Butterweck, 2010; Schwabl et al., 2013). The streamlined analysis of 68 different botanicals does not only highlight such versatility in potential biofunctional properties, but also prove that such multi-compounds may interact with various metabolic pathways (Morlock, 2021; Schreiner et al., 2021). Furthermore, MOCS may modulate their mutual resorption, but also for specific compounds from food or medicines and may also affect typical characteristics of smell and taste (Karalis et al., 2008; Ku et al., 2020).

Nevertheless, there is a strong trend in health policy and the pharmaceutical industry to replace complex natural MOCS, such as EOs, with isolated mono-substances in the future. The main reasons to prefer mono-substances may be simpler quality control, better application and standardization, straightforward clinical studies, with known active targets including side effects. In addition, authenticity control of EOs may be a major issue. By means of a broad portfolio of methods, like chiral gas chromatography, isotope-ratio mass spectrometry, NMR, thin-layer chromatography, vibrational spectroscopy, multi-dimensional chromatography, high-performance liquid chromatography, headspace chromatography, and combination with chemometrics-metabolomics, adulterated or synthetic oils may be identified (Do et al., 2015). The more complex a MOCS is, the more difficult it seems to verify its authenticity and genuineness. This seems to be another reason why biologically active mono-substances are often favored. When mono-substances are used, the potential of synergistic action is lost, which has recently been discovered in a number of natural MOCS (Ronzheimer et al., 2022; Schreiner et al., 2022). However, rising costs for mono-compound isolation and purification increasingly question the positive economic balance, especially in light of the growing awareness for the ecological impact and its ramifications. In addition, patient-centered medicine asks for complementary

approaches as a companion to conventional mono-substance therapies (Agarwal, 2018; Clark et al., 2021) and other effects and therapeutic benefits with reduced side effects can be achieved by applying MOCS compared to single compound application. Therefore, there is an urgent need to re-evaluate MOCS, and support sound studies to discover their full potential for human but also animal health in the context of integrative health approaches (Agarwal, 2018; Clark et al., 2021). This should go along with sustainable cultivation, not only to maintain and create jobs and to meet the demand for medicinal plants, but also to cultivate medicinal plants in an environmentally conscious manner, to preserve protected species and to protect wild stocks from uncontrolled collection (Silori and Badola, 2000; Akinyemi et al., 2018).

ESSENTIAL OILS AS CLASSICAL MOCS

Essential oils (EOs) are among the most versatile and long-term used medicinal plant preparations (Plant et al., 2019). They are produced in more than 17,500 aromatic species and are stored in various plant organs, *i.e.*, blossoms (*e.g.*, *Rosa* x *damascena* Herrm. (Rosaceae)*,* damask rose), leaves (*e.g.*, *Cymbopogon citratus* (DC.) Stapf (Poaceae), lemon grass), wood (*e.g.*, *Santalum acuminatum* (R.Br.) A.DC. (Santalaceae), sandalwood), roots (*e.g.*, *Chrysopogon zizanioides* L. (Poaceae), vetiver), rhizomes (*Zingiber officinale* Roscoe (Zingiberaceae), ginger; *Curcuma longa* L. (Zingiberaceae), turmeric), fruits (*e.g.*, *Pimpinella anisum* L. (Apiaceae), anise and *Carum carvi* L. (Apiaceae), caraway) (Regnault-Roger et al., 2012). Essential oils are defined as mixtures of secondary metabolites from plants (Ahmad et al., 2021) and typically exhibit a strong odor as they are MOCS containing a variety of volatile terpenes, aldehydes, alcohols, ketones and simple phenolics (Bakkali et al., 2008; Sadgrove et al., 2022). The European Chemicals Agency (ECHA) has defined EOs as "a volatile part of a natural product obtained by distillation, steam distillation or, in the case of citrus fruits, by squeezing. It contains mainly volatile hydrocarbons. Essential oils are derived from various parts of plants." (Essential oils - ECHA, 2022). In the plant, they play a central role in pollination, communication, and protection: They attract natural enemies of herbivores, protect against pathogens such as fungi and bacteria, are messengers between plants, attract seed dispersers and particularly pollinators, protect against extreme temperature fluctuations, etc. (Holopainen, 2004; Dudareva et al., 2006; Loreto et al., 2009; Loreto and D'Auria, 2022). As natural mixtures and the products obtained therefrom, EOs can vary in quality, quantity, and composition even when obtained from the same plant species. Not only the choice of the EO recovery process, but also the plant organ used and exogenous factors during plant growth such as climate, soil conditions, pest infestation, age and stage of the vegetation cycle play a decisive role (Masotti et al., 2003; Angioni et al., 2006). In addition, the composition of EOs may differ between individual plants in a population and sometimes even different chemotypes exist within a species. Furthermore, chemical varieties of EO-producing plants have also been bred, developed, and studied to improve

FIGURE 1 | Concept of EOs acting as MOCS with multi-target functional groups.
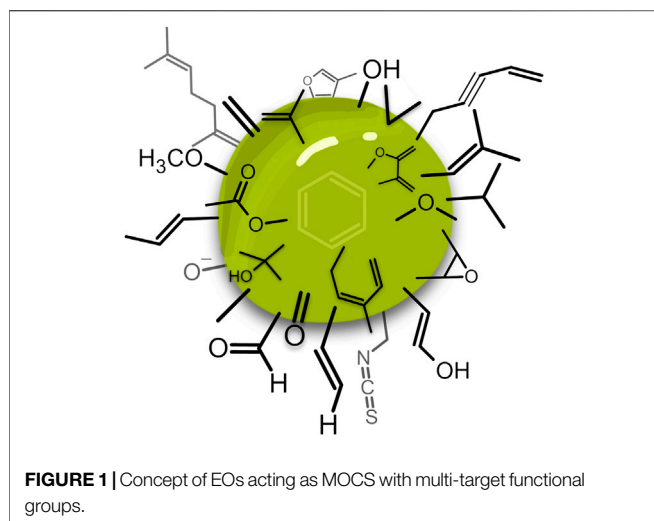
their EOs content, quality and composition (Toxopeus and Bouwmeester, 1992; Sarrou et al., 2017; Lal et al., 2018).

BIOSYNTHESIS AND CHEMICAL COMPOSITION

In aromatic and scented plants, the vast majority of volatile organic compounds originate from three precursor categories (**Figure 1**), namely phenolic compounds from shikimate and acetate malonate pathway, fatty acid derivatives, and isoprenoids (Sangwan et al., 2001; Caissard et al., 2004). The main constituents of EOs are often isoprenoids, which form the core structures of terpenoids (**Scheme 1**). The basic structure of isoprenoids consists of 2-methylbutane moieties (isoprene or 2-methylbutadiene units), which are biosynthesized in the cytosol via the mevalonic acid pathway and/or in plastids via the 2-C-methylerythritol-4-phosphate (MEP) pathway (Newman and Chappell, 1999). The universal precursors of all terpenoids are the active isoprene unit, isopentenyl diphosphate (IPP), and its isomer dimethylallyl diphosphate (DMAPP). Monoterpenoids are usually formed by the fusion of IPP in a head-to-tail manner to its isomer DMAPP, leading to geranyl diphosphate (GPP) (Dubey et al., 2003). In case of sesquiterpenoids GPP will be further head-to-tail elongated by a second IPP to the C15 farnesyl diphosphate.

The different biosynthetic pathways of EO substances constitute the fundament of their structural diversity. Beside terpenes another main group of EOs is composed of aromatic and aliphatic constituents.

A common analytical method for assessing commercially available EOs is chemical characterization by gas-liquid-chromatography coupled to mass spectrometry. In addition, analytical techniques such as nuclear magnetic resonance (NMR) spectroscopy and headspace gas chromatography play a role in characterizing and evaluating EOs quality and authenticity, especially for unstable EO molecules like

SCHEME 1 | Biosynthetic pathways of major volatile organic compounds. Modified according to Caissard et al. (2004).
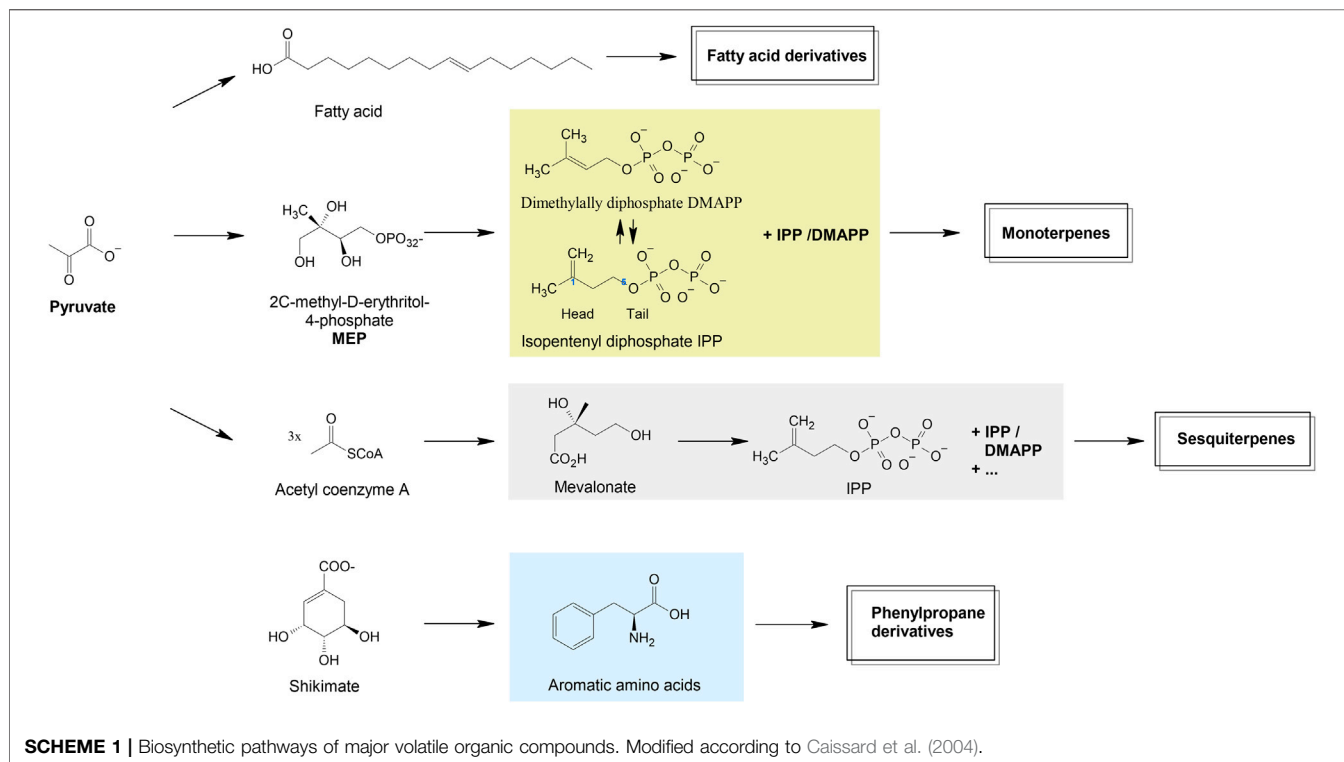
thermolabile sesquiterpenes, such as from *Curcuma caesia* Roxb. (Zingiberaceae) rhizome (Fakhari et al., 2005; Turek and Stintzing, 2011; Mahanta et al., 2020; Truzzi et al., 2021). According to Bakkali et al. (2008), about 3,000 EOs are known to date from a wide variety of plants and their organs, of which 300–400 are particularly important in the medicinal, pharmaceutical, agricultural, food, sanitary, cosmetics and perfume industries, as well as in dentistry, as adhesives and flavors (Ramezani et al., 2008; Turek and Stintzing, 2013; Ibrahim, 2020).

EOs are MOCS normally consisting of 20–200 single compounds, which divide into main constituents with concentrations ranging from 20 to 95%, minor compounds (1%–20%) and trace compounds (<1%) (Stahl-Biskup and Reher, 1987). The specific compound fingerprint is a result of multiple factors, such as plant species, plant part, growing conditions and time of harvest. In most cases, predominant constituents with low odor thresholds determine the typical olfactory EO character. For example, the quantitatively dominating compounds of oregano oil (*Origanum vulgare* 'Compactum' L.; Lamiaceae) are carvacrol (30%–80%) and thymol (27%–80%), whereas in fresh oregano leaves the main fragrance components are *γ*-terpinene, *p*-cymene, thymol, and carvacrol (Asadollahi-Baboli and Aghakhani, 2015). In coriander oil (*Coriandrum sativum* L.; Apiaceae) linalool (68%) dominates. In white wormwood oil (*Artemisia herba-alba* Asso; Asteraceae): *α*- and *β*-thujone (57%) and camphor (24%) are the quantitively dominating compounds. For camphor tree oil (*Cinnamomum camphora* (L.) J. Presl; Lauraceae), it is D-camphor (50%), for dill oil (*Anethum graveolens* L.; Apiaceae) *α*-phellandrene (up to 32%) and limonene (up to 32%) from leaf and carvone (up to 55%) and limonene (up to 45%) from the fruit. Peppermint oil (*Mentha* x *piperita* L.; Lamiaceae) is characterized by high amounts of menthol (up to 45%) and menthone (up to 15%) (Beigi et al., 2018; Bhavaniramya et al., 2019; Dobreva and Dimov, 2021; Poudel et al., 2021).

However, also minor or trace components may produce intense odors, which contribute to the characteristic flavor (Góra and Brud, 1983). For example, the fragrance of damask rose (*R. damascena*) is characterized by about 27 main compounds. However, only a few compounds (*i.e.*, *β*-damascenone, rose oxide, *trans*-nerolidol, rotundone, 4-(4-methylpent-3-en-1-yl)-2(5H)-furanone) represented by less than 1%, contribute to the distinctive scent of rose oil and account for about 90% of the odor content due to their low odor threshold (Naqvi et al., 2014; Ohashi et al., 2019). This means that not only a quantitative evaluation of compounds but also a qualitative view is required to reveal the full potential of EOs as a classical MOCS.

PRODUCTION OF EOs

Various methods to obtain EOs comprise conventional and modern techniques, including water or steam distillation, solvent extraction, expression, extraction with supercritical fluids and subcritical water (Edris, 2007). The focus of novel environmentally friendly extraction technologies is to minimize the use of solvents while producing high-quality extracts in a more cost-efficient and process-optimized manner (Chemat

et al., 2012). Hence, in addition to biotic and abiotic factors, reproducible and uniform extraction procedures play an important role in achieving consistent quality and composition of EOs. A reliable repertoire of methods exist to control and guarantee their quality, safety and efficacy (Bakkali et al., 2008).

Hydrodistillation, the boiling of plant material in water or the treatment of plant material by steam, is the predominant (historical) method to produce EOs. Nowadays, steam distillation is common for the recovery of most EOs. Hydrodistillation is a softer technique than dry distillation, normally used for wood and bark, because the plant components are exposed to lower temperatures to recover volatiles, and thus thermal decomposition of individual constituents and the production of artefacts in this process is reduced (Aziz et al., 2018).

Ideally, the EO should be distilled from a single species without removing or adding individual EO components. However, not all EOs meet these criteria; for example camphor oil and ylang-ylang oil are fractionated and corn mint is dementholized (Chen et al., 2013). In addition, low recoveries may be opposed to EO production from one plant species, which is why sometimes equivalent species are used, as in the case of anise EOs (Sultanbawa, 2016; Shahrajabian et al., 2019). Furthermore, in some cases it cannot be completely ruled out that another plant species of equal value also is harvested, which might be the case with spruce needle oils (Metsämuuronen and Sirén, 2019; Mofikoya et al., 2022). The chemical composition of EOs is not necessarily identical to that found in the respective living plant. Often, very high-boiling or low-boiling volatile plant compounds are simply lost because they do not even enter the vapor phase or readily evaporate and thereby escape during the production process. While most components shall be retained upon distillation, others may undergo chemical changes; such as the formation of chamazulene from matricin in chamomile (Ramadan et al., 2006). Thus, the composition of EOs represents the final image including the respective biosynthetic fingerprint but also the modified substances due to preceding processing. Furthermore, in some cases, individual compounds are intentionally removed because of their toxicity, such as hydrogen cyanide from bitter almond oil or methyl eugenol from rose oil (Rusanov et al., 2012; Zhang et al., 2019). One important modified oil, *e.g.*, by increasing the cineole content, while reducing the acid content, is eucalyptus oil (European Medicines Agency, 2014).

Some EOs may also be recovered by cold pressing. These cold-pressed oils are generally derived from citrus fruits, although distilled citrus oils are also produced. Unprocessed citrus oils may contain non-volatile phototoxic compounds (*i.e.*, furocoumarins) that, due to their molecular weight and non-covalent intermolecular binding forces, may remain in cold-pressed but not in distilled citrus oils (Ferhat et al., 2007). In addition, fragrance oils can also be extracted with organic solvents (*n*-hexane), producing concretes, absolutes or resinoids, with liquid or super-critical carbon dioxide, resulting in CO_2 extracts, or with some innovative methods like ionic liquid, or

FIGURE 2 | EOs as MOCS and their potential multi-target interactions with proteins.
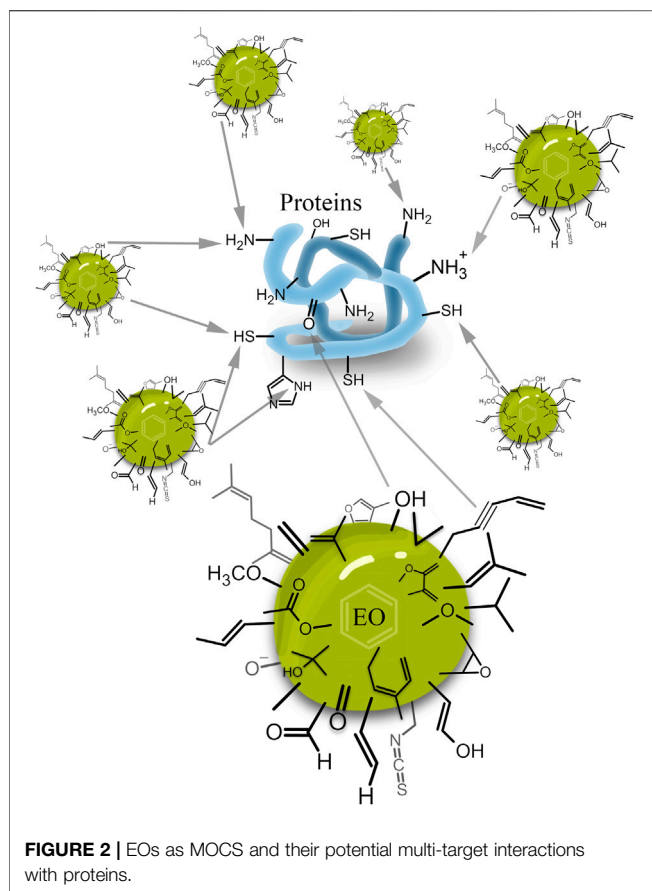
deep eutectics extraction (Lago et al., 2014; Erşan et al., 2018; Choi and Verpoorte, 2019). A concrete contains both volatile compounds and the non-volatile plant waxes and is prepared by washing the plant material with a non-polar solvent such as *n*-hexane. Absolutes are produced by re-extracting concentrated concretes with ethanol, subjecting to cold temperatures and then the soluble portion is concentrated to obtain fragrances devoid of waxes (Aycı et al., 2005). In addition, the enfleurage process is a very old method of extracting fragrances, in which volatile fragrance molecules from plant parts are transferred to fat in which they are embedded (Shankar et al., 2021).

EOs AND THEIR BIO-FUNCTIONAL PROPERTIES – RISKS AND SIDE EFFECTS OF IMPROPER APPLICATION

Because of the diverse structural diversity and number of constituents (**Figures 1**, **2**), EOs as a whole do not seem to have selective or singular cellular targets (Carson et al., 2002). Due to their different compound profiles, they can penetrate the cell wall of microorganisms and the cytoplasmic membrane of cells and thus disrupt the structural assembly of saccharides, proteins, fatty acids, and phospholipids, which modulate membrane permeability and fluidity (**Figure 3**). Such interactions with biomembranes are the basis of nearly all

biological activities of EOs and their metabolites to cross cellular compartments. In this way, EOs may cause depolarization of the mitochondrial membranes of eukaryotic cells, by decreasing the membrane potential, impairing the ionic Ca^{2+} cycle and other ionic channels thereby reducing the pH gradient. This may affect crucial metabolic processes such as the proton pump and the ATP (adenosine triphosphate) pool and may encompass cytotoxic activities (Richter and Schlegel, 1993; Novgorodov and Gudz, 1996; Vercesi et al., 1997). EOs may also modify the fluidity of membranes by making them more permeable, thus leading to the leakage of radicals, cytochrome C, calcium and other ions as well as proteins, as in the case of oxidative stress and bioenergetic failure. This may finally lead to cell death by apoptosis and necrosis (Yoon et al., 2000; Armstrong, 2006). Toxicity assessment of a substance or mixture is performed by means of the selectivity index (SI). The SI expresses the ratio between measured cytotoxicity towards normal cells and a desired measured activity, such as antiviral, or anticancerogenic activity. An ideal antiviral or anticancer compound would be cytotoxic against normal cells only at very high concentrations and exhibit antiviral or anticancer activity at very low concentrations (Prayong et al., 2008; Astani et al., 2010; Reichling, 2021). The cytotoxic properties are of great importance for the use of EOs against certain human or animal pathogens, parasites or abnormal cells but undesirable in cosmetic products (Bakkali et al., 2008). Due to their mode of action, acting on multiple targets simultaneously, resistance and adaptation phenomena towards EOs or individual compounds thereof have only scarcely been described. For example, resistance of *Bacillus cereus* to carvacrol has been detected after growth in the presence of a sublethal concentration of this component (Ultee et al., 2000; Di Pasqua et al., 2006). Furthermore, *Pseudomonas aeruginosa* showed increased tolerances to the EO of *Melaleuca alternifolia* (Maiden & Beche) Cheel, which was accompanied by changes in the barrier and energy functions of the outer membrane of the bacterium (Longbottom et al., 2004). This is a worthwhile aspect in finding alternatives to antibiotic therapy where resistance phenomena are increasingly being observed.

In the context of safety evaluation, not only cytotoxicity is relevant, but also mutagenicity and genotoxicity. Antimutagenic properties of an EO (*in vitro*) appear to be based on preventing mutagens from entering the cells, inactivating them by direct scavenging, neutralizing their radical oxygen species (ROS) by binding antioxidant molecules, or activating their own cell-protective antioxidant pathways. In addition, metabolic conversion of promutagens to mutagens can be inhibited by cytochrome P_{450} isoenzymes, or enzymatic processes metabolize harmful mutagens and other xenobiotics to harmless metabolites (Ramel et al., 1986; Kada and Shimoi, 1987; De Flora and Ramel, 1988; Hartman and Shankel, 1990; Kuo et al., 1992; Shankel et al., 1993; Waters et al., 1996; Sharma et al., 2001; Gomes-Carneiro et al., 2005; Ipek et al., 2005). ROS alone may trigger DNA mutation and antioxidants, such as some EO components, may inhibit this process and thus prevent the development of diseases (van Wyk and Wink, 2015). The reduced frequency of mutations caused by EOs was always accompanied by a synergistic
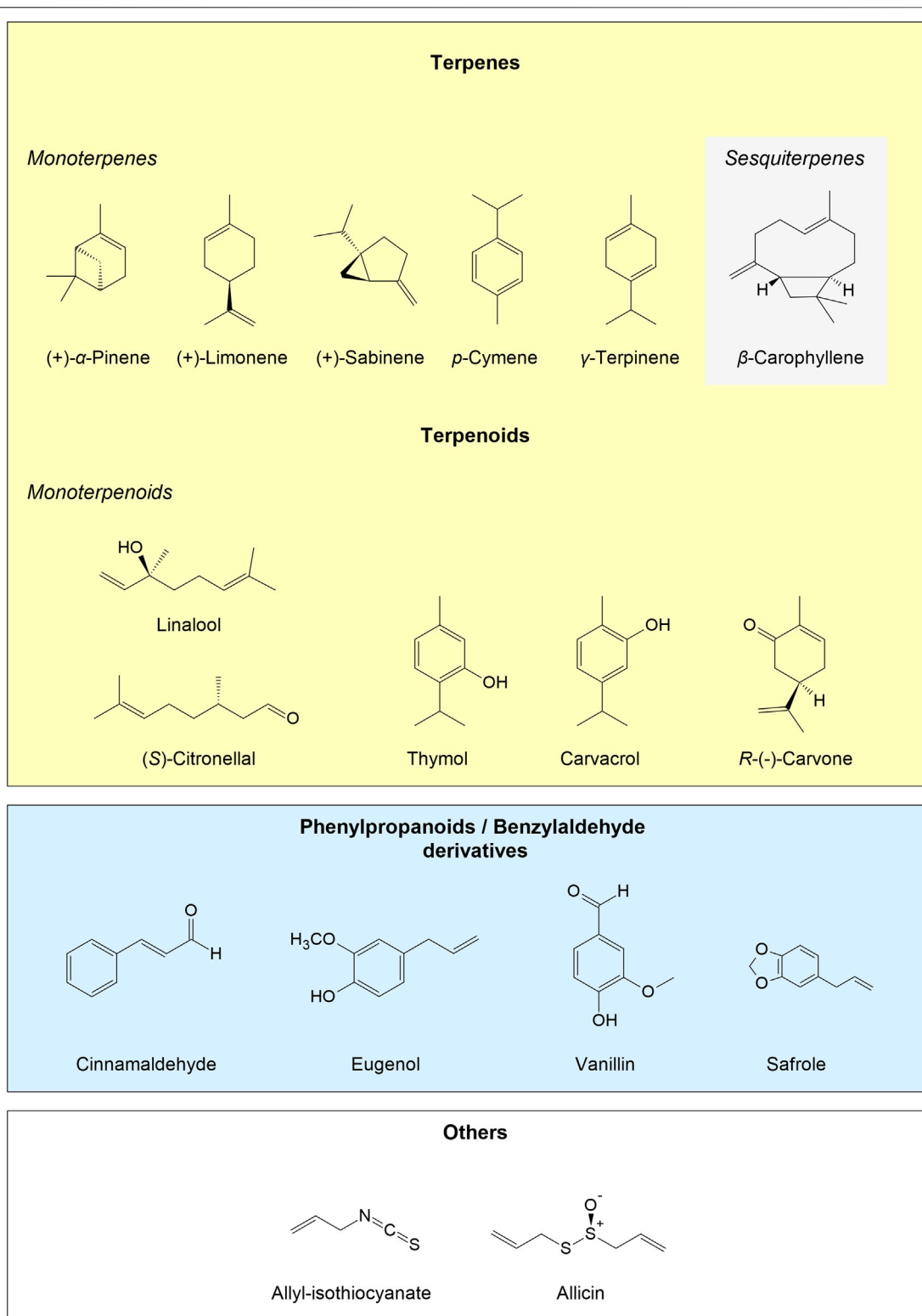
FIGURE 3 | Examples of chemical structures of EO constituents. Modified according to Hyldgaard et al. (2012).

induction of complete petite mutants (mitochondrial gene mutations of the respiratory chain). Moreover, EOs alone or in combination with other pharmaceuticals were shown to

induce mainly necrosis and not apoptosis. This supports the fact that petite mutants are true rho0 mutants. These are ultimately unable to induce apoptosis due to the lack of

functional mitochondria, but only passively induce necrosis (Van Houten et al., 2006).

A number of studies on various EOs and their isolated major constituents have shown that there is no evidence for a nuclear DNA mutation neither from the complete formulation nor the isolated constituents (Bakkali et al., 2005). However, some exceptions have been reported: *Artemisia dracunculus* L. (Asteraceae) EO was positive in rec-*Bacillus subtilis* assay (Zani et al., 1991). *Mentha spicata* L. (Lamiaceae), *A. graveolens, Pinus sylvestris* L. (Pinaceae) and *M. piperita* EOs were found to be genotoxic in different assays like the *Drosophila melanogaster* somatic mutations and recombination test (SMART) (Franzios et al., 1997; Karpouhtsis et al., 1998; Lazutka, JR et al., 2001); Anise EO, *trans*-anethol *e.g.* from fennel, β-asarone *e.g.* from *Acorus calamus* L. (Acoraceae), terpineol (*p*-menth-1-en-ol), *trans*-cinnamaldehyde, carvacrol, thymol and S (+)-carvone proved to be active in the AMES test (Nestmann and Lee, 1983; Hasheminejad and Caldwell, 1994; Gomes-Carneiro et al., 1998; Stammati et al., 1999). However, it appears questionable, whether concentrations, which showed harmful effects *in vitro*, may be reached *in vivo* upon proper application. Some of the phenylpropanoids are converted to epoxides in the liver, which can thus become mutagenic (Wink and Schimmer, 2010). Complementarily, it has been shown using yeast strains (*Saccharomyces cerevisiae*) *in vitro* that exposure to EOs can induce mitochondrial damage affecting mitochondrial membranes and DNA. This can lead to the formation of cytoplasmic petite mutants with respiratory deficits. The specific composition of an EO affected the rate of this induction, similar to cytotoxicity (Bakkali et al., 2005). In this context, special selections of plants are cultivated, like calamus (*A. calamus*), which are poor in β-asarone, for example (Bertea et al., 2005).

It can therefore be assumed that since most EOs have been shown to be cytotoxic but not mutagenic, it is likely that most of them are also non-carcinogenic. Nevertheless, some EO or some of their components can be considered as secondary carcinogens after metabolic activation. EOs like those from *Salvia sclarea* L. (Lamiaceae) and *Melaleuca quinquenervia* (Cav.) S.T.Blake (Myrtaceae) may cause estrogen-like secretions which may induce estrogen-dependent cancers (Cuba, 2001). Others (e.g., orange, lemon and *Litsea cubeba* (Lour.) Pers.; Lauraceae) may contain photosensitizing molecules, such as flavins, cyanins, porphyrins and hydrocarbons, and can cause skin erythema or even cancer (Kejlová et al., 2010). The photosensitizing furocoumarin psoralen found in some EOs is known to induce phototoxic effects and may induce skin irritation or cancer, like phytophotodermatitis, after formation of covalent DNA adducts when exposed to ultraviolet A or solar light (Averbeck et al., 1990; Averbeck and Averbeck, 1998; Nguyen et al., 2020). However, in the dark, the same oil is neither cytotoxic nor mutagenic by itself. So, there are EOs with phototoxic activities, non-phototoxic but cytotoxic activities *in vitro* (*Santalum spicatum* (R.Br.) A.DC. syn. *Fusanus spicatus* (Santalaceae) Australian wood EOs) and EOs with phototoxic and *in vitro* cytotoxic activities [*Citrus aurantium* subf. *dulcis* (Yu.Tanaka) M.Hiroe syn. *Citrus gracilis* subsp. *dulcis* (Rutaceae) and *C. citratus*; murine

fibroblastic cell line 3T3 and rabbit cornea derived cell line SIRC; (Dijoux et al., 2006)]. Recently, it has been demonstrated that furanocoumarins may protect terpenes from oxidation (Bitterling et al., 2022a; 2022b). So, it appears that interactions between the single compounds of an EO as well as between different types of MOCS (for example EOs and polyphenols) may have been overlooked in the past and deserve closer examinations.

The relevance assessment of these data and their importance for *in vivo* experiments is generally difficult since they were mostly collected *in vitro* or for single compounds or in unphysiologically high concentrations.

THERAPEUTIC USES OF EOs

The structural diversity as well as multi-component character of EOs led to a high number of physiological targets and the usability in different indication areas. Furthermore, therapeutical options of EOs are given by the distinct types of application. Inhalations can reach the upper and lower respiratory tract (Sadgrove et al., 2021). Through topical application substances can reach different skin layers, muscles and joints. Gargle solutions reach the mucous membranes and capsules or teas transport EOs to the gastrointestinal tract and lead to systemic absorption (Seyyedi et al., 2014; Alshehri, 2018; Filipović et al., 2020). A unique and very interesting way to achieve therapeutic effects with EOs is via smelling as scent impulses reach different brain areas via the olfactory nerve (Agatonovic-Kustrin and Morton, 2018; Zhang and Yao, 2019; Chandharakool et al., 2020). Consequently, EOs are part of interesting therapy options in case of respiratory diseases, rheumatic disorders, inflammatory skin diseases, gastrointestinal complaints as well as sleep and mental illnesses. Nevertheless, in all therapeutic treatments, the primary goal is the achievement of maximum therapeutic benefit while minimizing toxic and other undesirable side effects. The selection of the right essential oil, its dosage, method of application and integration in daily routine is correspondingly complex.

For most EOs, there is currently not enough reliable information regarding the active EO compounds and their molecular targeting *in vitro* and *in vivo*, but also regarding the best dosage to achieve the optimal efficacy and to minimize undesirable side effects for optimal safety. In our point of view, there are two consecutive ways to fill the knowledge gaps.

First, the efficacy and safety of an EO is evaluated based on the knowledge of other EOs with comparable composition or similar molecular structures. Since each component of a mixture exhibits its individual pharmacokinetic profile, the metabolic fate of an EO is assessed based on its individual substances and their known properties. This procedure is accepted and applied for most EOs (Tisserand and Young, 2014). Second, the complexity of EOs should be considered more in their entirety. In MOCS mutual interactions of individual compounds as well as interactions with their molecular environment may occur, resulting in synergistic, additive, or antagonistic effects. The latter are probably more rare

according to current data. Therefore, the assessment of a complex mixture based on its individual active principles will offer a first impression, but results may not be valid in all predicted assumptions in the living organism. Appropriate *in vitro* and *in vivo* methods should be developed and applied that evaluate a more complete picture of complex natural MOCS. In such studies, the different model parameters may be observed after testing/administration and compared to the assumed physiological effects of the individual compounds to evaluate the difference between single constituents and complex blends. The literature impressively shows numerous examples of the advantages of administering specific compounds as natural mixtures, including lower toxicity. For example, EOs or extracts with safrole showed the unexpected absence of genotoxicity and carcinogenicity when compared to the neat substance at the same concentration level (Ishidate et al., 1984; Bhide et al., 1991; Choudhary and Kale, 2002). The reduced acute toxicity in EOs with thymol is another prominent example (Karpouhtsis et al., 1998). Further investigations seem worthwhile to get an even more complete picture of the benefit of EOs as MOCS as compared to isolated compounds.

The specific composition of the EO, the method of administration, the dosage, the frequency, and the duration of administration influence bioavailability. In this context, the (relative) bioavailability of a substance is defined as the proportion of the administered dose that reaches systemic circulation in unchanged form. So, an intravenous administration of a substance is equivalent to 100% bioavailability (Koch-Weser, 1974; Atkinson, 2007). Three major routes of intake have been assessed for EOs: the respiratory tract (including the olfactory system), the gastrointestinal tract, and the skin/mucosa. Most studies report rapid absorption of lipophilic EOs components, following oral, dermal and inhalative, but also rectal and vaginal administration, nevertheless they differ with regard to ADME parameters and it is generally concluded that metabolic data on humans are still incomplete (Kohlert et al., 2000; Schmitt et al., 2009; Bach et al., 2021). Furthermore, bioavailability is highly individual, and the same substance can be metabolized differently in a collective despite choosing the same application route. This applies to quantitative (fast versus slow metabolizer) as well as qualitative aspects (different metabolic profiles). In addition, the same individual may process the same compound differently depending on food intake and comedication. Further factors are health status, diet, age, skin integrity, gut microbiota, and other metabolic variations that may depend, for example, on the time of day (chronobiology) (Hurst et al., 2007; Karalis et al., 2008; Zhang et al., 2021).

The most common routes of administration of EOs: Dermal/mucosal, inhalative (including olfactory system) and oral (via GI), will be discussed in more detail in the following.

Dermal/Mucosal (Topical) Administration

The skin is the largest organ of the human body with a thickness of about 3 mm and a layered structure. It provides protection from external insults, regulates the body temperature, but also the exchange of water and other compounds, such as minerals, fats, and various compounds resulting from metabolic transformations (Schommer and Gallo, 2013; Dąbrowska et al., 2018). The skin consists of an outer epidermis and the underlying dermis. The stratum corneum is the most important protective layer of the epidermis, consisting of dead cells embedded in a lipid matrix. Below the living epidermal cells are formed in the deep epidermis. The dermis below the epidermis consists of nerves, sweat and sebaceous glands, hair follicles, blood and lymph vessels, followed by the subcutaneous tissue, mainly fat (Ng and Lau, 2015). This general structure is variable and can differ depending on the body region. Therefore, different parts of the body may respond differently to EOs. Theoretically, there are two pathways for EOs absorption: the intercellular pathway (between skin cells) and the transcellular pathway (through cells) (Michaels et al., 1975). A third possible route of entry is through the hair follicles, bypassing the stratum corneum (Scheuplein and Blank, 1971; Meidan et al., 2005; Herman and Herman, 2015). Components that have been absorbed into the skin can be stored in the epidermis for a period of up to 72 h and then enter the systemic circulation via the dermis and its blood capillaries. However, the majority is absorbed within 24 h (Chidgey and Caldwell, 1986; Beckley-Kartey et al., 1997).

The protective stratum corneum consists of hydrophilic and lipophilic regions, which means that strongly water-soluble molecules such as glucose diffuse poorly through the lipophilic regions, while strongly lipophilic substances such as cholesterol and many other terpenoids can hardly cross aqueous regions (Wester and Maibach, 2000). To permeate through the skin barrier, substances should possess lipophilic properties as well as a certain degree of water solubility to facilitate the passage from the dermis into the bloodstream (Wepierre et al., 1968; Chacko et al., 2020). Numerous EO constituents appear to enhance their own and other substances' dermal absorption. For example, methyl salicylate may accomplish this in part by increasing local capillary blood flow and thus acting as a rubefaciens (Cross et al., 1999). Other compounds can temporarily alter the transport properties of the stratum corneum by interacting with intercellular lipids (Williams AC. and Barry BW., 1991; Williams A. C. and Barry, B. W. 1991). Carveol, α-pinene and terpinene-4-ol significantly boost permeation of water and ethanol in isolated human epidermis after 4 h (Magnusson et al., 1997). Also, (+)-limonene accelerates the transfer of citronellol and eugenol. Both α-pinene and β-myrcene similarly increase the permeation of phenylethanol (Schmitt et al., 2009). For rose oil components it was shown that all substances under investigation, except α-pinene and isomenthone, reveal skin permeation rates, which are several times higher when applied in rose oil as compared to the individual substance only (Schmitt et al., 2010). Cooperative interactions between EO constituents that promote the absorption of EOs and their own constituents may be the reason. EOs interact with lipids of the skin, reducing their highly ordered state and thus their barrier function, which facilitates passage through the dermis. Some terpenoids improve the transport properties of the skin in such an efficient manner that they are used intentionally to increase the absorption of various drugs. This should be considered

when treating skin with EOs, as they may modulate the absorption of drugs already applied to the skin (Gao and Singh, 1998; Hasan and Farooqui, 2021). Apart from the chemical EO composition, the absorption of EOs through the skin is dependent on several further factors, such as temperature, hydration, pressure, specific skin condition, skin microbiome, and age (Buck, 2004; Schmitt et al., 2009; Schommer and Gallo, 2013; Herman and Herman, 2015). In the last decade, it has become particularly evident that the skin microbiome not only influences skin appearance and disease (e.g., acne) but is also linked to the gut microbiome and plays a major role in immune defense (Beri, 2018; Nakouti et al., 2022). EOs and other natural MOCS can be used to rebalance the skin microbiome and the resulting clinical picture, promoting a healthy skin microbiology (Han et al., 2017; Wallen-Russell and Wallen-Russell, 2017; Białoń et al., 2019; Bunse et al., 2022).

Three other routes of topical EO administration, to bypass the gastrointestinal tract or hepatic first pass metabolism exist, namely the sensitive mucosa of the mouth, rectum, and vagina. This kind of application allows that the EO compounds reach their target unaltered. It also represents a most efficient way to administer a remedy locally to the lower colon or to treat vulval and vaginal, as well as mouth infections or irritations. An adequate dose is crucial because all three tissues covered with mucous membranes are highly sensitive to irritation, especially if the EO is unevenly dispersed. For example, rectal administration of 1,8-cineole, menthol or thymol resulted in high, moderate and zero elimination via the lungs in rats, respectively (Grisk and Fischer, 1969). An EO preparation administered for the treatment of vulvovaginitis, such as tea tree and geranium oil reaches the target site in a direct way and can reduce and eliminate infectious causes and inflammation (Blackwell, 1991; Maruyama et al., 2008). Oral infections, postoperative wounds or bad breath caused by bacteria, as well as xerostomia can be treated with appropriate EOs in e.g., mouthwashes (Fischman et al., 2004; Alshehri, 2018; Scotti et al., 2018; Filipović et al., 2020). *Syzygium aromaticum* (L.) Merr. & L.M.Perry syn. *Eugenia caryophyllata* L. (Myrtaceae), *Mentha arvensis* L. (Lamiaceae), *Leptospermum scoparium* J.R.Forst. & G.Forst. (Myrtaceae), *Thymus capitatus* Cav. (Lamiaceae) and *Thymus vulgaris* L. (Lamiaceae) essential oils showed *in vitro* antibacterial activities on oral pathogenic bacteria (Tardugno et al., 2018). Thus, as an example, mouth rinses with chamomile (*Matricaria chamomilla* L.; Asteraceae) essential oils might be applied to treat oral mucosal lesions and alleviate the suffering of recurrent aphthous stomatitis (RAS) patients (Seyyedi et al., 2014; Salehi et al., 2019).

Inhalative Administration

During inhalation, substances pass through the trachea into the bronchi and from there into the increasingly fine bronchioles and finally into the microscopic, sac-like alveoli of the lungs, where gas exchange with the blood mainly takes place. Components of EOs can be absorbed extremely efficiently into the bloodstream via the alveoli. Uptake depends on the speed of blood flow through the lungs, the rhythm and depth of respiration, and the specific lipophilicity of the molecules (Breuninger et al., 1970;

Jaradat et al., 2016). EOs components that find their way into the bloodstream via inhalation can easily reach the central nervous system. So, caution should be taken with neurotoxic compounds. Previous studies on EOs that entered the bloodstream via inhalation showed no undesired effects, as the concentration of EOs or their substances hardly reached a dangerous level in the ambient air or in the body (Falk et al., 1990; Buchbauer et al., 1991; Jirovetz et al., 1992; Falk-Filipsson et al., 1993). The situation may be different with neurotoxic ingredients, such as pinocamphone or thujones. However, there is currently insufficient information available to define which constituents represent an inhalational risk. Furthermore, molecules and drugs can be absorbed through the olfactory epithelium and its membranes and enter the bloodstream (Kristensson and Olsson, 1971; Conway and Ghori, 2022). In addition, EOs can bind and modulate receptor proteins of the olfactory bulbs which can directly transmit signals via synapsis to electrochemical nerves and to the brain (Angelucci et al., 2014). More than 1000 different types of olfactory receptor genes are known for mammals, and less than 400 genes which play role in human olfactory system. EO individual compounds can interact with these receptors and thus affect behavior and physiological conditions. These effects can be used in aromatherapy (Firestein, 2001; Koyama and Heinbockel, 2020): Different EOs which have an effect on the psyche may be used to reduce anxiety, to treat sleep disorders and improve attention and memory performance (Lizarraga-Valderrama, 2021). Various studies showed that some of the EO substances interact with most neurotransmitter systems, *e.g.*, in the limbic system (amygdala-hippocampal complex) by acting on different receptor proteins (López et al., 2017; Kennedy et al., 2018; Kontaris et al., 2020). Lavender oil is another prominent example, which acts on the serotonin 1A receptor (Baldinger et al., 2014).

Oral Administration

Oral administration has several advantages: The patient can take the preparation him- or herself, the dosage is easier and often there is a high bioavailability. For example, following ingestion of capsules containing 1,8-cineol, limonene and α-pinene as most abundant compounds, a treatment of bronchitis and sinusitis, the bioavailability of the main constituent 1,8-cineole reached 95.6% (Zimmermann et al., 1995). When taken orally, higher doses can be applied, but also require greater care in dosing. However, it should also be noted that the absorption of substances from EOs can be modulated by the simultaneous intake of food or comedication (Kohlert et al., 2000; Zhang et al., 2016; Stevanović et al., 2018). Furthermore, EOs can provoke mucosal irritation in sensitive individuals (Fischman et al., 2004). Since irritation depends on the local concentration, EOs should never be taken undiluted, but in formulations *e.g.*, with edible oil or encapsulated. In case of an overdose or an adverse reaction, nausea and vomiting of incorrectly administered EOs may occur (Woolf, 1999). Gastric digestive enzymes are capable of degrading and converting individual ingredients (Michiels et al., 2008; Stevanovic et al., 2020). For example, esters can be hydrolyzed in the stomach resulting in metabolites with altered

physico-chemical properties and modulated absorption. After absorption of the substances into the bloodstream, they reach the liver, where a significant portion is converted in first-pass metabolism. However, a few compounds may also become toxic as a result (Hoskins, 1984; Wink and Schimmer, 2010; Zárybnický et al., 2018). Therefore, dosage, frequency of ingestion, patient age, medical history, and life circumstances are discussable circumstances to successful oral administration of EOs, and self-medication without medical or pharmaceutical supervision is not advised. Rather, the potential of EOs can only fully be exploited when applied with knowledge and care.

METABOLISM

In the body, a large proportion of externally supplied compounds are metabolized for example by the gut microbiome (Bento et al., 2013). A compound may be converted into one or more different metabolites, with altered physical, chemical and biological properties. During this process, the metabolite usually becomes more hydrophilic than its parent compound and can thus be excreted more quickly via the kidneys. Furthermore, excretion routes are the skin and the respiratory tract (Brown, 1985; Heaney et al., 2016; Elpa et al., 2021). The liver is the most important metabolizing organ for EO compounds, but the skin, nervous tissue, kidneys, lungs, intestinal mucosa, blood plasma, adrenal glands and placenta also show metabolic capacities (Gropper and Smith, 2012). As EOs are MOCS each component has its own metabolic fate, therefore, it is very complex to specify the metabolism of an EO not only *in vitro* but especially *in vivo*. Typically, a compound undergoes multiple stages of transformation, and each constituent is eliminated from the body by one or more pathways with specific kinetics (Kohlert et al., 2000).

In phase 1 reactions, particularly reactive functional groups undergo changes such as hydrolysis, for example by non-specific esterases. Or, cinnamic acid methyl ester is hydrolyzed, thus releasing cinnamic acid and methanol and salicylic acid methyl ester is transformed into salicylic acid and methanol (Gibbs, 1908; Davison et al., 1961; Fahelbum and James, 1977). In addition, reactions such as oxidation, *e.g.*, by cytochrome P_{450} enzymes, and reduction are important mechanisms of metabolization of EO compounds (Michaels et al., 1975; Miyazawa and Haigou, 2011). In phase 2 reactions (conjunction reactions) substances are covalently bound to polar endogenous molecules, to substantially reduce their lipophilicity and facilitate their excretion. Most drug and EO constituents undergo reactions of this type (Bowman et al., 1982; Miyazawa et al., 2002). This includes glucuronidation, sulfation, and glutathione conjugation, whereby the first is the most common phase 2 reaction in mammals for detoxifying foreign substances (Dutton, 2019; Jäger and Höferl, 2020). Interestingly, recent results showed that phase 2 metabolism of phenolic compounds and terpenoids is significantly more complex than previously thought. Depending on the concentration and specific structural elements different metabolism via sulfotransferases and glucuronic acid transferases take place (Tremmel et al., 2021). Also, the

excretion route seems to play a significant role. Oral intake of a thyme extract to humans led to the detection of thymol sulfate in plasma and urine, whereas thymol glucuronide was only present in urine (Kohlert et al., 2002). In contrast, for L-menthol a glucuronic acid conjugate was observed in humans as the main metabolite in plasma and urine (Hiki et al., 2011).

The liver plays a central role in the metabolism of EOs. Some EO components have been reported to alter the production and activity of drug metabolizing enzymes. In particular, these responses have been reported for enzymes of the cytochrome P_{450} family (Zehetner et al., 2019). In many cases, enzyme induction results in decreased rather than increased toxicity because the toxic chemicals are more readily eliminated. For example, eugenol can increase the activities of specific liver enzymes when administered to rats, and linalool increases the activity of cytochrome $b5$ (Parke et al., 1974; Rompelberg et al., 1993; Zehetner et al., 2019), which forms part of the respiratory enzyme chain. In all cases relatively high doses were administered by either oral or intraperitoneal injection routes and it seems highly unlikely that humans would be exposed to equivalent amounts of EOs under physiological conditions. Therefore, it can be assumed that EOs do not pose a significant risk of affecting blood levels in humans by cytochrome P_{450} induction when applied topically or orally.

INTERACTIONS BETWEEN EO COMPOUNDS – SAFETY ASSESSMENT

Upon EOs application, interactions may occur between one or more of its ingredients, as well as with matrix compounds and individual active pharmaceutical ingredients or food components. Often, the major constituents reflect quite well the biophysical and biological properties of the EOs from which they were isolated, with the extent of their effects mainly depending on their respective concentration when tested alone or in EOs (Ipek et al., 2005). Such interactions are difficult to predict but may be categorized. The simplest is additivity, where the effects and potency of the mixture are as predicted by the known effects and amounts of its ingredients, *i.e.,* there is no mutual influence of individual compound properties. The second possibility is synergy (synergism, potentiation), which means the effect of the mixture is significantly increased. Different molecules and their active groups thus enhance their properties when applied in combination. Nevertheless, possible synergism between individual compounds of an EO is complex and cannot be limited exclusively to a few major constituents (Ronzheimer et al., 2022; Schreiner et al., 2022). Thirdly, antagonistic effects may be observed which is the opposite of synergy. This means the different ingredients of a mixture or when two substances are administered causes a weakening of the effect compared to what is expected from the individual compounds (Chou, 2006; Elshafie and Camele, 2016; Połeć et al., 2022). The fourth effect described for EOs components is cooperative interaction. For example, limonene can enhance the permeation of citronellol and eugenol in human skin epidermis (*in vitro*) (Schmitt et al., 2009).

PRECLINICAL DATA

As an example, investigation into the biological activity of linalyl acetate, terpineol, and (±)-camphor individually or in combination against human colon cancer cell lines *in vitro* demonstrated a synergistic mode of the constituents in the mixture. Neither camphor nor terpineol alone had any effect or activity and that of linalyl acetate was only marginal. Together with terpineol, the activity was increased to moderate (33 and 45% reduction in proliferation, respectively; concentration 10^{-3} M each). However, when all three substances were used together in the natural blend, proliferation in the two human cancer cell lines HCT-116 (p53$^{+/+}$ and p53$^{-/-}$) was reduced by 50 and 64% (concentration 10^{-3} M each), respectively. No toxic effect on normal intestinal cells was reported (Itani et al., 2008).

The lower toxicity of carvacrol in the presence of thymol is an example of antagonistic action (Karpouhtsis et al., 1998). In thyme oil, high levels of thymol and/or carvacrol, totaling 31%–80% thymol and carvacrol, were found to be associated with antagonistic properties. In feeding studies with rats, the acute oral toxicity (LD$_{50}$ values) of these two compounds were 980 mg/kg BW and 810 mg/kg BW, respectively. Assuming an average LD$_{50}$ of 895 mg/kg BW each, the LD$_{50}$ of a thymol/ carvacrol thyme oil would range from 1.1 to 2.9 mg/kg BW. In fact, the oral LD$_{50}$ for this thyme oil in the feeding study was 4,700 mg/kg BW, which is about half as toxic as the thymol and carvacrol content would suggest. Interactions with further EO compounds naturally present in the oil could of course not be excluded. However, this influence of only two compounds in combination alone shows how complex a biological effect in MOCS may be composed. Further data are reported for antagonism in skin sensitization, which is known as quenching. In cinnamaldehyde-sensitive subjects, a quenching effect on sensitization by cinnamaldehyde was shown for (+)-limonene in three of 11 human subjects, and in combination with eugenol, a quenching effect was shown in seven of the same 11 subjects. It has been postulated that this may be due to competitive inhibition at the receptor level (Guin et al., 1984). To confirm this assumption, further studies should follow.

EOs contain complex mixtures of substances that may be harmful and/or protective. Plants use them in order to protect themselves against reactive oxygen species (ROS) produced automatically during the process of photosynthesis. Especially phenolic EO constituents, such as thymol, have antioxidant properties. Such properties of these molecules can mediate reduced toxicity, such as attenuation of phototoxicity, allergenicity or mutagenicity. This is evident *e.g.*, for carvacrol, thymol, and eugenol and their antihepatotoxic effects (Jiménez et al., 1993; Kumaravelu et al., 1995), for 1,8-cineole and its gastro protective effect (Santos et al., 2001), for thymoquinone and its antinephrotoxic action (Badary, 1999) and for linalool and its antimutagenic action (Berić et al., 2008).

The quality of these effects may be considered either antidotal to possible toxicity or simply therapeutic, *e.g.*, the antispasmodic effect of anise oil from *P. anisum* or cumin oil from *Cuminum cyminum* L. of the Apiaceae family (Pourgholami et al., 1999;

Sayyah et al., 2002), the anti-asthmatic action of turmeric oil (*C. longa*), may chang oil from *L. cubeba* (Venugopal and Dhanish, 2018; Smruti, 2021) and the anticarcinogenic action of (+)-limonene and perillic acid in skin cancer (Lluria-Prevatt et al., 2002; Raphael and Kuttan, 2003). Biological properties of a mixture can thus be enhanced or attenuated by its constituents. So, the presence of large amounts of antioxidant, antimutagenic, and anticarcinogenic constituents in EO, which contains low amounts of carcinogens, may render this oil harmless. In that sense, for biological purposes, it is more informative to study the entire oil containing assigned single effective substances, rather than only single components, because the concept of interactions appears to be more meaningful for therapeutic purposes. In addition, other minor components can modulate the activity of the main compounds. (Franzios et al., 1997; Santana-Rios et al., 2001; Hoet et al., 2006).

THERAPEUTIC POTENTIALS OF MOCS IN HUMANS

As mentioned above essential oils consist of a plethora of different secondary metabolites from various metabolic pathways. The biological activity of these complex mixtures has hardly been investigated in its entirety on a molecular level. Nevertheless, the available methods are not designed for such diverse MOCS, their specific multi-activities can currently only be assessed more precisely based on their known individual compounds. A look at the known modes of action of secondary plant constituents may help to provide a more complete picture of EOs.

Interactions With Biomembranes

Biomembranes are barriers of eukaryotic and prokaryotic cells which separate the cells from the environment and compartmentalize specific metabolic entities or cell organelles like mitochondria, chloroplasts etc. They consist of a semi-liquid double layer, which is mainly built up by phospholipids, glycolipids, and cholesterol. Membrane proteins, ionic channels, receptors, transporters, and carbohydrates are also incorporated or attached. The most important tasks of biomembranes comprise the transport of substances, the communication, and the exchange of substances with other cells and tissues (Gennis, 1989; Bondar, 2019). Lipophilic secondary plant compounds like EO constituents can interact with the biomembrane, *e.g.*, by attachment or incorporation. For example, carvacrol, *p*-cymene, thymol and *γ*-terpinene may act as substitutional impurities forming gross perturbation of the lipophilic fraction of the plasma membrane of microorganisms (Cristani et al., 2007). Further studies showed that *β*-caryophyllene and *β*-caryophyllene oxide are able to interact with the phospholipid bilayers (*in vitro* biomembrane model of dimyristoylphosphatidylcholine multilamellar vesicles; Sarpietro et al., 2015). This can lead to altered membrane fluidity and increased permeability. Some plant constituents may also modulate ion channel activity, such as mint oil affecting calcium channels and intestinal smooth muscle cell motility.

Adenosine transport in endothelial cells is also inhibited by some essential oils, which may be associated with spasmolytic and local anesthetic effects (Melzig and Teuscher, 1991).

Disruption or lysis of the biomembrane usually leads to necrotic cell death. This mechanism could be found for some EOs with antibacterial activities (van Wyk, 2015; van Wyk and Wink, 2015, 2017). The first inherent step of most EOs, and thus their ability to interact with multiple targets, is to cross membranes.

Modification of Proteins

Due to their diversity of carbon skeletons in combination with a multitude of functional groups (*e.g.*, aldehyde group, SH group, epoxide group, double bond, triple bond, etc.; **Figure 3**), originating from evolution processes, plant secondary metabolites exhibit diverse chemical structures/variations with different chemical and physiological properties (Polya, 2003; Teuscher and Lindequist, 2010; Wink, 2010; Velu et al., 2018). Several of these functionalities, especially unsaturated carbonyls, may build covalent bonds with proteins, peptides, but also DNA (Wink, 2008; Wink, 2012). Furthermore, aldehydes can form amides or imines with amino groups of proteins, amino acids, or DNA bases. Epoxides react with amino and SH groups of proteins as well as DNA bases. Isothiocyanates bind to amino or SH groups and allicin (from garlic) or exocyclic methylene groups (*e.g.* in sesquiterpene lactones) can bind to SH groups and glutathione (Wink, 2015). The modifications usually target cell proteins, such as enzymes, receptors, transcription factors, ion channels, transport, or cytoskeletal proteins. Thus, the protein conformation may be modified resulting in altered receptor binding affinity, protein-protein recognition, catalytic activity, etc. This also includes proteins involved in diseases, like Creutzfeldt–Jakob disease, Gerstmann–Sträussler syndrome or Alzheimer's disease, and possibly some more, which are unknown to date (Palmer et al., 1991; Karakaya et al., 2019). In addition, reactions between proteins and oxidized polyphenols may decrease allergenicity, which was shown for apple fruits (Siekierzynska et al., 2021). The same protective mechanisms are likely found in other multi-target-actions of natural MOCS, such as EOs.

Also, phenolic compounds from EOs may influence proteins and peptides (**Figure 3**) with their hydroxyl groups by forming hydrogen bonds. Furthermore, phenolic OH groups can dissociate, resulting in phenolate ions under physiological conditions, which easily form ionic bonds to positively charged ammonium groups of amino acids (*e.g.*, lysine, arginine) (Wink, 2005, 2008; Wink, 2012; van Wyk, 2015; van Wyk and Wink, 2015, 2017). If numerous hydrogen and ion bonds are formed with a protein or its functional units, conformation and thus also the functionality of the protein will be modified. If transcription factors are affected, gene regulation is altered as well (Pakalapati et al., 2009; Holtrup et al., 2011; El-Readi et al., 2013).

Interactions With Nucleic Acids

Due to their diverse functionality, plant secondary metabolites can also intercalate or alkylate DNA, which can lead to mutations and even cancer. Wink also described, that important alkylating secondary metabolites are pyrrolizidine alkaloids in the Boraginaceae and some Asteraceae representatives, aristolochic acids in Aristolochiaceae, furanocoumarins in the Apiaceae, and ptaquiloside in the fern *Pteridium aquilinum* (L.) Kuhn (Dennstaeditiaceae) as well as cycasine in Cycadaceae (Wink and Schimmer, 2010; El-Shazly and Wink, 2014; van Wyk, 2015; van Wyk and Wink, 2015, 2017). EOs have also been reported to interact with nucleic acids or associated enzymes of viruses and inhibit their replication, which might offer promising therapeutic opportunities in the treatment of influenza or COVID-19 (Asif et al., 2020; Da Silva et al., 2020; Panikar et al., 2021; Wani et al., 2021).

Antioxidant Properties

Reactive oxygen species (ROS), which inevitably occur in plant cells during photosynthesis, can alter functional proteins, lipids and nucleic acids. ROS can oxidize the DNA base guanosine to 8-oxoguanosine. While guanosine would normally pair with cytosine, 8-oxoguanosine no longer pairs with cytosine but with adenosine. This will lead to mutations. ROS can lead to cell damage in the plant, which protect themselves against oxygen radicals by biosynthesizing antioxidant molecules such as phenolics and terpenoids. Under physiological conditions, the formation of ROS also occurs in human tissues.

In the case of long-term oxidative stress, an overdose of ROS can lead to various health disorders, usually chronic, such as diabetes, metabolic syndrome, cardiovascular disease, and even cancer (due to DNA mutations). Medicinal plants, herbal medicines and products derived from algae, which are rich in polyphenols, often exhibit antioxidant effects in addition to other pharmacological activities and therefore may prevent and help to cure disorders (van Wyk, 2015; van Wyk and Wink, 2015, 2017; Wink, 2022).

As about 22,000 isoprenoids and more than 100,000 of other secondary metabolites are known, the studies carried out so far can only be the beginning to exploit the therapeutic potential of MOCS in general and that of EOs in particular. The multi-component nature of natural extracts like EOs, results in an almost inexhaustible pharmacological toolbox with versatile modes of action (Schreiner et al., 2021). The multi-target sites of action of EOs are due to their nature being mixtures. The mutual physico-chemical interactions with molecular targets but also with the tissues they pass through offer the possibility of a complex effect that cannot be reached with single compounds. This versatility gives hope that EOs and other MOCS might play a central role in combating modern health challenges.

One of these future challenges, *i.e.*, the antibiotic resistance will be discussed here in more detail.

ANTIBIOTIC RESISTANCE AND EOs AS POTENTIAL ANSWERS

Antibiotic resistance is a major and growing problem in health care and livestock farming. Resistance phenomena arising

TABLE 1 | *In vitro* synergistic action between EOs and antibiotics. Methods used: Checkerboard assay (isobologram, fractional inhibitory concentration (FIC) index) or time-kill assay or fold reduction in minimum inhibitory concentration (MIC) or change in inhibition zone in the presence of EO vapor. [Adapted and compiled from Langeveld et al. (2014)].

	Ciprofloxacin	Gentamicin	Tobramycin	Vancomycin	Amikacin	Imipenem	Meropenem	Ampicillin	Cefoperazone	Chloramphenicol	Piperacillin	Tetracycline	Kanamycin	Streptomycin	Neomycin	Ceftiofur	Ceftriaxone	Doxycycline	Florfenicol	Levofloxacin	Lincomycin	Maquindox	Polymyxin	Sarafloxacin	Erythromycin	Oxytetracycline	Norfloxacin	Cefixime	Pristinamycin	Amoxicillin
A. baumannii		8 9 10 3			9 10	9 10	9 10		8	8	8	8																		
B. cereus	1 2	11 1 2 3																										1 2	1 2	
B. subtilis	1 2	11 1 2 3																									5	1 2	1 2	
E. aerogenes										19																				
E. coli	1 2	3 11 12 1 2	3						12	19			11			11	11	11	11	11	11	11	11	11	12	12	5	1 2	1 2	11
Ent. Cloacae	1 2	1 2																										1 2	1 2	
K. pneumonia	3 4 5 6 1 2 7	1 2																										1 2	1 2	
M. luteus	1 2	1 2																										1 2	1 2	
P. aeruginosa	1 2	13 1 2			13					19				13														1 2	1 2	
P. mirabilis	5																													
S. aureus	3 4 5 6 2 7	3 13 11 14 2	3	3 14	13													13									5 17 18	14 2	14 2	
S. epidermidis		15																												
S. marcescens		3 11																												
S. typhimurium													16	16																
Salmonella sp.	1 2	1 2																										1 2	1 2	
V. cholera	1 2	1 2																										1 2	1 2	
Y. enterocolitica		3 11																												

clear synergy (green)	1	Thyme (*Thymus broussonetii*)	5	Rose geranium (*Pelargonium graveolens*)	9	Cinnamon (*Cinnamomum zeylanicum*)	13	*Lippia sidoides*	17	Thyme (*Thymus magnus*)

clear synergy — 1 Thyme (*Thymus broussonetii*)
possible synergy — 2 Thyme (*Thymus maroccanus*)
additivity — 3 Australian tea tree (*Melaleuca alternifolia*)
antagonism — 4 *Mentha piperita*

5 Rose geranium (*Pelargonium graveolens*)
6 Rosemary (*Rosmarinus officinalis*)
7 Thyme (*Thymus vulgaris*)
8 Coriander (*Coriandrum sativum*)

9 Cinnamon (*Cinnamomum zeylanicum*)
10 Lemon (*Citrus limon*)
11 Oregano (*Origanum vulgare*)
12 Peppermint (*Mentha piperita*)

13 *Lippia sidoides*
14 Shiraz oregano (*Zataria multiflora*)
15 Cinnamon/Cassia (*Cinnamomum burmannii*)
16 Lemongrass (*Cymbopogon citratus*)

17 Thyme (*Thymus magnus*)
18 Thyme (*Thymus quinquecostatus*)
19 Curry plant (*Helichrysum italicum*)

TABLE 2 | *In vitro* synergistic action between EO constituents and antibiotics. Methods used: Checkerboard assay (isobologram, fractional inhibitory concentration (FIC) index) or time-kill assay or fold reduction in minimum inhibitory concentration (MIC) or change in inhibition zone in the presence of EO vapor. [Adapted and compiled from Langeveld et al. (2014)].

	Ciprofloxacin	Gentamicin	Vancomycin	Amikacin	Ampicillin	Chloramphenicol	Tetracycline	Streptomycin	Neomycin	Polymyxin	Erythromycin	Oxytetracycline	Norfloxacin	Bacitracin	Nalidixic acid	Nitrofurantoin	Novobiocin	Penicillin	Sulfamethoxazole	Clindamycin	Clarithromycin	Oxacillin	Rifampicin	Sparfloxacin
A.actinomycetemcomitans		6			6																			
C. difficile																				3				
E. aerogenes	4		4	4	4	6	6			6	4		6					6					6	6
		6			6						6		7				7							
					7																			
E. coli	4	8	4	4	2	6	3			6	2	8	6	2	2		2	2					6	6
		6			3		6				3			3			3	2						
					4		9				4			6			6	3						
					6						6			9			9	6						
					6						6							6						
					8						8							8						
					9						9							9						
Ent. cloacae																2		7						
F. nucleatum		6			6																			
K. oxytoca					2											2	2							
					3												3							
					6												6							
					9												9							
M. tuberculosis				4																			4	
																							5	
M. avium				4																	4			4
P. aeruginosa	4	9	4	4	4	6	6		9	6	4		6					6					6	6
		6		9	6						6													
P. intermedia		6			6																			
P. gingivalis		6			6																			
P. vulgaris		6			6	6	6			6	6		6					6					6	6
Methicillin resistant S. aureus													1											
S. aureus	4	9	4	4	2			9			4		9	2				2				4		
				9	3									3				6						
					4									6				7						
					6									9				8						
					9													9						
																		9						
S. typhimurium			6		2	2	2	2		6	2		6	2	2		2	2		2	2		6	6
					3	6	3	3			3			3			3	3		3	3			
					6	6	6	6			6			6			6	6		6	6			
					6	9	6	9			6			9			9	6		9				
					9		9				9							9						
					9		9																	
S. pyogenes											2													
											3													
											6													
											9													
S. derby																2								
S. enteritidis																2								
S. minnesota																2								
S. anginosus		6			6																			
S. criceti		6			6																			
S. gordonii		6			6																			
S. mutans		6			6																			
S. sobrinus		6			6																			
S. ratti		6			6																			
S. sanguinis		6																						

Legend		
clear synergy	1 Bergamottin/ coumarin epoxide	5 *cis*-Cinnamic acid
possible synergy	2 Carvacrol	6 Eugenol
additivity	3 *trans*-Cinnamaldehyde	7 Geraniol
antagonism	4 *trans*-Cinnamic acid	8 Menthol
		9 Thymol

from mutation are common among pathogenic bacteria. The molecular and structural determinants underlying resistance towards the major antibiotic classes are as diverse as nature. Most hitherto identified mutations leading to antibiotic resistances can be categorized into target modification, drug inactivation, and drug transport (efflux). Recent research on the development of resistance also suggests that changes in the metabolic pathway of bacteria, including mutations of the relevant genes, may lead to possible antibiotic resistance (Lopatkin et al., 2021). Since changes in individual proteins are the underlying principle of most of these resistance mechanisms, natural MOCS like EOs offer a great potential for overcoming multidrug-resistant infections through their multi-target properties. This

antimicrobial potential of EOs for human and animal health is an evolutionary side effect due to plant interaction and defense against various pathogens.

Synergistic Actions Between EOs and Antibiotics

Since the extensive use of antibiotics from 1945 onwards, bacteria have increasingly been selected for resistance to single or multiple (multi-resistance) antibiotics. All over the world, people are aware of the increasing ineffectiveness of these antibiotics and are intensively searching for novel active substances and new targets. Therapeutically used natural derived antibiotics are usually produced by fungi and bacteria, but plants have successfully developed multi-component-based strategies to defend themselves against germs for thousands of years. Thus, it is a promising challenge in the future to develop multi-component-based antibiotic strategies adapted from nature, or at least consist of a combination of MOCS and conventional antibiotics. Studies on EOs and their ingredients in combination with known antibiotic drugs show promising interactions (**Tables 1**, **2**). For example, synergism may occur when different compounds simultaneously attack different sites of a bacterial cell (multi-target effect). Alternatively, there may be pharmacokinetic or physicochemical interactions, such as enhancement of solubility or bioavailability. The most commonly reported test method for assessing interactions with antibiotics is the checkerboard assay with calculation of the FIC (fractional inhibitory concentration) index (Hemaiswarya et al., 2008; Wagner and Ulrich-Merzenich, 2009).

Synergistic effects of antibacterial agents in combination with antibiotics on different targets are thought to be most efficient. Also, it has been shown that *in vitro* synergism between EOs or EO ingredients and beta-lactam antibiotics do occur, as EOs often act on cell membranes whereas beta lactams target the cell wall. Oregano oil showed synergistic effects in combination with fluoroquinolones, doxycycline, lincomycin, maquindox or florfenicol against extended-spectrum *β*-lactamase (ESBL)-producing *Escherichia coli* (Si et al., 2008). As described before, MOCS are highly complex mixtures and their effects are based on the interaction of their individual compounds both on a quantitative and qualitative level. If individual ingredients are lacking or are present in an altered ratio, changes in the overall properties of an EO may occur. Therefore, basic research on naturally derived extracts (MOCS), on preparations derived therefrom, and derived pharmaceutical applications is an important basis to understand and apply the mechanisms of action appropriately. Consequently, an exact phytochemical characterization of MOCS is an always indispensable prerequisite. It is interesting to note that synergistic effects through pharmacokinetic and physicochemical actions have also been observed for secondary metabolites that do not possess pharmacological activity themselves. *p*-Cymene is such an ingredient which, in combination with carvacrol, improves its activity against *B. cereus*, presumably by accumulation in the bacterial membrane, thus modifying its structure and barrier function (Ultee et al., 2002).

Further *in vitro* synergism was monitored between oregano oil and doxycycline, florfenicol, or sarafloxacin against ESBL-producing *E. coli* from chickens (Si et al., 2008). Furthermore, oregano oil showed *in vitro* synergistic effects with gentamicin against *B. cereus*, *B. subtilis*, and a strain of *Staphylococcus aureus* (Rosato et al., 2010). In contrast, the combination with gentamicin was less effective (rather additive than synergistic) against *E. coli*, *Acinetobacter baumannii*, and another strain of *S. aureus*; the isobologram method showed some synergism, while the FIC index indicated an additive effect (Rosato et al., 2010). The combination of oregano oil and gentamicin only yielded an additive *in vitro* effect against *Yersinia enterocolitica* (Rosato et al., 2010). The combination of oregano oil with the antibiotics levofloxacin and maquindox against *E. coli* revealed low synergism (FIC index 0.5) (Si et al., 2008). A study on thyme oil showed synergistic *in vitro* effects against *S. aureus* and *Klebsiella pneumoniae* when applied in combination with ciprofloxacin (van Vuuren et al., 2009). The EO of Shiraz thyme (*Zataria multiflora* Boiss.) demonstrated synergistic action with vancomycin against methicillin-sensitive *S. aureus* (MSSA) and 12 clinical methicillin-resistant *S. aureus* (MRSA) isolates, although FIC data for individual strains were not reported (Mahboubi and Bidgoli, 2010). Vancomycin is among the few antibiotics available to treat MRSA infections, and yet resistance has already been reported according to Mahboubi and Bidgoli (2010). The composition of this Shiraz thyme EO (thymol 39%, carvacrol 15% and *p*-cymene 10%) is similar to oregano oils (Burt, 2004; Mahboubi and Bidgoli, 2010) and thus may offer a solution to possibly bypass vancomycin resistances and reduce antibiotic use.

Essential oils from cloves (*S. aromaticum*) and cinnamon (*Cinnamomum verum* J.Presl; Lauraceae) combined with lysozyme amplify the effects of a carbapenem- (imipenem) and an aminoglycoside-antibiotic (gentamicin) against the bacterial pathogens *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The results indicate that the essential oils of both plant species reduce the minimum inhibitory concentrations of gentamicin and imipenem against multi-drug resistant clinical isolates of the two Gram-negative bacterial species and thus significantly increase the antibiotic effects (Sakr et al., 2021).

In addition, Australian tea tree oil (*M. alternifolia*) was studied *in vitro* in combination with aminoglycoside antibiotics. This revealed synergistic effects when treating *E. coli*, *Y. enterocolitica*, *Serratia marcescens*, and *S. aureus* with the EO and the antibiotic gentamicin (Rosato et al., 2010). When applying this combination against *A. baumannii*, *B. subtilis*, and a further strain of *S. aureus*, the FIC index was in the borderline range between additivity and synergism. Furthermore, tea tree oil combined with tobramycin also showed a synergism against *E. coli* and *S. aureus* (D'Arrigo et al., 2010). The mechanism is characterized by a multi-target effect because the aminoglycosides inhibited protein biosynthesis and tea tree oil damaged the cytoplasmic membrane of the bacteria. In contrast, tea tree oil has been shown to exhibit additive/undifferentiated activity *in vitro* with the glycopeptide vancomycin to control a clinical MRSA isolate, and antagonistic activity together with ciprofloxacin (LaPlante, 2007).

An overview of possible *in vitro* interactions of further antibiotics with EOs (**Table 1**) shows that there are still many gaps (empty fields) to be filled in this area of research. The need for research in this direction could be forward-looking. In addition, *in vivo* studies should be performed that investigate the combination of intravenously administered antibiotics with orally administered EOs.

Interrelation Between Individual EOs Constituents and Antibiotics

Most studies on the interaction of EO ingredients and antibiotics have been performed *in vitro* and the underlying mechanisms have not yet been further investigated. However, since antibiotics specifically focus on one target and EO metabolites attack diverse sites of bacterial cells, it can be assumed that multi-target effects are working in most cases. However, a few effects can also be attributed to synergisms between antibiotics and EO constituents (**Table 2**) that target bacterial resistance mechanisms, such as inhibition of efflux pumps (Shahverdi et al., 2007; Lorenzi et al., 2009; Johny et al., 2010), which may also be due to membrane damage and metabolic disruption (Gibbons, 2008).

The EO constituent eugenol was tested *in vitro* in combination with antibiotics from eight different groups against the bacteria *E. coli*, *Enterobacter aerogenes*, *Proteus vulgaris*, *P. aeruginosa* and *S. typhimurium*. Synergistic effects were found among all antibiotics. These were most evident with ampicillin, polymyxin B, norfloxacin, tetracycline, rifampicin, and vancomycin, but synergisms were also detected in combination with penicillin and chloramphenicol (Hemaiswarya and Doble, 2009). Noteworthy, carvacrol and thymol seem to show stronger effects on antibiotic-resistant *S. typhimurium*, *E. coli* and *S. aureus* strains compared to eugenol. The mechanism has been suggested to be increased by antibiotic penetration across permeabilized membranes and/or inhibition of protective enzymes (Palaniappan and Holley, 2010). In fact, even minor differences in the molecular structure of EO constituents can have a significant impact on their ability to synergize with antibiotics. For example, carvacrol and thymol are structural isomers and only differ in the position of their hydroxyl group. While, carvacrol was found to act synergistically against *Klebsiella oxytoca* in combination with ampicillin and nitrofurantoin, thymol was indifferent (Zhang et al., 2011). In this regard, a benzene ring with prop-2-enal side group appears to be less synergistically active than methylethyl- and methyl side groups (Palaniappan and Holley, 2010; Zhang et al., 2011).

The results show that EOs may contain quite effective single compounds. Nevertheless, the efficacy can neither be attributed to these mono-substances alone nor to the quantitatively leading compounds. Rather, the mixture should be assessed in its complex overall composition and the understanding of possible mechanisms of action should be approached with the help of individual compounds. The study results of studies on individual compounds show how precisely adjusted the compounds in their respective composition may act and justify the assumed multi-target mechanisms of action. Of course, it will be necessary to adapt existing methods for the investigation of complex mixtures or to develop completely new experimental procedures to meet the requirements of complexity (Ronzheimer et al., 2022; Schreiner et al., 2022). Our current scientific techniques seem to have reached a limit.

CONCLUDING ASPECTS FOR FUTURE RESEARCH

The long-term use of plant derived EOs, but also other naturally derived MOCS, does not come by chance. As the history of our medicine impressively demonstrates, medicinal plants, extracts, and formulations therefrom, are the basis of many pharmaceutical achievements of modern times. It seems to be true that "There's an herb for every ailment", or better that "there is a MOCS or single compound from nature" for every ailment.

With the help of new technologies, the extraction and processing of herbal preparations and the active ingredients derived therefrom have been improved and several single compounds have been discovered as leads. Whereas the search for single compounds from nature is still ongoing, the research on MOCS has stalled due to lacking experimental approaches limiting the look on the entire repertoire of the toolbox.

MOCS, using EOs as an example, impressively demonstrate how diverse and valuable complex mixtures are. With the help of their uncountable molecular structures and functional groups, they possess mechanisms of action, both known and unknown to date, whose chemical properties can complement and potentiate each other in the form of synergisms, antagonistically neutralize toxic effects or additively contribute to a stable basic structure.

In the case of EOs, the individual compounds not only seem to interact with each other, they also interact with their environment and can thus influence the activity or conformation of molecular targets, often proteins. At the same time, they can bind to receptors and trigger physiological and psychological reactions. These biological activities are reflected in the pharmacological and therapeutic effect of EOs as MOCS. In addition, EOs as natural mixtures can achieve a characteristic multifaceted effect, which, compared to an isolated compound, has not only one site of action, but multi-targets. MOCS thus do not only use one target, but likely the entire toolbox. These multi-target properties of EOs could for example positively influence the successful treatment of infections due to (multi-)resistant bacteria and thus help save lives. Studies have shown that natural EOs in combination with antibiotics are quite capable of enhancing the antibiotic effect. This could minimize or prevent the careless use of antibiotics and the associated selection of resistant bacteria. When complex EOs are used against pathogenic bacteria, the bacterium is attacked at many different sites simultaneously, which means that it usually cannot develop a targeted resistance mechanism and can thus be treated successfully. Homolog mechanisms have likely long been used in the plant kingdom for resistance to pathogens and have evolved steadily in evolutionary terms.

It is worthwhile to broaden our view and to integrate data from studies on the effectiveness of single, isolated compounds as individual pieces of the puzzle into the overall picture of complex effectiveness. Humans themselves and the nature around them consist of myriad of substances and a complete reduction to a few compounds does not seem to do justice to the real picture. To date, it has not been fully understood how drugs interact and react with endogenous enzymes, the variable human microbiome, foods, feeds, chronobiologic factors, ethnic-, age- and gender-specific characteristics, or even with other drugs. Much more research is needed in this area, and the complexity of possible interactions seemingly pushes our current methods to their limits. Therefore, new methods and techniques need to be developed and existing ones improved. The goal of helping people recover in the best possible way should be at the forefront. The benefits of phytotherapy using EOs and other MOCS, which have been approved for thousands of years, should not be forgotten, or underestimated. There is a great chance not only for phytochemical and pharmacological achievements, but also for the development of new methods for the evaluation of complex natural mixtures in connection with biological processes, for future, sustainable and affordable healthy therapeutic strategies.

AUTHOR CONTRIBUTIONS

Conceptualization, preparation and editing: MB, RD, CG, JH, DK, MK, UL, MM, GM, HS, RS, MS, FS, MW. All authors have read and agreed to the published version of the manuscript.

FUNDING

REFERENCES

Agarwal, V. (2018). Complementary and Alternative Medicine Provider Knowledge Discourse on Holistic Health. *Front. Commun.* 3. doi:10.3389/fcomm.2018.00015

Agatonovic-Kustrin, S., and Morton, D. W. (2018). "Essential Oils and Cognitive Performance," in *Front. Nat. Produc..* Editor Atta-ur-Rahman (Sharjah: Bentham Science Publishers), 91–118. doi:10.2174/9781681087252118040005

Ahmad, A., Elisha, I. L., van Vuuren, S., and Viljoen, A. (2021). Volatile Phenolics: A Comprehensive Review of the Anti-infective Properties of an Important Class of Essential Oil Constituents. *Phytochemistry* 190, 112864. doi:10.1016/j.phytochem.2021.112864

Alshehri, F. A. (2018). The Use of Mouthwash Containing Essential Oils (LISTERINE®) to Improve Oral Health: A Systematic Review. *Saudi Dent. J.* 30, 2–6. doi:10.1016/j.sdentj.2017.12.004

Angelucci, F. L., Silva, V. V., Dal Pizzol, C., Spir, L. G., Praes, C. E., and Maibach, H. (2014). Physiological Effect of Olfactory Stimuli Inhalation in Humans: an Overview. *Int. J. Cosmet. Sci.* 36, 117–123. doi:10.1111/ics.12096

Angioni, A., Barra, A., Coroneo, V., Dessi, S., and Cabras, P. (2006). Chemical Composition, Seasonal Variability, and Antifungal Activity of *Lavandula Stoechas* L. Ssp. *Stoechas* Essential Oils from Stem/leaves and Flowers. *J. Agric. Food Chem.* 54, 4364–4370. doi:10.1021/jf0603329

Armstrong, J. S. (2006). Mitochondrial Membrane Permeabilization: The Sine Qua Non for Cell Death. *BioEssays* 28, 253–260. doi:10.1002/bies.20370

Asadollahi-Baboli, M., and Aghakhani, A. (2015). Headspace Adsorptive Microextraction Analysis of Oregano Fragrance Using Polyaniline-Nylon-6 Nanocomposite, GC-MS, and Multivariate Curve Resolution. *Int. J. Food Prop.* 18, 1613–1623. doi:10.1080/10942912.2014.923909

Asif, M., Saleem, M., Saadullah, M., Yaseen, H. S., and Al Zarzour, R. (2020). COVID-19 and Therapy with Essential Oils Having Antiviral, Anti-inflammatory, and Immunomodulatory Properties. *Inflammopharmacology* 28, 1153–1161. doi:10.1007/s10787-020-00744-0

Atkinson, A. J. (2007). "Drug Absorption and Bioavailability,". *Principles of Clinical Pharmacology*. Editors A. J. AtkinsonJR., D. R. Abernethy, C. E. Daniels, R. Dedrick, and S. P. Markey (Burlington: Elsevier Science), 37–49. doi:10.1016/b978-012369417-1/50044-4

Averbeck, D., and Averbeck, S. (1998). DNA Photodamage, Repair, Gene Induction and Genotoxicity Following Exposures to 254 Nm UV and 8-methoxypsoralen Plus UVA in a Eukaryotic Cell System. *Photochem. Photobiol.* 68, 289–295. doi:10.1111/j.1751-1097.1998.tb09683.x

Averbeck, D., Averbeck, S., Dubertret, L., Young, A. R., and Morlière, P. (1990). Genotoxicity of Bergapten and Bergamot Oil in *Saccharomyces cerevisiae*. *J. Photochem Photobiol. B* 7, 209–229. doi:10.1016/1011-1344(90)85158-s

Ayçı, F., Aydınlı, M., Bozdemir, Ö. A., and Tutaş, M. (2005). Gas Chromatographic Investigation of Rose Concrete, Absolute and Solid Residue. *Flavour Fragr. J.* 20, 481–486. doi:10.1002/ffj.1487

Aziz, Z. A. A., Ahmad, A., Setapar, S. H. M., Karakucuk, A., Azim, M. M., Lokhat, D., et al. (2018). Essential Oils: Extraction Techniques, Pharmaceutical and Therapeutic Potential - A Review. *Curr. Drug Metab.* 19, 1100–1110. doi:10.2174/1389200219666180723144850

Bach, A., Maneja, R., Zaldo-Aubanell, Q., Romanillos, T., Llusià, J., Eustaquio, A., et al. (2021). Human Absorption of Monoterpenes after a 2-h Forest Exposure: A Field Experiment in a Mediterranean Holm Oak Forest. *J. Pharm. Biomed. Anal.* 200, 114080. doi:10.1016/j.jpba.2021.114080

Badary, O. A. (1999). Thymoquinone Attenuates Ifosfamide-Induced Fanconi Syndrome in Rats and Enhances its Antitumor Activity in Mice. *J. Ethnopharmacol.* 67, 135–142. doi:10.1016/S0378-8741(98)00242-6

Bakkali, F., Averbeck, S., Averbeck, D., and Idaomar, M. (2008). Biological Effects of Essential Oils-Aa Review. *Food Chem. Toxicol.* 46, 446–475. doi:10.1016/j.fct.2007.09.106

Bakkali, F., Averbeck, S., Averbeck, D., Zhiri, A., and Idaomar, M. (2005). Cytotoxicity and Gene Induction by Some Essential Oils in the Yeast *Saccharomyces cerevisiae*. *Mutat. Res.* 585, 1–13. doi:10.1016/j.mrgentox.2005.03.013

Baldinger, P., Höflich, A. S., Mitterhauser, M., Hahn, A., Rami-Mark, C., Spies, M., et al. (2014). Effects of Silexan on the serotonin-1A Receptor and Microstructure of the Human Brain: a Randomized, Placebo-Controlled, Double-Blind, Cross-Over Study with Molecular and Structural Neuroimaging. *Int. J. Neuropsychopharmacol.* 18, 1–9. doi:10.1093/ijnp/pyu063

Barnes, J. (2007). *Herbal Medicines*. London and Chicago: Pharmaceutical Press. 9780853696230.

Beckley-Kartey, S. A., Hotchkiss, S. A., and Capel, M. (1997). Comparative *In Vitro* Skin Absorption and Metabolism of Coumarin (1,2-benzopyrone) in Human, Rat, and Mouse. *Toxicol. Appl. Pharmacol.* 145, 34–42. doi:10.1006/taap.1997.8154

Beigi, M., Torki-Harchegani, M., and Ghasemi Pirbalouti, A. (2018). Quantity and Chemical Composition of Essential Oil of Peppermint (Mentha × Piperita L.) Leaves under Different Drying Methods. *Int. J. Food Prop.* 21, 267–276. doi:10.1080/10942912.2018.1453839

Bento, M., Ouwehand, A., Tiihonen, K., Lahtinen, S., Nurminen, P., Saarinen, M., et al. (2013). Essential Oils and Their Use in Animal Feeds for Monogastric

Animals – Effects on Feed Quality, Gut Microbiota, Growth Performance and Food Safety: a Review. *Veterinarni Med.* 58, 449–458. doi:10.17221/7029-VETMED

Beri, K. (2018). Perspective: Stabilizing the Microbiome Skin-Gut-Brain axis with Natural Plant Botanical Ingredients in Cosmetics. *Cosmetics* 5, 37. doi:10.3390/cosmetics5020037

Berić, T., Nikolić, B., Stanojević, J., Vuković-Gacić, B., and Knezević-Vukcević, J. (2008). Protective Effect of Basil (*Ocimum Basilicum* L.) against Oxidative DNA Damage and Mutagenesis. *Food Chem. Toxicol.* 46, 724–732. doi:10.1016/j.fct.2007.09.102

Bertea, C. M., Azzolin, C. M., Bossi, S., Doglia, G., and Maffei, M. E. (2005). Identification of an EcoRI Restriction Site for a Rapid and Precise Determination of Beta-asarone-free Acorus calamus Cytotypes. *Phytochemistry* 66, 507–514. doi:10.1016/j.phytochem.2005.01.007

Bhavaniramya, S., Vishnupriya, S., Al-Aboody, M. S., Vijayakumar, R., and Baskaran, D. (2019). Role of Essential Oils in Food Safety: Antimicrobial and Antioxidant Applications. *Grain Oil Sci. Technol.* 2, 49–55. doi:10.1016/j.gaost.2019.03.001

Bhide, S. V., Zariwala, M. B., Amonkar, A. J., and Azuine, M. A. (1991). Chemopreventive Efficacy of a Betel Leaf Extract against Benzo[a]pyrene-Induced Forestomach Tumors in Mice. *J. Ethnopharmacol.* 34, 207–213. doi:10.1016/0378-8741(91)90039-G

Białoń, M., Krzyśko-Łupicka, T., Nowakowska-Bogdan, E., and Wieczorek, P. P. (2019). Chemical Composition of Two Different Lavender Essential Oils and Their Effect on Facial Skin Microbiota. *Molecules* 24. doi:10.3390/molecules24183270

Bitterling, H., Lorenz, P., Vetter, W., Kammerer, D. R., and Stintzing, F. C. (2022a). Photo-protective Effects of Selected Furocoumarins on β-pinene, R-(+)-limonene and γ-terpinene upon UV-A Irradiation. *J. Photochem. Photobiol. A Chem.* 424, 113623. doi:10.1016/j.jphotochem.2021.113623

Bitterling, H., Mailänder, L., Vetter, W., Kammerer, D. R., and Stintzing, F. C. (2022b). Photo-protective Effects of Furocoumarins on Terpenes in Lime, Lemon and Bergamot Essential Oils upon UV Light Irradiation. *Eur. Food Res. Technol.* 248, 1049–1057. doi:10.1007/s00217-021-03945-1

Blackwell, A. L. (1991). Tea Tree Oil and Anaerobic (Bacterial) Vaginosis. *Lancet* 337, 300. doi:10.1016/0140-6736(91)90910-H

Bondar, A. N. (2019). Introduction: Biomembrane Structure, Dynamics, and Reactions. *Chem. Rev.* 119, 5535–5536. doi:10.1021/acs.chemrev.9b00093

Bowman, M. C., Oller, W. L., Nony, C. R., Rowland, K. L., and Billedeau, S. M. (1982). Metabolism and Distribution of Two 14C-Benzidine-Congener-Based Dyes in Rats as Determined by GC, HPLC, and Radioassays. *J. Anal. Toxicol.* 6, 164–174. doi:10.1093/jat/6.4.164

Breuninger, H., Hildmann, A., and Hildmann, H. (1970). Zur nasalen Anwendung ätherischer Öle im Säuglings- und Kleinkindesalter. *Int. Z. Vitaminforsch.* 40, 800–804.

Brown, D. J. (1985). A Method for Determining the Excretion of Volatile Substances through Skin. *Methods Find. Exp. Clin. Pharmacol.* 7, 269–274.

Buchbauer, G., Jirovetz, L., Jäger, W., Dietrich, H., and Plank, C. (1991). Aromatherapy: Evidence for Sedative Effects of the Essential Oil of Lavender after Inhalation. *Z Naturforsch C J. Biosci.* 46, 1067–1072. doi:10.1515/znc-1991-11-1223

Buck, P. (2004). Skin Barrier Function: Effect of Age, Race and Inflammatory Disease. *Int. J. Aromather.* 14, 70–76. doi:10.1016/j.ijat.2004.04.005

Bunse, M., Mailänder, L. K., Lorenz, P., Stintzing, F. C., and Kammerer, D. R. (2022). Evaluation of *Geum Urbanum* L. Extracts with Respect to Their Antimicrobial Potential. *Chem. Biodivers.* 19, e202100850. doi:10.1002/cbdv.202100850

Burt, S. (2004). Essential Oils: Their Antibacterial Properties and Potential Applications in Foods-Aa Review. *Int. J. Food. Microbiol.* 94, 223–253. doi:10.1016/j.ijfoodmicro.2004.03.022

Caesar, L. K., and Cech, N. B. (2019). Synergy and Antagonism in Natural Product Extracts: when 1 + 1 Does Not Equal 2. *Nat. Prod. Rep.* 36, 869–888. doi:10.1039/c9np00011a

Caissard, J.-C., Joly, C., Bergougnoux, V., Hugueney, P., Mauriat, M., and Baudino, S. (2004). Secretion Mechanisms of Volatile Organic Compounds in Specialized Cells of Aromatic Plants. *Recent Res. Dev. Cell. Biol.* 2, 1–15.

Carson, C. F., Mee, B. J., and Riley, T. V. (2002). Mechanism of Action of *Melaleuca Alternifolia* (Tea Tree) Oil on *Staphylococcus aureus* Determined by Time-Kill, Lysis, Leakage, and Salt Tolerance Assays and Electron Microscopy. *Antimicrob. Agents Chemother.* 46, 1914–1920. doi:10.1128/AAC.46.6.1914-1920.2002

Chacko, I. A., Ghate, V. M., Dsouza, L., and Lewis, S. A. (2020). Lipid Vesicles: A Versatile Drug Delivery Platform for Dermal and Transdermal Applications. *Colloids Surf. B Biointerfaces* 195, 111262. doi:10.1016/j.colsurfb.2020.111262

Chandharakool, S., Koomhin, P., Sinlapasorn, J., Suanjan, S., Phungsai, J., Suttipromma, N., et al. (2020). Effects of Tangerine Essential Oil on Brain Waves, Moods, and Sleep Onset Latency. *Molecules* 25. doi:10.3390/molecules25204865

Chemat, F., Vian, M. A., and Cravotto, G. (2012). Green Extraction of Natural Products: Concept and Principles. *Int. J. Mol. Sci.* 13, 8615–8627. doi:10.3390/ijms13078615

Chen, W., Vermaak, I., and Viljoen, A. (2013). Camphor--a Fumigant during the Black Death and a Coveted Fragrant Wood in Ancient Egypt and Babylon--a Review. *Molecules* 18, 5434–5454. doi:10.3390/molecules18055434

Chidgey, M. A., and Caldwell, J. (1986). Studies on Benzyl Acetate. I. Effect of Dose Size and Vehicle on the Plasma Pharmacokinetics and Metabolism of [methylene-14C]benzyl Acetate in the Rat. *Food Chem. Toxicol.* 24, 1257–1265. doi:10.1016/0278-6915(86)90056-6

Choi, Y. H., and Verpoorte, R. (2019). Green Solvents for the Extraction of Bioactive Compounds from Natural Products Using Ionic Liquids and Deep Eutectic Solvents. *Curr. Opin. Food Sci.* 26, 87–93. doi:10.1016/j.cofs.2019.04.003

Chou, T. C. (2006). Theoretical Basis, Experimental Design, and Computerized Simulation of Synergism and Antagonism in Drug Combination Studies. *Pharmacol. Rev.* 58, 621–681. doi:10.1124/pr.58.3.10

Choudhary, D., and Kale, R. K. (2002). Antioxidant and Non-toxic Properties of *Piper Betle* Leaf Extract: *In Vitro* and *In Vivo* Studies. *Phytother. Res.* 16, 461–466. doi:10.1002/ptr.1015

Clark, D., Edwards, E., Murray, P., and Langevin, H. (2021). Implementation Science Methodologies for Complementary and Integrative Health Research. *J. Altern. Complement. Med.* 27, S7–S13. doi:10.1089/acm.2020.0446

Conway, B. R., and Ghori, M. U. (2022). "Controlled Drug Delivery via the Nasal Route," in *Fundamentals of Drug Delivery*. Editors H. A. E. Benson, M. S. Roberts, A. C. Williams, and X. Liang (John Wiley & Sons Incorporated), 393–432.

Cristani, M., D'Arrigo, M., Mandalari, G., Castelli, F., Sarpietro, M. G., Micieli, D., et al. (2007). Interaction of Four Monoterpenes Contained in Essential Oils with Model Membranes: Implications for Their Antibacterial Activity. *J. Agric. Food Chem.* 55, 6300–6308. doi:10.1021/jf070094x

Cross, S. E., Megwa, S. A., Benson, H. A., and Roberts, M. S. (1999). Self Promotion of Deep Tissue Penetration and Distribution of Methylsalicylate after Topical Application. *Pharm. Res.* 16, 427–433. doi:10.1023/A:1018834021066

Cuba, R. (2001). Toxicity Myths Essential Oils and Their Carcinogenic Potential. *Int. J. Aromather.* 11, 76–83. doi:10.1016/S0962-4562(01)80021-7

D'Arrigo, M., Ginestra, G., Mandalari, G., Furneri, P. M., and Bisignano, G. (2010). Synergism and Postantibiotic Effect of Tobramycin and *Melaleuca Alternifolia* (Tea Tree) Oil against *Staphylococcus aureus* and *Escherichia coli*. *Phytomedicine* 17, 317–322. doi:10.1016/j.phymed.2009.07.008

Dąbrowska, A. K., Spano, F., Derler, S., Adlhart, C., Spencer, N. D., and Rossi, R. M. (2018). The Relationship between Skin Function, Barrier Properties, and Body-dependent Factors. *Skin. Res. Technol.* 24, 165–174. doi:10.1111/srt.12424

Dajic Stevanovic, Z., Sieniawska, E., Glowniak, K., Obradovic, N., and Pajic-Lijakovic, I. (2020). Natural Macromolecules as Carriers for Essential Oils: From Extraction to Biomedical Application. *Front. Bioeng. Biotechnol.* 8, 563. doi:10.3389/fbioe.2020.00563

Davison, C., Zimmerman, E. F., and Smith, P. K. (1961). On the Metabolism and Toxicity of Methyl Salicylate. *J. Pharmacol. Exp. Ther.* 132, 207–211.

De Flora, S., and Ramel, C. (1988). Mechanisms of Inhibitors of Mutagenesis and Carcinogenesis. Classification and Overview. *Mutat. Res.* 202, 285–306. doi:10.1016/0027-5107(88)90193-5

Di Pasqua, R., Hoskins, N., Betts, G., and Mauriello, G. (2006). Changes in Membrane Fatty Acids Composition of Microbial Cells Induced by Addiction of Thymol, Carvacrol, Limonene, Cinnamaldehyde, and Eugenol

in the Growing Media. *J. Agric. Food Chem.* 54, 2745–2749. doi:10.1021/jf052722l

Dijoux, N., Guingand, Y., Bourgeois, C., Durand, S., Fromageot, C., Combe, C., et al. (2006). Assessment of the Phototoxic Hazard of Some Essential Oils Using Modified 3T3 Neutral Red Uptake Assay. *Toxicol. Vitro* 20, 480–489. doi:10.1016/j.tiv.2005.08.018

Do, T. K. T., Hadji-Minaglou, F., Antoniotti, S., and Fernandez, X. (2015). Authenticity of Essential Oils. *TrAC Trends Anal. Chem.* 66, 146–157. doi:10.1016/j.trac.2014.10.007

Dobreva, K. z., and Dimov, M. D. (2021). Study of the Changes in the Chemical Composition of Bulgarian Dill Essential Oils. *IOP Conf. Ser. Mat. Sci. Eng.* 1031, 012108. doi:10.1088/1757-899X/1031/1/012108

Dubey, V. S., Bhalla, R., and Luthra, R. (2003). An Overview of the Non-mevalonate Pathway for Terpenoid Biosynthesis in Plants. *J. Biosci.* 28, 637–646. doi:10.1007/bf02703339

Dudareva, N., Negre, F., Nagegowda, D. A., and Orlova, I. (2006). Plant Volatiles: Recent Advances and Future Perspectives. *Crit. Rev. Plant Sci.* 25, 417–440. doi:10.1080/07352680600899973

Dufault, R. J., Hassell, R., Rushing, J. W., McCutcheon, G., Shepard, M., and Keinath, A. (2001). Revival of Herbalism and its Roots in Medicine. *J. Agromedicine* 7, 21–29. doi:10.1300/J096v07n02_03

Dutton, G. J. (2019). *Glucuronidation of Drugs and Other Compounds.* Chapman and Hall/CRC. 9780429264177.

Edris, A. E. (2007). Pharmaceutical and Therapeutic Potentials of Essential Oils and Their Individual Volatile Constituents: A Review. *Phytother. Res.* 21, 308–323. doi:10.1002/ptr.2072

El-Readi, M. Z., Eid, S., Ashour, M. L., Tahrani, A., and Wink, M. (2013). Modulation of Multidrug Resistance in Cancer Cells by Chelidonine and *Chelidonium Majus* Alkaloids. *Phytomedicine* 20, 282–294. doi:10.1016/j.phymed.2012.11.005

El-Shazly, A., and Wink, M. (2014). Diversity of Pyrrolizidine Alkaloids in the Boraginaceae Structures, Distribution, and Biological Properties. *Diversity* 6, 188–282. doi:10.3390/d6020188

Elpa, D. P., Chiu, H. Y., Wu, S. P., and Urban, P. L. (2021). Skin Metabolomics. *Trends Endocrinol. Metab.* 32, 66–75. doi:10.1016/j.tem.2020.11.009

Elshafie, H. S., and Camele, I. (2016). "Investigating the Effects of Plant Essential Oils on Post-Harvest Fruit Decay," in *Fungal Pathogenicity*. Editor S. Sultan (London: IntechOpen). doi:10.5772/62568

Erşan, S., Güçlü Üstündağ, Ö., Carle, R., and Schweiggert, R. M. (2018). Subcritical Water Extraction of Phenolic and Antioxidant Constituents from Pistachio (Pistacia Vera L.) Hulls. *Food Chem.* 253, 46–54. doi:10.1016/j.foodchem.2018.01.116

Essential oils (2022). *Substance-Identification.* https://echa.europa.eu/de/support/substance-identification/sector-specific-support-for-substance-identification/essential-oils (Accessed April 14, 2022).

European Medicines Agency (2014). *Assessment Report on Eucalyptus Globulus Labill., Eucalyptus Polybractea R.T. Baker And/or Eucalyptus Smithii R.T. Baker, Aetheroleum.* Available at: https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-eucalytus-globulus-labill-eucalyptus-polybractea-rt-baker/eucalyptus-smithii-rt-baker-aetheroleum_en.pdf (Accessed May 27, 2022).

Fahelbum, I. M., and James, S. P. (1977). The Absorption and Metabolism of Methyl Cinnamate. *Toxicology* 7, 123–132. doi:10.1016/0300-483X(77)90044-0

Fakhari, A. R., Salehi, P., Heydari, R., Ebrahimi, S. N., and Haddad, P. R. (2005). Hydrodistillation-headspace Solvent Microextraction, a New Method for Analysis of the Essential Oil Components of Lavandula Angustifolia Mill. *J. Chromatogr. A* 1098, 14–18. doi:10.1016/j.chroma.2005.08.054

Falk, A. A., Hagberg, M. T., Löf, A. E., Wigaeus-HjelmE M Zhiping, E. M., and Wang, Z. P. (1990). Uptake, Distribution and Elimination of Alpha-Pinene in Man after Exposure by Inhalation. *Scand. J. Work Environ. Health* 16, 372–378. doi:10.5271/sjweh.1771

Falk-Filipsson, A., Löf, A., Hagberg, M., Hjelm, E. W., and Wang, Z. (1993). D-Limonene Exposure to Humans by Inhalation: Uptake, Distribution, Elimination, and Effects on the Pulmonary Function. *J. Toxicol. Environ. Health* 38, 77–88. doi:10.1080/15287399309531702

Ferhat, M. A., Meklati, B. Y., and Chemat, F. (2007). Comparison of Different Isolation Methods of Essential Oil fromCitrus Fruits: Cold Pressing, Hydrodistillation and Microwave 'dry' Distillation. *Flavour Fragr. J.* 22, 494–504. doi:10.1002/ffj.1829

Ferreira, T. S., Moreira, C. Z., Cária, N. Z., Victoriano, G., Silva Jr, W. F., Jr, and Magalhães, J. C. (2014). Phytotherapy: an Introduction to its History, Use and Application. *Rev. Bras. Plantas Med.* 16, 290–298. doi:10.1590/S1516-05722014000200019

Filipović, G., Stevanović, M. D., Stojanović-Radić, Z., Obradović, R., Randjelović, P. J., and Radulović, N. S. (2020). Choosing the Right Essential Oil for a Mouthwash: Chemical, Antimicrobial and Cytotoxic Studies. *Chem. Biodivers.* 17, e2000748. doi:10.1002/cbdv.202000748

Firestein, S. (2001). How the Olfactory System Makes Sense of Scents. *Nature* 413, 211–218. doi:10.1038/35093026

Fischman, S. L., Aguirre, A., and Charles, C. H. (2004). Use of Essential Oil-Containing Mouthrinses by Xerostomic Individuals: Determination of Potential for Oral Mucosal Irritation. *Am. J. Dent.* 17, 23–26.

Franzios, G., Mirotsou, M., Hatziapostolou, E., Kral, J., Scouras, Z. G., and Mavragani-Tsipidou, P. (1997). Insecticidal and Genotoxic Activities of Mint Essential Oils. *J. Agric. Food Chem.* 45, 2690–2694. doi:10.1021/jf960685f

Freitas, I. R., and Cattelan, M. G. (2018). "Antimicrobial and Antioxidant Properties of Essential Oils in Food Systems-An Overview," in *Microbial Contamination and Food Degradation: A Volume in Handbook of Food Bioengineering.* Editors A. M. Holban and A. M. Grumezescu (Academic Press), 443–470. doi:10.1016/b978-0-12-811515-2.00015-9

Fürst, R., and Zündorf, I. (2015). Evidence-based Phytotherapy in Europe: Where Do We Stand? *Planta Med.* 81, 962–967. doi:10.1055/s-0035-1545948

Gao, S., and Singh, J. (1998). *In Vitro* percutaneous Absorption Enhancement of a Lipophilic Drug Tamoxifen by Terpenes. *J. Control. Release* 51, 193–199. doi:10.1016/S0168-3659(97)00168-5

Gœra, J., and Brud, W. (1983). Progress in Synthesis of Sensory Important Trace Components of Essential Oils and Natural Flavours. *Nahrung* 27, 413–428. doi:10.1002/food.19830270509

Gennis, R. B. (1989). *Biomembranes: Molecular Structure and Function.* New York, NY: Springer. 9781475720655.

Gibbons, S. (2008). Phytochemicals for Bacterial Resistance-Sstrengths, Weaknesses and Opportunities. *Planta Med.* 74, 594–602. doi:10.1055/s-2008-1074518

Gibbs, H. D. (1908). Methylsalicylate. The analytical separation and determination of salicylic acid and methylsalicylate, and the hydrolysis of the ester. *J. Am. Chem. Soc.* 30, 1465–1470. doi:10.1021/ja01951a022

Gomes-Carneiro, M. R., Dias, D. M., De-Oliveira, A. C., and Paumgartten, F. J. (2005). Evaluation of mutagenic and antimutagenic activities of alpha-bisabol in the Salmonella/microsome assay. *Mutat. Res.* 585, 105–112. doi:10.1016/j.mrgentox.2005.04.007

Gomes-Carneiro, M. R., Felzenszwalb, I., and Paumgartten, F. J. (1998). Mutagenicity testing (+/-)-camphor, 1,8-cineole, citral, citronellal, (-)-menthol and terpineol with the Salmonella/microsome assay. *Mutat. Res.* 416, 129–136. doi:10.1016/s1383-5718(98)00077-1

Gorlenko, C. L., Kiselev, H. Y., Budanova, E. V., Zamyatnin, A. A., and Ikryannikova, L. N. (2020). Plant secondary metabolites in the battle of drugs and drug-resistant bacteria: New heroes or worse clones of antibiotics? *Antibiot. (Basel)* 9. doi:10.3390/antibiotics9040170

Grisk, A., and Fischer, W. (1969). Zur pulmonalen Ausscheidung von Cineol, Menthol und Thymol bei Ratten nach rektaler Applikation. *Z. Arztl. Fortbild. (Jena)* 63, 233–236.

Gropper, S. S., and Smith, J. L. (2012). *Advanced Nutrition and Human Metabolism.* Australia: Cengage Learning. 9781285401133.

Guin, J. D., Meyer, B. N., Drake, R. D., and Haffley, P. (1984). The effect of quenching agents on contact urticaria caused by cinnamic aldehyde. *J. Am. Acad. Dermatol.* 10, 45–51. doi:10.1016/S0190-9622(84)80040-7

Han, X., Beaumont, C., and Stevens, N. (2017). Chemical composition analysis and *In Vitro* biological activities of ten essential oils in human skin cells. *Biochim. Open* 5, 1–7. doi:10.1016/j.biopen.2017.04.001

Hartman, P. E., and Shankel, D. M. (1990). Antimutagens and anticarcinogens: A survey of putative interceptor molecules. *Environ. Mol. Mutagen.* 15, 145–182. doi:10.1002/em.2850150305

Hasan, A., and Farooqui, H. (2021). A review on role of essential oil as penetration enhancer in transdermal drug delivery system. *Syst. Rev. Pharm.* 12, 439–444.

Hasheminejad, G., and Caldwell, J. (1994). Genotoxicity of the alkenylbenzenes alpha- and beta-asarone, myristicin and elimicin as determined by the UDS assay in cultured rat hepatocytes. *Food Chem. Toxicol.* 32, 223–231. doi:10.1016/0278-6915(94)90194-5

Heaney, L. M., Ruszkiewicz, D. M., Arthur, K. L., Hadjithekli, A., Aldcroft, C., Lindley, M. R., et al. (2016). Real-time monitoring of exhaled volatiles using atmospheric pressure chemical ionization on a compact mass spectrometer. *Bioanalysis* 8, 1325–1336. doi:10.4155/bio-2016-0045

Hemaiswarya, S., and Doble, M. (2009). Synergistic interaction of eugenol with antibiotics against Gram negative bacteria. *Phytomedicine* 16, 997–1005. doi:10.1016/j.phymed.2009.04.006

Hemaiswarya, S., Kruthiventi, A. K., and Doble, M. (2008). Synergism between natural products and antibiotics against infectious diseases. *Phytomedicine* 15, 639–652. doi:10.1016/j.phymed.2008.06.008

Herman, A., and Herman, A. P. (2015). Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: A review. *J. Pharm. Pharmacol.* 67, 473–485. doi:10.1111/jphp.12334

Hiki, N., Kaminishi, M., Hasunuma, T., Nakamura, M., Nomura, S., Yahagi, N., et al. (2011). A phase I study evaluating tolerability, pharmacokinetics, and preliminary efficacy of L-menthol in upper gastrointestinal endoscopy. *Clin. Pharmacol. Ther.* 90, 221–228. doi:10.1038/clpt.2011.110

Hoet, S., Stévigny, C., Hérent, M. F., and Quetin-Leclercq, J. (2006). Antitrypanosomal compounds from the leaf essential oil of *Strychnos spinosa*. *Planta Med.* 72, 480–482. doi:10.1055/s-2005-916255

Holopainen, J. K. (2004). Multiple functions of inducible plant volatiles. *Trends Plant Sci.* 9, 529–533. doi:10.1016/j.tplants.2004.09.006

Holtrup, F., Bauer, A., Fellenberg, K., Hilger, R. A., Wink, M., and Hoheisel, J. D. (2011). Microarray analysis of nemorosone-induced cytotoxic effects on pancreatic cancer cells reveals activation of the unfolded protein response (UPR). *Br. J. Pharmacol.* 162, 1045–1059. doi:10.1111/j.1476-5381.2010.01125.x

Holzinger, M. (2013). *Paracelsus: Das Buch Paragranum: Septem Defensiones*. Berlin: Holzinger. 97814848049662.

Hoskins, J. A. (1984). The occurrence, metabolism and toxicity of cinnamic acid and related compounds. *J. Appl. Toxicol.* 4, 283–292. doi:10.1002/jat.2550040602

Hurst, S., Loi, C. M., Brodfuehrer, J., and El-Kattan, A. (2007). Impact of physiological, physicochemical and biopharmaceutical factors in absorption and metabolism mechanisms on the drug oral bioavailability of rats and humans. *Expert Opin. Drug Metab. Toxicol.* 3, 469–489. doi:10.1517/17425255.3.4.46910.1517/17425225.3.4.469

Hyldgaard, M., Mygind, T., and Meyer, R. L. (2012). Essential oils in food preservation: mode of action, synergies, and interactions with food matrix components. *Front. Microbiol.* 3, 12. doi:10.3389/fmicb.2012.00012

Ibrahim, S. S. (2020). "Essential Oil Nanoformulations as a Novel Method for Insect Pest Control in Horticulture," in *Horticultural Crops*. Editors H. Kossi Baimey, N. Hamamouch, and Y. Adjiguita Kolombia (London: IntechOpen), 195–208. doi:10.5772/intechopen.80747

Ipek, E., Zeytinoglu, H., Okay, S., Tuylu, B. A., Kurkcuoglu, M., and Baser, K. H. C. (2005). Genotoxicity and antigenotoxicity of *Origanum* oil and carvacrol evaluated by Ames Salmonella/microsomal test. *Food Chem.* 93, 551–556. doi:10.1016/j.foodchem.2004.12.034

Ishidate, M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., et al. (1984). Primary mutagenicity screening of food additives currently used in Japan. *Food Chem. Toxicol.* 22, 623–636. doi:10.1016/0278-6915(84)90271-0

Itani, W. S., El-Banna, S. H., Hassan, S. B., Larsson, R. L., Bazarbachi, A., and Gali-Muhtasib, H. U. (2008). Anti colon cancer components from Lebanese sage (*Salvia libanotica*) essential oil: Mechanistic basis. *Cancer Biol. Ther.* 7, 1765–1773. doi:10.4161/cbt.7.11.6740

Jäger, W., and Höferl, M. (2020). "Metabolism of Terpenoids in Animal Models and Humans," in *Handbook of Essential Oils*. Editors K. H. C. Baser and G. Buchbauer (Florida: CRC Press), 27–41.

Jamshidi-Kia, F., Lorigooini, Z., and Amini-Khoei, H. (2018). Medicinal plants: Past history and future perspective. *J. Herbmed Pharmacol.* 7, 1–7. doi:10.15171/jhp.2018.01

Jaradat, N. A., Al Zabadi, H., Rahhal, B., Hussein, A. M., Mahmoud, J. S., Mansour, B., et al. (2016). The effect of inhalation of *Citrus sinensis* flowers and *Mentha spicata* leave essential oils on lung function and exercise performance: a quasi-

experimental uncontrolled before-and-after study. *J. Int. Soc. Sports Nutr.* 13, 36. doi:10.1186/s12970-016-0146-7

Jiménez, J., Navarro, M. C., Montilla, M. P., Martin, A., and Martinez, A. (1993). Thymus zygis Oil: Its Effects on CCI4-Induced Hepatotoxicity and Free Radical Scavenger Activity. *J. Essent. Oil Res.* 5, 153–158. doi:10.1080/10412905.1993.9698194

Jirovetz, L., Jger, W., Koch, H.-P., and Remberg, G. (1992). Investigations of volatile constituents of the essential oil of Egyptian garlic (*Allium sativum* L.) by means of GC-MS and GC-FTIR. *Z. Leb. Unters. Forch.* 194, 363–365. doi:10.1007/BF01193221

Johny, A. K., Hoagland, T., and Venkitanarayanan, K. (2010). Effect of subinhibitory concentrations of plant-derived molecules in increasing the sensitivity of multidrug-resistant *Salmonella enterica serovar* Typhimurium DT104 to antibiotics. *Foodborne Pathog. Dis.* 7, 1165–1170. doi:10.1089/fpd.2009.0527

Kada, T., and Shimoi, K. (1987). Desmutagens and bio-antimutagens--their modes of action. *BioEssays* 7, 113–116. doi:10.1002/bies.950070305

Karakaya, S., Koca, M., Yılmaz, S. V., Yıldırım, K., Pınar, N. M., Demirci, B., et al. (2019). Molecular docking studies of coumarins isolated from extracts and essential oils of *Zosima absinthifolia* Link as potential inhibitors for Alzheimer's disease. *Molecules* 24. doi:10.3390/molecules24040722

Karalis, V., Macheras, P., van Peer, A., and Shah, V. P. (2008). Bioavailability and bioequivalence: focus on physiological factors and variability. *Pharm. Res.* 25, 1956–1962. doi:10.1007/s11095-008-9645-9

Karpouhtsis, I., Pardali, E., Feggou, E., Kokkini, S., Scouras, Z. G., and Mavragani-Tsipidou, P. (1998). Insecticidal and genotoxic activities of oregano essential oils. *J. Agric. Food Chem.* 46, 1111–1115. doi:10.1021/jf970822o

Kejlová, K., Jírová, D., Bendová, H., Gajdoš, P., and Kolářová, H. (2010). Phototoxicity of essential oils intended for cosmetic use. *Toxicol. Vitro* 24, 2084–2089. doi:10.1016/j.tiv.2010.07.025

Kennedy, D., Okello, E., Chazot, P., Howes, M. J., Ohiomokhare, S., Jackson, P., et al. (2018). Volatile Terpenes and Brain Function: Investigation of the Cognitive and Mood Effects of Mentha × Piperita L. Essential Oil with *In Vitro* Properties Relevant to Central Nervous System Function. *Nutrients* 10. doi:10.3390/nu10081029

Koch-Weser, J. (1974). Bioavailability of drugs (first of two parts). *N. Engl. J. Med.* 291, 233–237. doi:10.1056/NEJM197408012910505

Kohlert, C., Schindler, G., März, R. W., Abel, G., Brinkhaus, B., Derendorf, H., et al. (2002). Systemic availability and pharmacokinetics of thymol in humans. *J. Clin. Pharmacol.* 42, 731–737. doi:10.1177/009127002401102678

Kohlert, C., van Rensen, I., März, R., Schindler, G., Graefe, E. U., and Veit, M. (2000). Bioavailability and pharmacokinetics of natural volatile terpenes in animals and humans. *Planta Med.* 66, 495–505. doi:10.1055/s-2000-8616

Kontaris, I., East, B. S., and Wilson, D. A. (2020). Behavioral and neurobiological convergence of odor, mood and emotion: A review. *Front. Behav. Neurosci.* 14, 35. doi:10.3389/fnbeh.2020.00035

Koyama, S., and Heinbockel, T. (2020). The Effects of Essential Oils and Terpenes in Relation to Their Routes of Intake and Application. *Int. J. Mol. Sci.* 21. doi:10.3390/ijms21051558

Kristensson, K., and Olsson, Y. (1971). Uptake of exogenous proteins in mouse olfactory cells. *Acta. Neuropathol.* 19, 145–154. doi:10.1007/BF00688493

Ku, Y. S., Contador, C. A., Ng, M. S., Yu, J., Chung, G., and Lam, H. M. (2020). The effects of domestication on secondary metabolite composition in Legumes. *Front. Genet.* 11, 581357. doi:10.3389/fgene.2020.581357

Kumaravelu, P., Dakshinamoorthy, D. P., Subramaniam, S., Devaraj, H., and Devaraj, N. S. (1995). Effect of eugenol on drug-metabolizing enzymes of carbon tetrachloride-intoxicated rat liver. *Biochem. Pharmacol.* 49, 1703–1707. doi:10.1016/0006-2952(95)00083-C

Kuo, M. L., Lee, K. C., and Lin, J. K. (1992). Genotoxicities of nitropyrenes and their modulation by apigenin, tannic acid, ellagic acid and indole-3-carbinol in the Salmonella and CHO systems. *Mutat. Res.* 270, 87–95. doi:10.1016/0027-5107(92)90119-m

Lago, S., Rodríguez, H., Arce, A., and Soto, A. (2014). Improved concentration of citrus essential oil by solvent extraction with acetate ionic liquids. *Fluid Phase Equilibria* 361, 37–44. doi:10.1016/j.fluid.2013.10.036

Lal, R. K., Gupta, P., Chanotiya, C. S., and Sarkar, S. (2018). "Traditional Plant Breeding in Ocimum," in *The Ocimum Genome*. Editors A. K. Shasany and

C. Kole (Cham: Springer International Publishing), 89–98. doi:10.1007/978-3-319-97430-9_7

Langeveld, W. T., Veldhuizen, E. J., and Burt, S. A. (2014). Synergy between essential oil components and antibiotics: A review. *Crit. Rev. Microbiol.* 40, 76–94. doi:10.3109/1040841X.2013.763219

LaPlante, K. L. (2007). *In Vitro* activity of lysostaphin, mupirocin, and tea tree oil against clinical methicillin-resistant *Staphylococcus aureus*. *Diagn. Microbiol. Infect. Dis.* 57, 413–418. doi:10.1016/j.diagmicrobio.2006.09.007

Lazutka, J. R., Mierauskiene, J., Slapsyte, G., and Dedonyte, V. (2001). Genotoxicity of dill (Anethum graveolens L.), peppermint (Menthaxpiperita L.) and pine (Pinus sylvestris L.) essential oils in human lymphocytes and *Drosophila melanogaster*. *Food Chem. Toxicol.* 39, 485–492. doi:10.1016/s0278-6915(00)00157-5

Lizarraga-Valderrama, L. R. (2021). Effects of essential oils on central nervous system: Focus on mental health. *Phytother. Res.* 35, 657–679. doi:10.1002/ptr.6854

Lluria-Prevatt, M., Morreale, J., Gregus, J., Alberts, D. S., Kaper, F., Giaccia, A., et al. (2002). Effects of perillyl alcohol on melanoma in the TPras mouse model. *Cancer Epidemiol. Biomarkers Prev.* 11, 573–579.

Longbottom, C. J., Carson, C. F., Hammer, K. A., Mee, B. J., and Riley, T. V. (2004). Tolerance of *Pseudomonas aeruginosa* to *Melaleuca alternifolia* (tea tree) oil is associated with the outer membrane and energy-dependent cellular processes. *J. Antimicrob. Chemother.* 54, 386–392. doi:10.1093/jac/dkh359

Lopatkin, A. J., Bening, S. C., Manson, A. L., Stokes, J. M., Kohanski, M. A., Badran, A. H., et al. (2021). Clinically relevant mutations in core metabolic genes confer antibiotic resistance. *Science* 371. doi:10.1126/science.aba0862

López, V., Nielsen, B., Solas, M., Ramírez, M. J., and Jäger, A. K. (2017). Exploring pharmacological mechanisms of lavender (*Lavandula angustifolia*) essential oil on central nervous system targets. *Front. Pharmacol.* 8, 280. doi:10.3389/fphar.2017.00280

Lorenzi, V., Muselli, A., Bernardini, A. F., Berti, L., Pagès, J. M., Amaral, L., et al. (2009). Geraniol restores antibiotic activities against multidrug-resistant isolates from Gram-negative species. *Antimicrob. Agents Chemother.* 53, 2209–2211. doi:10.1128/AAC.00919-08

Loreto, F., Bagnoli, F., and Fineschi, S. (2009). One species, many terpenes: matching chemical and biological diversity. *Trends Plant Sci.* 14, 416–420. doi:10.1016/j.tplants.2009.06.003

Loreto, F., and D'Auria, S. (2022). How Do plants sense volatiles sent by other plants? *Trends Plant Sci.* 27, 29–38. doi:10.1016/j.tplants.2021.08.009

Magnusson, B. M., Runn, P., and Koskinen, L. O. (1997). Terpene-enhanced transdermal permeation of water and ethanol in human epidermis. *Acta Derm. Venereol.* 77, 264–267. doi:10.2340/0001555577264267

Mahanta, B. P., Sut, D., Kemprai, P., Paw, M., Lal, M., and Haldar, S. (2020). A 1 H-NMR spectroscopic method for the analysis of thermolabile chemical markers from the essential oil of black turmeric (Curcuma caesia) rhizome: application in post-harvest analysis. *Phytochem. Anal.* 31, 28–36. doi:10.1002/pca.2863

Mahboubi, M., and Bidgoli, F. G. (2010). Antistaphylococcal activity of *Zataria multiflora* essential oil and its synergy with vancomycin. *Phytomedicine* 17, 548–550. doi:10.1016/j.phymed.2009.11.004

Makarska-Białokoz, M. (2020). History and significance of phytotherapy in the human history 3. The development of phytotherapy from the Middle Ages to modern times. *APGR* 24, 17–22.

Maruyama, N., Takizawa, T., Ishibashi, H., Hisajima, T., Inouye, S., Yamaguchi, H., et al. (2008). Protective activity of geranium oil and its component, geraniol, in combination with vaginal washing against vaginal candidiasis in mice. *Biol. Pharm. Bull.* 31, 1501–1506. doi:10.1248/bpb.31.1501

Masotti, V., Juteau, F., Bessière, J. M., and Viano, J. (2003). Seasonal and phenological variations of the essential oil from the narrow endemic species *Artemisia molinieri* and its biological activities. *J. Agric. Food Chem.* 51, 7115–7121. doi:10.1021/jf034621y

Meidan, V. M., Bonner, M. C., and Michniak, B. B. (2005). Transfollicular drug delivery--is it a reality? *Int. J. Pharm.* 306, 1–14. doi:10.1016/j.ijpharm.2005.09.025

Melzig, M., and Teuscher, E. (1991). Untersuchungen zum Einfluß ätherischer Öle und ihrer Hauptkomponenten auf die Adenosinaufnahme kultivierter Endothelzellen. *Planta Med.* 57, 41–42. doi:10.1055/s-2006-960013

Metsämuuronen, S., and Sirén, H. (2019). Bioactive phenolic compounds, metabolism and properties: a review on valuable chemical compounds in Scots pine and Norway spruce. *Phytochem. Rev.* 18, 623–664. doi:10.1007/s11101-019-09630-2

Michaels, A. S., Chandrasekaran, S. K., and Shaw, J. E. (1975). Drug permeation through human skin: Theory andinvitro experimental measurement. *AIChE J.* 21, 985–996. doi:10.1002/aic.690210522

Michiels, J., Missotten, J., Dierick, N., Fremaut, D., Maene, P., and De Smet, S. (2008). *In Vitro* degradation and *In Vivo* passage kinetics of carvacrol, thymol, eugenol and trans -cinnamaldehyde along the gastrointestinal tract of piglets. *J. Sci. Food Agric.* 88, 2371–2381. doi:10.1002/jsfa.3358

Miyazawa, M., and Haigou, R. (2011). Determination of cytochrome P450 enzymes involved in the metabolism of (-)-terpinen-4-ol by human liver microsomes. *Xenobiotica* 41, 1056–1062. doi:10.3109/00498254.2011.596230

Miyazawa, M., Sugie, A., and Shindo, M. (2002). Biotransformation of (-)-verbenone by human liver microsomes. *Biosci. Biotechnol. Biochem.* 66, 2458–2460. doi:10.1271/bbb.66.2458

Mofikoya, O. O., Mäkinen, M., and Jänis, J. (2022). Compositional analysis of essential oil and solvent extracts of Norway spruce sprouts by ultrahigh-resolution mass spectrometry. *Phytochem. Anal.* 33, 392–401. doi:10.1002/pca.3097

Morlock, G. E. (2021). High-performance thin-layer chromatography combined with effect-directed assays and high-resolution mass spectrometry as an emerging hyphenated technology: A tutorial review. *Anal. Chim. Acta* 1180, 338644. doi:10.1016/j.aca.2021.338644

M. Wink (Editor) (2010). *Functions and Biotechnology of Plant Secondary Metabolites* (Ames, Iowa: Wiley-Blackwell).

Nahrstedt, A., and Butterweck, V. (2010). Lessons learned from herbal medicinal products: the example of St. John's Wort (perpendicular). *J. Nat. Prod.* 73, 1015–1021. doi:10.1021/np1000329

Nakouti, I., Hobbs, G., and Alston, M. (20222022). Acne vulgaris: the skin microbiome, antibiotics and whether natural products could be considered a suitable alternative treatment? Journal of Natural Products Discovery, Vol 1 No 1JOURNAL OF NATURAL PRODUCTS DISCOVERY (JNPD). *J. Nat. Prod. Disc.* 1. doi:10.24377/JNPD.ARTICLE652

Naqvi, K. J., Ansari, S. H., Ali, M., and Najmi, A. (2014). Volatile oil composition of *Rosa damascena* Mill.(Rosaceae). *J. Pharmacogn. Phytochem.*, 130–134.

Nestmann, E. R., and Lee, E. G. (1983). Mutagenicity of constituents of pulp and paper mill effluent in growing cells of *Saccharomyces cerevisiae*. *Mutat. Res.* 119, 273–280. doi:10.1016/0165-7992(83)90172-0

Newman, J. D., and Chappell, J. (1999). Isoprenoid biosynthesis in plants: Carbon partitioning within the cytoplasmic pathway. *Crit. Rev. Biochem. Mol. Biol.* 34, 95–106. doi:10.1080/10409239991209228

Ng, K. W., and Lau, W. M. (2015). "Skin Deep: The Basics of Human Skin Structure and Drug Penetration," in *Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Drug Manipulation Strategies and Vehicle Effects*. Editors N. Dragicevic and H. I. Maibach (Berlin, Heidelberg, New York, NY, Dordrecht, London: Springer), 3–11. doi:10.1007/978-3-662-45013-0_1

Nguyen, D. A., Muhammad, M. K., and Lee, G. L. (2020). "Phytophotodermatitis," in *Dermatological Manual of Outdoor Hazards*. Editors J. Trevino and A. Y.-Y. Chen (Cham: Springer International Publishing; Imprint Springer), 43–56. doi:10.1007/978-3-030-37782-3_4

Novgorodov, S. A., and Gudz, T. I. (1996). Permeability transition pore of the inner mitochondrial membrane can operate in two open states with different selectivities. *J. Bioenerg. Biomembr.* 28, 139–146. doi:10.1007/BF02110644

Ohashi, T., Miyazawa, Y., Ishizaki, S., Kurobayashi, Y., and Saito, T. (2019). Identification of Odor-Active Trace Compounds in Blooming Flower of Damask Rose (Rosa damascena). *J. Agric. Food Chem.* 67, 7410–7415. doi:10.1021/acs.jafc.9b03391

Pakalapati, G., Li, L., Gretz, N., Koch, E., and Wink, M. (2009). Influence of red clover (*Trifolium pratense*) isoflavones on gene and protein expression profiles in liver of ovariectomized rats. *Phytomedicine* 16, 845–855. doi:10.1016/j.phymed.2009.03.003

Palaniappan, K., and Holley, R. A. (2010). Use of natural antimicrobials to increase antibiotic susceptibility of drug resistant bacteria. *Int. J. Food. Microbiol.* 140, 164–168. doi:10.1016/j.ijfoodmicro.2010.04.001

Palmer, M. S., Dryden, A. J., Hughes, J. T., and Collinge, J. (1991). Homozygous prion protein genotype predisposes to sporadic Creutzfeldt-Jakob disease. *Nature* 352, 340–342. doi:10.1038/352340a0

Panikar, S., Shoba, G., Arun, M., Sahayarayan, J. J., Usha Raja Nanthini, A., Chinnathambi, A., et al. (2021). Essential oils as an effective alternative for the treatment of COVID-19: Molecular interaction analysis of protease (Mpro) with pharmacokinetics and toxicological properties. *J. Infect. Public Health* 14, 601–610. doi:10.1016/j.jiph.2020.12.037

Parke, D. V., Rahman, K. M. Q., and Walker, R. (1974). The absorption, distribution and excretion of linalool in the rat. *Biochem. Soc. Trans.* 2, 612–615. doi:10.1042/bst0020612

Plant, R. M., Dinh, L., Argo, S., and Shah, M. (2019). The essentials of essential oils. *Adv. Pediatr.* 66, 111–122. doi:10.1016/j.yapd.2019.03.005

Połeć, K., Wyżga, B., Olechowska, K., and Hąc-Wydro, K. (2022). On the synergy/antagonism of selected terpenes in the effect on lipid membranes studied in model systems. *J. Mol. Liq.* 349, 118473. doi:10.1016/j.molliq.2022.118473

Polya, G. (2003). *Biochemical Targets of Plant Bioactive Compounds*. London: CRC Press. 9780429214981.

Poudel, D. K., Rokaya, A., Ojha, P. K., Timsina, S., Satyal, R., Dosoky, N. S., et al. (2021). The chemical profiling of essential oils from different tissues of *Cinnamomum camphora* L. and their antimicrobial activities. *Molecules* 26, 5132. doi:10.3390/molecules26175132

Pourgholami, M. H., Majzoob, S., Javadi, M., Kamalinejad, M., Fanaee, G. H., and Sayyah, M. (1999). The fruit essential oil of *Pimpinella anisum* exerts anticonvulsant effects in mice. *J. Ethnopharmacol.* 66, 211–215. doi:10.1016/S0378-8741(98)00161-5

Ramadan, M., Goeters, S., Watzer, B., Krause, E., Lohmann, K., Bauer, R., et al. (2006). Chamazulene carboxylic acid and matricin: a natural profen and its natural prodrug, identified through similarity to synthetic drug substances. *J. Nat. Prod.* 69, 1041–1045. doi:10.1021/np0601556

Ramel, C., Alekperov, U. K., Ames, B. N., Kada, T., and Wattenberg, L. W. (1986). International commission for protection against environmental mutagens and carcinogens. ICPEMC Publication No. 12. Inhibitors of mutagenesis and their relevance to carcinogenesis. Report by ICPEMC Expert Group on Antimutagens and Desmutagens. *Mutat. Res.* 168, 47–65. doi:10.1016/0165-1110(86)90021-7

Ramezani, S., Saharkhiz, M. J., Ramezani, F., and Fotokian, M. H. (2008). Use of essential oils as bioherbicides. *J. Essent. Oil Bear. Plants* 11, 319–327. doi:10.1080/0972060X.2008.10643636

Raphael, T. J., and Kuttan, G. (2003). Effect of naturally occurring monoterpenes carvone, limonene and perillic acid in the inhibition of experimental lung metastasis induced by B16F-10 melanoma cells. *J. Exp. Clin. Cancer Res.* 22, 419–424.

Rasoanaivo, P., Wright, C. W., Willcox, M. L., and Gilbert, B. (2011). Whole plant extracts versus single compounds for the treatment of malaria: synergy and positive interactions. *Malar. J.* 10 (Suppl. 1), S4. doi:10.1186/1475-2875-10-S1-S4

Regnault-Roger, C., Vincent, C., and Arnason, J. T. (2012). Essential oils in insect control: Low-risk products in a high-stakes world. *Annu. Rev. Entomol.* 57, 405–424. doi:10.1146/annurev-ento-120710-100554

Richter, C., and Schlegel, J. (1993). Mitochondrial calcium release induced by prooxidants. *Toxicol. Lett.* 67, 119–127. doi:10.1016/0378-4274(93)90050-8

Rompelberg, C. J., Verhagen, H., and van Bladeren, P. J. (1993). Effects of the naturally occurring alkenylbenzenes eugenol and trans-anethole on drug-metabolizing enzymes in the rat liver. *Food Chem. Toxicol.* 31, 637–645. doi:10.1016/0278-6915(93)90046-2

Ronzheimer, A., Schreiner, T., and Morlock, G. E. (2022). Multiplex planar bioassay detecting estrogens, antiestrogens, false-positives and synergists as sharp zones on normal phase. *Phytomedicine* 103, 154230. doi:10.1016/j.phymed.2022.154230

Rosato, A., Piarulli, M., Corbo, F., Muraglia, M., Carone, A., Vitali, M. E., et al. (2010). *In Vitro* synergistic antibacterial action of certain combinations of gentamicin and essential oils. *Curr. Med. Chem.* 17, 3289–3295. doi:10.2174/092986710792231996

Rusanov, K., Kovacheva, N., Rusanova, M., and Atanassov, I. (2012). Reducing methyl eugenol content in *Rosa damascena* Mill rose oil by changing the

traditional rose flower harvesting practices. *Eur. Food Res. Technol.* 234, 921–926. doi:10.1007/s00217-012-1703-1

Sadgrove, N. J., Padilla-González, G. F., Leuner, O., Melnikovova, I., and Fernandez-Cusimamani, E. (2021). Pharmacology of natural volatiles and essential oils in food, therapy, and disease prophylaxis. *Front. Pharmacol.* 12, 740302. doi:10.3389/fphar.2021.740302

Sadgrove, N. J., Padilla-González, G. F., and Phumthum, M. (2022). Fundamental chemistry of essential oils and volatile organic compounds, methods of analysis and authentication. *Plants* 11, 789. doi:10.3390/plants11060789

Sahoo, N., Manchikanti, P., and Dey, S. (2010). Herbal drugs: standards and regulation. *Fitoterapia* 81, 462–471. doi:10.1016/j.fitote.2010.02.001

Sakkas, H., and Papadopoulou, C. (2017). Antimicrobial activity of basil, oregano, and thyme essential oils. *J. Microbiol. Biotechnol.* 27, 429–438. doi:10.4014/jmb.1608.08024

Sakr, H., Schmidt, S., Bereswill, S., Heimesaat, M. M., and Melzig, M. F. (2021). Ätherische Öle aus Zimt und Gewürznelken verstärken die Wirkung von Antibiotika gegen multiresistente bakterielle Krankheitserreger. *Z. für Phytother.* 42, 233–240. doi:10.1055/a-1584-5376

Salehi, B., Lopez-Jornet, P., Pons-Fuster López, E., Calina, D., Sharifi-Rad, M., Ramírez-Alarcón, K., et al. (2019). Plant-derived bioactives in oral mucosal lesions: A key emphasis to curcumin, lycopene, chamomile, aloe vera, green tea and coffee properties. *Biomolecules* 9. doi:10.3390/biom9030106

Sangwan, N. S., Farooqi, A. H. A., Shabih, F., and Sangwan, R. S. (2001). Regulation of essential oil production in plants. *Plant Growth Regul.* 34, 3–21. doi:10.1023/A:1013386921596

Santana-Rios, G., Orner, G. A., Amantana, A., Provost, C., Wu, S. Y., and Dashwood, R. H. (2001). Potent antimutagenic activity of white tea in comparison with green tea in the Salmonella assay. *Mutat. Res.* 495, 61–74. doi:10.1016/s1383-5718(01)00200-5

Santos, F. A., Silva, R. M., Tomé, A. R., Rao, V. S., Pompeu, M. M., Teixeira, M. J., et al. (2001). 1,8-cineole protects against liver failure in an *in-vivo* murine model of endotoxemic shock. *J. Pharm. Pharmacol.* 53, 505–511. doi:10.1211/0022357011775604

Sarpietro, M. G., Di Sotto, A., Accolla, M. L., and Castelli, F. (2015). Interaction of β-caryophyllene and β-caryophyllene oxide with phospholipid bilayers: Differential scanning calorimetry study. *Thermochim. Acta* 600, 28–34. doi:10.1016/j.tca.2014.11.029

Sarrou, E., Tsivelika, N., Chatzopoulou, P., Tsakalidis, G., Menexes, G., and Mavromatis, A. (2017). Conventional breeding of Greek oregano (Origanum vulgare ssp. hirtum) and development of improved cultivars for yield potential and essential oil quality. *Euphytica* 213. doi:10.1007/s10681-017-1889-1

Sayyah, M., Peirouvi, A., and Kamalinezhad, M. (2002). Anti-Nociceptive Effect of the Fruit Essential Oil of *Cuminum cyminum* L. in Rat. *Iran. Biomed. J.* 6, 141–145.

Scheuplein, R. J., and Blank, I. H. (1971). Permeability of the skin. *Physiol. Rev.* 51, 702–747. doi:10.1152/physrev.1971.51.4.702

Schmitt, S., Schaefer, U. F., Doebler, L., and Reichling, J. (2009). Cooperative interaction of monoterpenes and phenylpropanoids on the *In Vitro* human skin permeation of complex composed essential oils. *Planta Med.* 75, 1381–1385. doi:10.1055/s-0029-1185744

Schmitt, S., Sporer, F., and Reichling, J. (2010). *Comparative Study on the* in Vitro *Human Skin Permeation of Monoterpenes and Phenylpropanoids Applied in Rose Oil and in Form of Neat Single Compounds*, 0031-7144, 102–105. doi:10.1691/ph.2010.9716

Schommer, N. N., and Gallo, R. L. (2013). Structure and function of the human skin microbiome. *Trends Microbiol.* 21, 660–668. doi:10.1016/j.tim.2013.10.001

Schreiner, T., Sauter, D., Friz, M., Heil, J., and Morlock, G. E. (2021). Is our natural food our homeostasis? Array of a thousand effect-directed profiles of 68 herbs and spices. *Front. Pharmacol.* 12, 755941. doi:10.3389/fphar.2021.755941

Schreiner, T., Ronzheimer, A., Friz, M., and Morlock, G. E. (2022). Multiplex planar bioassay with reduced diffusion on normal phase, identifying androgens, verified antiandrogens and synergists in botanicals *via* 12D hyphenation. *Food Chem.*. doi:10.1016/j.foodchem.2022.133610

Schwabl, H., Vennos, C., and Saller, R. (2013). Tibetische Rezepturen als pleiotrope Signaturen - Einsatz von Netzwerk-Arzneien bei Multimorbidität. *Complement. Med. Res.* 20, 35–40. doi:10.1159/000351718

Scotti, F., Decani, S., Sardella, A., Iriti, M., Varoni, E. M., and Lodi, G. (2018). Anti-inflammatory and wound healing effects of an essential oils-based bioadhesive

gel after oral mucosa biopsies: preliminary results. *Cell. Mol. Biol. (Noisy-le-grand)* 64, 78–83. doi:10.14715/cmb/2018.64.8.12

Sertürner, F. A. (1806). Darstellung der reinen Mohnsäure (Opiumsäure) nebst einer Untersuchung des Opiums mit vorzüglicher Hinsicht auf einen darin neu entdeckten Stoff und die dahin gehörigen Bemerkungen. Vom Herrn Sertürner in Paderborn. *J. der Pharm.* 14, 47–93.

Seyyedi, S. A., Sanatkhani, M., Pakfetrat, A., and Olyaee, P. (2014). The therapeutic effects of chamomilla tincture mouthwash on oral aphtae: A Randomized Clinical Trial. *J. Clin. Exp. Dent.* 6, e535–8. doi:10.4317/jced.51472

Shahrajabian, M. H., Sun, W., and Cheng, Q. (2019). Chinese star anise and anise, magic herbs in traditional Chinese medicine and modern pharmaceutical science. *Asian J. Med. Biol. Res.* 5, 162–179. doi:10.3329/ajmbr.v5i3.43584

Shahverdi, A. R., Monsef-Esfahani, H. R., Tavasoli, F., Zaheri, A., and Mirjani, R. (2007). Trans-cinnamaldehyde from *Cinnamomum zeylanicum* bark essential oil reduces the clindamycin resistance of *Clostridium difficile In Vitro. J. Food Sci.* 72, S055–S058. doi:10.1111/j.1750-3841.2006.00204.x

Shankar, S., Prasad, S., Owaiz, M., Yadav, S., Manhas, S., and Yaqoob, M. (2021). Essential oils, components and their applications: A review. *Plant arch.* 21, 2027–2033. doi:10.51470/plantarchives.2021.v21.s1.331

Shankel, D. M., Kuo, S., Haines, C., and Mitscher, L. A. (1993). Extracellular interception of mutagens. *Basic Life Sci.* 61, 65–74. doi:10.1007/978-1-4615-2984-2_5

Sharma, N., Trikha, P., Athar, M., and Raisuddin, S. (2001). Inhibition of benzo[a]pyrene- and cyclophoshamide-induced mutagenicity by *Cinnamomum cassia. Mutat. Res.* 480-481, 179–188. doi:10.1016/s0027-5107(01)00198-1

Si, H., Hu, J., Liu, Z., and Zeng, Z. L. (2008). Antibacterial effect of oregano essential oil alone and in combination with antibiotics against extended-spectrum beta-lactamase-producing *Escherichia coli. FEMS Immunol. Med. Microbiol.* 53, 190–194. doi:10.1111/j.1574-695X.2008.00414.x

Siekierzynska, A., Piasecka-Kwiatkowska, D., Myszka, A., Burzynska, M., Sozanska, B., and Sozanski, T. (2021). Apple allergy: Causes and factors influencing fruits allergenic properties-Review. *Clin. Transl. Allergy* 11, e12032. doi:10.1002/clt2.12032

Silori, C. S., and Badola, R. (2000). Medicinal Plant Cultivation and Sustainable Development. *Mt. Res. Dev.* 20, 272–279. doi:10.1659/0276-4741(2000)020[0272:mpcasd]2.0.co;2

Silva, J. K. R. D., Figueiredo, P. L. B., Byler, K. G., and Setzer, W. N. (2020). Essential oils as antiviral agents. potential of essential oils to treat SARS-CoV-2 infection: An *in-silico* investigation. *Int. J. Mol. Sci.* 21. doi:10.3390/ijms21103426

Smruti, P. (2021). A review on natural remedies used for the treatment of respiratory disorders. *Int. J. Pharmacogn.* 8, 104–111.

So, O., O, A., and Ka, J. (2018). Medicinal plants and sustainable human health: a review. *HIJ* 2, 194–195. doi:10.15406/hij.2018.02.00051

Stahl-Biskup, E., and Reher, G. (1987). Geschmack und Geruch. Die chemischen Sinne des Menschen und die Chemie der Geschmack-und Riechstoffe. Teil I: Geschmack. *Dtsch. Apoth. Ztg.* 127, 2529.

Stammati, A., Bonsi, P., Zucco, F., Moezelaar, R., Alakomi, H. L., and von Wright, A. (1999). Toxicity of selected plant volatiles in microbial and mammalian short-term assays. *Food Chem. Toxicol.* 37, 813–823. doi:10.1016/s0278-6915(99)00075-7

Staub, P. O., Casu, L., and Leonti, M. (2016). Back to the roots: A quantitative survey of herbal drugs in Dioscorides' De Materia Medica (ex Matthioli, 1568). *Phytomedicine* 23, 1043–1052. doi:10.1016/j.phymed.2016.06.016

Stevanović, Z. D., Bošnjak-Neumüller, J., Pajić-Lijaković, I., Raj, J., and Vasiljević, M. (2018). Essential oils as feed additives-Future perspectives. *Molecules* 23. doi:10.3390/molecules23071717

Sultanbawa, Y. (2016). "Anise Myrtle (Syzygium anisatum) Oils," in *Essential Oils in Food Preservation, Flavor and Safety.* Editor V. R. Preedy (Amsterdam, Boston, Heidelberg: AP Academic Press an imprint of Elsevier), 215–219. doi:10.1016/b978-0-12-416641-7.00023-7

Tardugno, R., Pellati, F., Iseppi, R., Bondi, M., Bruzzesi, G., and Benvenuti, S. (2018). Phytochemical composition and *In Vitro* screening of the antimicrobial activity of essential oils on oral pathogenic bacteria. *Nat. Prod. Res.* 32, 544–551. doi:10.1080/14786419.2017.1329730

Teuscher, E., and Lindequist, U. (2010). *Biogene Gifte: Biologie, Chemie, Pharmakologie, Toxikologie.* Stuttgart: Wissenschaftliche Verlagsgesellschaft Stuttgart. 9783804729919.

Tisserand, R., and Young, R. (2014). "Kinetics and dosing," in *Essential Oil Safety: A Guide for Health Care Professionals.* Editors R. Tisserand and R. Young (Edinburgh: Churchill Livingstone Elsevier), 39–67. doi:10.1016/b978-0-443-06241-4.00004-7

Toxopeus, H., and Bouwmeester, H. J. (1992). Improvement of caraway essential oil and carvone production in The Netherlands. *Industrial Crops Prod.* 1, 295–301. doi:10.1016/0926-6690(92)90031-P

Tremmel, M., Kiermaier, J., and Heilmann, J. (2021). *In Vitro* metabolism of six C-glycosidic flavonoids from *Passiflora incarnata* L. *Int. J. Mol. Sci.* 22. doi:10.3390/ijms22126566

Truzzi, E., Marchetti, L., Benvenuti, S., Ferroni, A., Rossi, M. C., and Bertelli, D. (2021). Novel Strategy for the Recognition of Adulterant Vegetable Oils in Essential Oils Commonly Used in Food Industries by Applying 13C NMR Spectroscopy. *J. Agric. Food Chem.* 69, 8276–8286. doi:10.1021/acs.jafc.1c02279

Turek, C., and Stintzing, F. C. (2011). Application of high-performance liquid chromatography diode array detection and mass spectrometry to the analysis of characteristic compounds in various essential oils. *Anal. Bioanal. Chem.* 400, 3109–3123. doi:10.1007/s00216-011-4976-5

Turek, C., and Stintzing, F. C. (2013). Stability of essential oils: A review. *Compr. Rev. Food Sci. Food Saf.* 12, 40–53. doi:10.1111/1541-4337.12006

Ultee, A., Bennik, M. H., and Moezelaar, R. (2002). The phenolic hydroxyl group of carvacrol is essential for action against the food-borne pathogen *Bacillus cereus. Appl. Environ. Microbiol.* 68, 1561–1568. doi:10.1128/AEM.68.4.1561-1568.2002

Ultee, A., Kets, E. P., Alberda, M., Hoekstra, F. A., and Smid, E. J. (2000). Adaptation of the food-borne pathogen *Bacillus cereus* to carvacrol. *Arch. Microbiol.* 174, 233–238. doi:10.1007/s002030000199

Van Houten, B., Woshner, V., and Santos, J. H. (2006). Role of mitochondrial DNA in toxic responses to oxidative stress. *DNA Repair (Amst)* 5, 145–152. doi:10.1016/j.dnarep.2005.03.002

van Vuuren, S. F., Suliman, S., and Viljoen, A. M. (2009). The antimicrobial activity of four commercial essential oils in combination with conventional antimicrobials. *Lett. Appl. Microbiol.* 48, 440–446. doi:10.1111/j.1472-765X.2008.02548.x

van Wyk, B.-E. (2015). *Handbuch der Arzneipflanzen: Ein Bildatlas.* Stuttgart: Wissenschaftliche Verlagsgesellschaft Stuttgart. 9783804735361.

van Wyk, B.-E., and Wink, M. (2017). *Medicinal Plants of the World: An Illustrated Scientific Guide to Important Medicina Plants and Theier Uses.* Wallingford: CABI. 9781786393258.

van Wyk, B.-E., and Wink, M. (2015). *Phytomedicines, Herbal Drugs, and Poisons.* ChicagoKew: Royal Botanic GardensThe University of Chicago Press. 9780226204918.

Velu, G., Palanichamy, V., and Rajan, A. P. (2018). "Phytochemical and pharmacological importance of plant secondary metabolites in modern medicine," in *Bioorganic Phase in Natural Food: An Overview.* Editors S. M. Roopan and G. Madhumitha (Cham: Springer International Publishing), 135–156. doi:10.1007/978-3-319-74210-6_8

Venugopal, A., and Dhanish, J. (2018). Medicinal properties of black turmeric: A Review. *Int. J. Sci.* 4, 1–4.

Vercesi, A. E., Kowaltowski, A. J., Grijalba, M. T., Meinicke, A. R., and Castilho, R. F. (1997). The role of reactive oxygen species in mitochondrial permeability transition. *Biosci. Rep.* 17, 43–52. doi:10.1023/a:1027335217774

Wagner, H., and Ulrich-Merzenich, G. (2009). Synergy research: approaching a new generation of phytopharmaceuticals. *Phytomedicine* 16, 97–110. doi:10.1016/j.phymed.2008.12.018

Wallen-Russell, C., and Wallen-Russell, S. (2017). Meta analysis of skin microbiome: New link between skin microbiota diversity and skin health with proposal to use this as a future mechanism to determine whether cosmetic products damage the skin. *Cosmetics* 4, 14. doi:10.3390/cosmetics4020014

Wani, A. R., Yadav, K., Khursheed, A., and Rather, M. A. (2021). An updated and comprehensive review of the antiviral potential of essential oils and their chemical constituents with special focus on their mechanism of action against various influenza and coronaviruses. *Microb. Pathog.* 152, 104620. doi:10.1016/j.micpath.2020.104620

Waters, M. D., Stack, H. F., Jackson, M. A., Brockman, H. E., and De Flora, S. (1996). Activity profiles of antimutagens: *In Vitro* and *In Vivo* data. *Mutat. Res.* 350, 109–129. doi:10.1016/0027-5107(95)00097-6

Wepierre, J., Cohen, Y., and Valette, G. (1968). Percutaneous absorption and removal by the body fluids of 14C ethyl alcohol, 3H perhydrosqualene and 14C p-cymene. *Eur. J. Pharmacol.* 3, 47–51. doi:10.1016/0014-2999(68)90047-2

Wester, R. C., and Maibach, H. I. (2000). Understanding percutaneous absorption for occupational health and safety. *Int. J. Occup. Environ. Health.* 6, 86–92. doi:10.1179/oeh.2000.6.2.86

Williams, A. C., and Barry, B. W. (1991a). Terpenes and the lipid-protein-partitioning theory of skin penetration enhancement. *Pharm. Res.* 8, 17–24. doi:10.1023/A:1015813803205

Williams, A. C., and Barry, B. W. (1991b). The enhancement index concept applied to terpene penetration enhancers for human skin and model lipophilic (oestradiol) and hydrophilic (5-fluorouracil) drugs. *Int. J. Pharm.* 74, 157–168. doi:10.1016/0378-5173(91)90232-D

Wink, M. (2003). Evolution of secondary metabolites from an ecological and molecular phylogenetic perspective. *Phytochemistry* 64, 3–19. doi:10.1016/S0031-9422(03)00300-5

Wink, M. (2015). Modes of action of herbal medicines and plant secondary metabolites. *Med. (Basel)* 2, 251–286. doi:10.3390/medicines2030251

Wink, M. (2022). Current Understanding of Modes of Action of Multicomponent Bioactive Phytochemicals: Potential for Nutraceuticals and Antimicrobials. *Annu. Rev. Food Sci. Technol.* 13, 337–359. doi:10.1146/annurev-food-052720-100326

Wink, M. (2008). *Evolutionary Advantage and Molecular Modes of Action of Multi-Component Mixtures Used in Phytomedicine.* Schardscha: Bentham Science Publishers.

Wink, M. (2012). "Molecular modes of action of drugs used in phytomedicine," in *Herbal Medicines: Development and Validation of Plant-Derived Medicines for Human Health.* Editor G. Bagetta (Boca Raton: CRC Press), 161–172.

Wink, M., and Schimmer, O. (2010). "Molecular modes of action of defensive secondary metabolites," in *Functions and Biotechnology of Plant Secondary Metabolites.* Editor M. Wink (Ames, Iowa: Wiley-Blackwell), 21–161. doi:10.1002/9781444318876.ch2

Wink, M. (2005). Wie funktionieren Phytopharmaka? - Wirkmechanismen der Vielstoffgemische. *Z. für Phytother.* 26, 262–270. doi:10.1055/s-2005-925480

Woolf, A. (1999). Essential oil poisoning. *J. Toxicol. Clin. Toxicol.* 37, 721–727. doi:10.1081/clt-100102450

Xie, W., Weng, A., and Melzig, M. F. (2016). MicroRNAs as new bioactive components in medicinal plants. *Planta Med.* 82, 1153–1162. doi:10.1055/s-0042-108450

Yoon, H. S., Moon, S. C., Kim, N. D., Park, B. S., Jeong, M. H., and Yoo, Y. H. (2000). Genistein induces apoptosis of RPE-J cells by opening mitochondrial PTP. *Biochem. Biophys. Res. Commun.* 276, 151–156. doi:10.1006/bbrc.2000.3445

Zani, F., Massimo, G., Benvenuti, S., Bianchi, A., Albasini, A., Melegari, M., et al. (1991). Studies on the genotoxic properties of essential oils with *Bacillus subtilis* rec-assay and Salmonella/microsome reversion assay. *Planta Med.* 57, 237–241. doi:10.1055/s-2006-960081

Zárybnický, T., Boušová, I., Ambrož, M., and Skálová, L. (2018). Hepatotoxicity of monoterpenes and sesquiterpenes. *Arch. Toxicol.* 92, 1–13. doi:10.1007/s00204-017-2062-2

Zehetner, P., Höferl, M., and Buchbauer, G. (2019). Essential oil components and cytochrome P450 enzymes: a review. *Flavour. Fragr. J.* 34, 223–240. doi:10.1002/ffj.3496

Zhang, D., Hu, H., Rao, Q., and Zhao, Z. (2011). Synergistic effects and physiological responses of selected bacterial isolates from animal feed to four natural antimicrobials and two antibiotics. *Foodborne Pathog. Dis.* 8, 1055–1062. doi:10.1089/fpd.2010.0817

Zhang, L., Zhao, M., Chen, J., Wang, M., and Yu, X. (2019). Reduction of cyanide content of bitter almond and its oil using different treatments. *Int. J. Food Sci. Technol.* 54, 3083–3090. doi:10.1111/ijfs.14223

Zhang, N., and Yao, L. (2019). Anxiolytic effect of essential oils and their constituents: A review. *J. Agric. Food Chem.* 67, 13790–13808. doi:10.1021/acs.jafc.9b00433

Zhang, X., Han, Y., Huang, W., Jin, M., and Gao, Z. (2021). The influence of the gut microbiota on the bioavailability of oral drugs. *Acta Pharm. Sin. B* 11, 1789–1812. doi:10.1016/j.apsb.2020.09.013

Zhang, Y., Wang, Q. C., Yu, H., Zhu, J., de Lange, K., Yin, Y., et al. (2016). Evaluation of alginate-whey protein microcapsules for intestinal delivery of lipophilic compounds in pigs. *J. Sci. Food Agric.* 96, 2674–2681. doi:10.1002/jsfa.7385

Zimmermann, T., Seiberling, M., Thomann, P., and Karabelnik, D. (1995). Untersuchungen zur relativen Bioverfügbarkeit und zur Pharmakokinetik von Myrtol standardisiert. *Arzneimittelforschung* 45, 1198–1201.