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Research Article

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Essential Oils: Biosynthesis, Chemistry and Biological Functions

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ABSTRACT

Since ancient times, essential oils have been used for many purposes; the most important uses are the treatment of disease in various ancient civilizations and cultures around the world and used widely for bactericidal, virucidal, fungicidal, antiparasitical, insecticidal, medicinal and cosmetic applications, as well as pharmaceutical, agricultural and food industries. Essential oils are natural products obtained from plant raw material by different extraction methods techniques and found in various parts of the plant organs. The mostly essential oils extraction by distillation from aromatic plants, they contain a variety of volatile molecules such as terpenes, terpenoids, phenylpropanoids and other components. Essential oils have the broad range biological activities which are due to the chemical compounds that make up essential oils.

Keywords: Essential oil; Chemistry; Biosynthesis; Biological activities

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INTRODUCTION

A Brief History of Essential Oils

Since ancient times, essential oils have been used for many purposes, where herbs and essential oils were used in medicine as an important part of their philosophy in healing and perfume [1]. Myrrh, cinnamon, frankincense, hyssop, thyme, clove, rosemary, lavender, spikenard and cedarwood essential oils have been mentioned many times for the treatment of a lot of diseases [2-7]. Now, essential oils had become one of the high-value agricultural products, especially for developing countries and as a result of increased demand as consumers prefer natural products, World's total annual production of essential oils ranges from 100,000-110,000 tons. Global essential oil market demand was 178.800 tons in 2015 and is expected to exceed 370.000 tons by 2024, growing at a compound annual growth rate (CAGR) of 8.4% from 2016 to 2024. Major producers of essential oils are Brazil, China, USA, Egypt, India, Mexico, Guatemala and Indonesia [8]. The global essential oil market size exceeded USD 6.0 billion in 2015 and expected to reach USD 11.67 billion by 2022, and 13.94 billion by 2024 [9]. Most of the essential oils trade occurs in the European Union, followed by North America as the major regional markets. South America and East Asia was the third and is expected to emerge as the fastest growing region in the global industry owing to rising awareness about products derived from natural sources [10]. The principal import markets are EU, USA and Japan occupying over 75% of the total import [11]. According to the European Pharmacopoeia [12], essential oils are natural products defined as the product obtained from plant raw material by different methods techniques. Hydro distillation and steam distillation are the predominant extraction methods used [13,14]. Essential oils are stored in special secretory structures and found in various parts of the plant organs (flowers, fruits, seeds, leaves, stems, and roots). Essential oils were synthesized and stored in special secretory structures, such as glandular trichomes, epidermal cells, secretory cells, secretory cavities and secretory ducts [15].

Essential Oils Biosynthesis

Terpenes

The compounds containing C10H16 were named terpenes (isoprenoides) [13]. A terpene consisting of two or more units of isoprene units [16]. Based on the number of isoprene units, terpenes are divided into monoterpenes (2 units), sesquiterpenes (3 units), diterpenes (4 units). Monoterpenes (C10H16) and sesquiterpenes (C15H24) are the most abundant in essential oil. The biosynthesis of terpenes involves two precursors: isopentenyl pyrophosphate (IPP) and dimethylallyl diphosphate (DMAPP). IPP is biosynthesized through two pathways: mevalonate pathway (MVA) and non-mevalonate (mevalonate independent) or deoxyxylulose phosphate pathway, schematized in Figure 1.

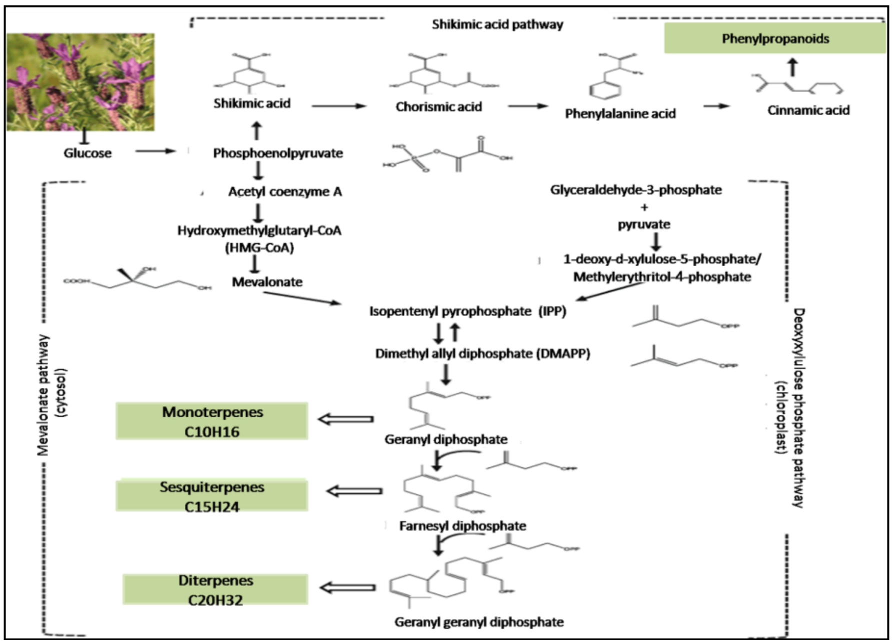

Figure 1: Terpenoids and phenylpropanoids biosynthesis in plants

In the mevalonate pathway, IPP is formed through mevalonic acid that results from the condensation of 3 acetylcoenzyme-A moieties. In the non-mevalonate pathway, 2 C-metil-D-erythritol-4-phosphate (MEP) and 1-deoxy-d-xylulose-5-phosphate (DOXP) are involved, resulting from the condensation of glyceraldehydes phosphate and pyruvate [13]. The former takes place in the cytoplasm and leads to the formation of most sesquiterpenes whereas the latter occurs in the chloroplasts, producing primarily monoterpenes and diterpenes [17]. IPP and DMAPP lead to geranyl diphosphate (GPP), the immediate precursor of monoterpenes. The condensation of GPP with IPP leads to farnesyl diphosphate (FPP), the immediate precursor of sesquiterpenes, and the condensation of FPP with IPP results in geranyl geranyl diphosphate, the precursor of phytol, other diterpenes, and carotenoids. Monoterpenes and sesquiterpenes are the main compounds found in essential oils [18]. Heavier terpenes, such as diterpenes, may also be present but usually do not contribute to the odor of essential oils [19].

Henylpropanoids

Phenylpropanoids are synthetized via the shikimic acid pathway (Figure 1), their main precursors being cinnamic acid and *p*-hydroxycinnamic acid, originated from the aromatic amino acids phenylalanine and tyrosine, respectively [14,20]. Shikimic acid is synthesized from erythrose 4-phosphate and phosphoenolpyruvate. Elimination of one of the ring alcohols of shikimic acid and reaction with phosphoenol pyruvate gives chorismic acid. This compound forms the phenylpropionic acid skeleton. Amination and reduction of the ketone function produces the amino acid phenylalanine while reduction and elimination leads to cinnamic acid that produces *o* and *p*-coumaric acids. Moreover, aromatization of shikimic acid gives benzoic acid derivatives, present in several essential oils [21].

Essential Oils Constituents

According to their chemical structures, the essential oils constituents are divided into:

- Terpene hydrocarbons [monoterpenes (C10), sesquiterpenes (C15), and diterpenes (C20)].
- Terpenes containing oxygen (terpenoids) [alcohols, ketones, aldehydes, esters, lactones, and coumarins].
- Phenylpropanoids and aromatic compounds derived from phenylpropane which are the least existent. As well as some other compounds.

Terpene Hydrocarbons

Monoterpenes (C10 H16):

Monoterpenes is the most common compounds found in essential oils and consists of two isoprene units [19] and acting also as precursors of the more complex, such as limonene found in dill, mint, citrus essential oils [22], and as the precursor of carvone and menthol constituents [23].

Sesquiterpenes (C15 H24):

One of the largest terpenes groups, such as β-sesquiphellandrene in Eryngium caucasicum and bisabolene in chamomile [24,25].

Diterpenes (C20 H32):

Diterepenes are found in essential oils in very low amounts and rarely found in most essential oils, such as camphorene, and cembrene found in *Commiphora wightii* [13,26]. Figure 2 illustrates some chemical structure of some terpene hydrocarbons found in essential oils.

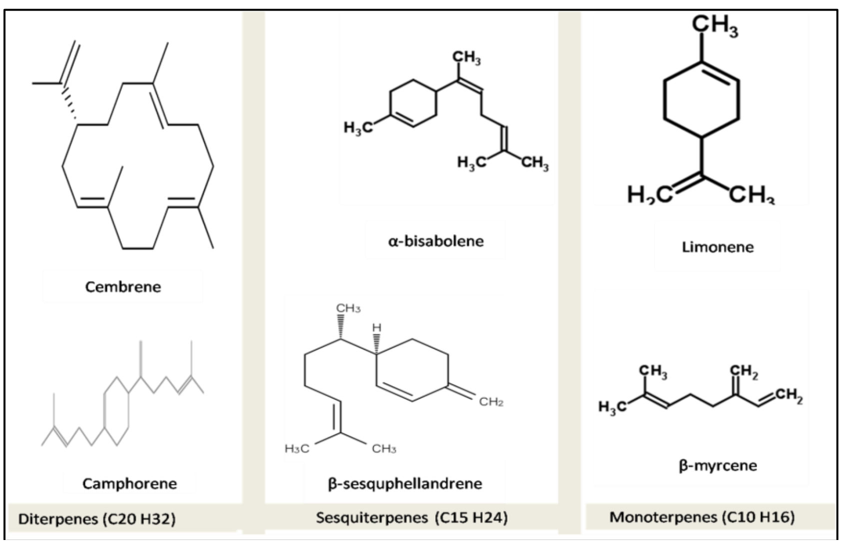

Figure 2: Chemical structure of some terpene hydrocarbons found in essential oils

Oxygenated Compounds

The oxygenated compounds are grouped as (esters, aldehydes, ketone, alcohols, phenols and oxides), and consists of a combination of carbon, hydrogen and oxygen atoms. Scientists have identified more than 3,000 compounds and there is a discovery for more continually.

Alcohols:

Alcohols have a great importance in the perfume industry [27], for example; monoterpene alcohols like, linalool found in coriander [28], terpinen-4-ol found in *Marjorana hortensis* [29], menthol in peppermint oil [30], geraniol and citronellol in rose oil [31], borneol in rosemary oil [32]; sesquiterpene alcohols like α-bisabolol in chamomile [24], α-santalol in sandalwood [33] oils; and diterpene alcohols such as phytol found in coriander [24], manool and scareol found in *Salvia officinalis* and *Salvia sclarea*, respectively [34,35].

Phenols:
The major monoterpene phenols like thymol and carvacrol found in thyme [36]. Eugenol in basil [37].
Aldehydes:
Such as citral, found in citrus lemon grass oils [38], also geranial and citronellal in lemon balm [39].
Ketones:
Monoterpenoid ketones are cyclic compounds produced by oxidation of alcohols. Monocyclic ketones such as pulegone found in *Mentha pulegium* [40], carvone in caraway seed oil, *Carum carvi* [41]; bicyclic ketones like camphor found in (*Cinnamomum camphora*) [42]; Thujone from sage (*Salvia officinalis*) [43] and isopinocamphone is the main constituent of oil of hyssop *Hyssopus officinalis* [44].
Esters:
Linalyl acetate in lavender oil [45]; neryl acetate and geranyl acetate in *Dracocephalum moldavica* [46].
Oxides:
1,8-cineole in rosemary [47] and ascaridole in *Chenopodium ambrosioides* (American wormseed oil) [48].
Ethers:
Like anethole found in aniseed [49], and safrole found in star anise [50].
Lactones and coumarins:
Sesquiterpene lactones consist of one and half terpenes (or six isoprene units) attached to a lactone ring like artemisinin in *Artemisia annua* [51]. Coumarins, such as furocoumarin – bergapten in bergamot oil [52]. Figure 3 illustrates some chemical structure of some oxygenated compounds found in essential oils.

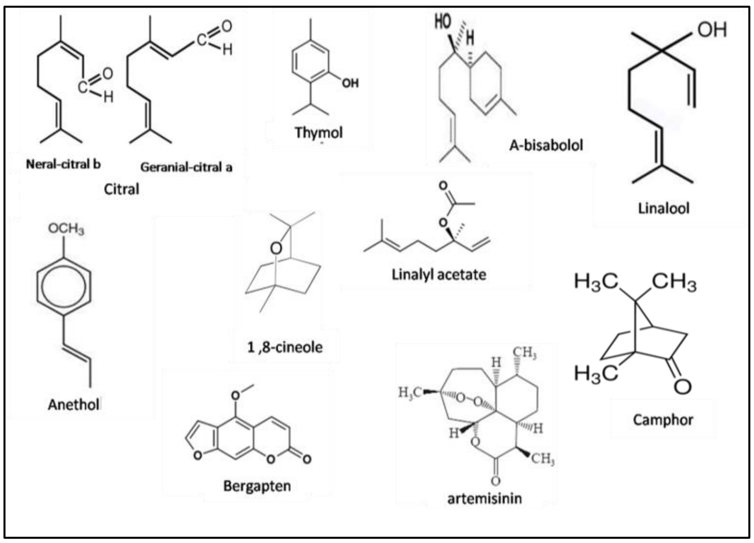

Figure 3: Chemical structure of some oxygenated compounds found in essential oils

Irregular Terpenoids

There are two major types of irregular monoterpenes have been identified. The first are substituted cycloheptane monoterpenes (tropones), such as eucarvone which found in *Zieria* species essential oils [53], and the second those compounds that do not fit the regular head-to-tail coupling such as Artemisia ketone in *Artemisia annua* [54] and Santolinatriene found in *Artemisia alba* and *Santolina corsica* [55,56] (Figure 4).

Other Compounds

Sulfur-containing compounds:
Plants such as garlic and onion contain volatile sulfur compounds, namely allyl sulfide, dimethylthiophene, dimethyl sulfide, allicin, diallyl disulfide, diallyl trisulfide [57,58]; and also, allyl isothiocyanate; butyl isothiocyanate; butenyl isothiocyanate1; allyl disulfide and phenylethyl isothiocyanate found in Brassica rapa var. rapifera [59].

Nitrogen-containing compounds:
For example, methyl anthranilate present in several citrus oils [60] and *Murraya paniculata* [61]; also, Methyl-5-hexenenitrile; Hexanedinitrile and Benzenepropanenitrile found in Brassica rapa var. rapifera [59] as seen in Figure 4.

Sulphur and nitrogen containing compounds:
4-methylthiobutyl-isothiocyanate (Erucin); 5-methylthio-pentanonitrile from the leaves of *Eruca sativa* essential oil [62] as seen in Figure 4.

Phenylpropanoids:
These compounds have no acceptable classification. It contains one or more C6-C3 fragments, The C6 unit being a benzene ring [13]. Most plant families contain these compounds are Apiaceae, Lamiaceae, Myrtaceae, and Rutaceae families [22]. Examples of these compounds in volatile oils Examples are anethole in anise and fennel [63,64]. Apiol in celery and parsley [65]. Eugenol in clove *Syzgium aromaticum* [66]. Methyleugenol found in rose oil [67]. Methylchavicol in basil [37]. Myristicin in parsley [65] as seen in Figure 4.

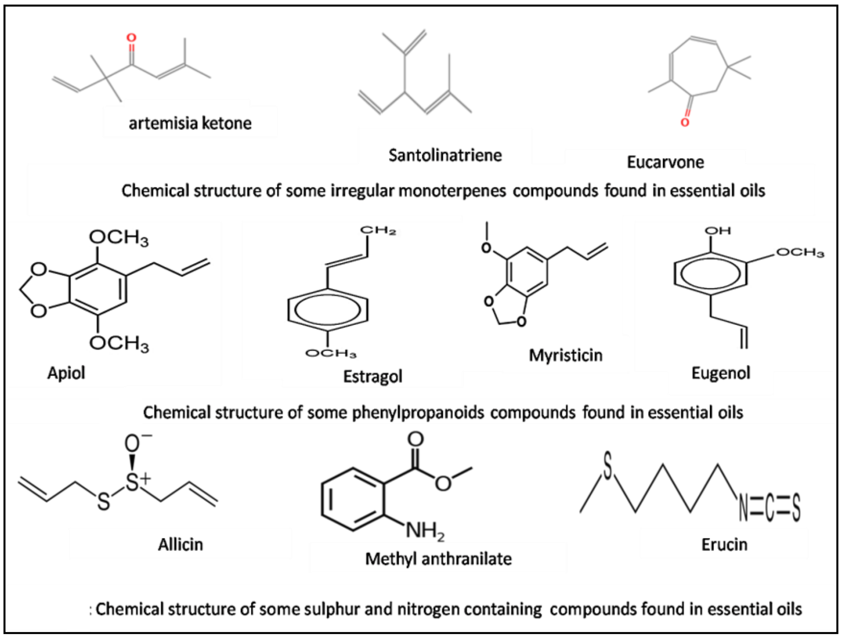

Figure 4: Chemical structure of some sulphur and nitrogen containing compounds found in essential oils

Biological Functions
Scientists have discovered the multiple biological uses of volatile oil such as bactericidal, virucidal, fungicidal, antiparasitical, insecticidal, and other applications. Scientists' efforts are continuing to discover more useful uses of volatile oils [68,69]. The scientists attributed the broad range biological activities of essential oils to chemical compounds that make up essential oils [70], among those the wide range of biological effects of essential oils.

Cytotoxicity
Cytotoxicity is the toxicity of any substance being toxic to cells and can damage an organism [71]. Toxicity may affect and cause damage to the whole organism or affecting a cell (cytotoxicity) or an organ such as the liver (hepatotoxicity). The toxicity of essential oils on bacteria, virus, fungi and yeasts [72-75] causing the membrane damage, coagulate the cytoplasm and damage lipids and proteins [76-78] leading to leakage of molecules and to lysis [79]. Some studies have shown the essential oils cytotoxicity against a large variety of organisms including bacteria [80], virus [81], fungi [82], protozoa [83], parasites [84], acarids [85], larvae [86], worms, insects [87,88] and mollusks [89]. Therefore, this cytotoxic property of essential oils has great benefit in their applications against human and animal pathogens or parasites and the preservation of agricultural and marine products. For mammals, essential oil cytotoxicity caused induction of apoptosis and necrosis. In experiments on DNA and repair DNA synthesis, Burkey et al. [90] found that the components of essential oil such as eugenol and safrole induced

cytotoxicity and genotoxicity in rat and mouse hepatocytes. The same result was achieved by the essential oil for the basil and the main component was estragole, in hamster fibroblastic cells. This is usually the effect of chemotherapy in cancer treatment where it reduces the ability of cancer cells to grow, divide and to induce cell damage and death. The scientists demonstrated the use of volatile oils for alternative or complementary cancer treatments after verifying for their cytotoxic and antiproliferative actions in cancer cell lines or tumor bearing animals [91,92]. As an example, essential oil of *Melissa officinalis* proved to be antibacterial, antifungal, and spasmolytic activities [93-95], and an anti-tumor effect of lung, colon, breast and leukemia human cancer cell lines and in a mouse melanoma cell line [96].

Interestingly, the monoterpene citral, which is the main compound in *Melissa officinalis* has the cytotoxic activity [97] and its ability to induce apoptosis in resistant cells that express MRP1 (Multidrug resistance protein) suggests their potential for tumor treatment. There are different mechanics of the cytotoxic effect of volatile oils and their ability to treat cancer, include induction of cell death by apoptosis and/or necrosis, cell cycle arrest, and loss of key organelles function. Also, essential oils act as antioxidants, affecting the cellular redox state [98-100].

Phototoxicity

Phototoxicity (photoirritation) is a chemically induced skin irritation. It is a type of photosensitivity and requiring light [101,102]. Some essential oils contain photoactive molecules like furocoumarins found in the essential oils of *Citrus bergamia, Citrus aurantium dulcis* and *Cymbopogon citratus* which bind to DNA under ultraviolet light exposure producing mono- and bi-adducts that are cytotoxic and highly mutagenic [103,104].

Thus, when studying an essential oil, it may be of interest to determine its cytotoxic as well as its possible phototoxic capacity, especially in essential oils which use in cosmetic and food products and should be minimized and reconsidered [105].

Nuclear Mutagenicity

Genetically: a mutagen is the change that occurs in the genetic material, usually DNA, and therefore the probability of mutations and these mutations may cause cancer. So the mutagenic factors are likely to be carcinogenic.

Some essential oils are genotoxic causing nuclear mutations such as, essential oils of *Artemisia dracunculus* in *Bacillus subtilis* [106] and *Mentha spicata* and *Anethum graveolens* in Drosophila melanogaster [107-109], also *Anethum graveolens*, *Pinus sylvestris* and *Mentha piperita* essential oils were genotoxic on human lymphocytes [110]. One of the compounds of essential oils that cause genotoxic and carcenogenic is the mentone from mint [108,111], and anethol from fennel and anise essential oils [112,113].

Asarone from *Acorus calamus* essential oil caused mutagenic (carcenogenic) in hepatocytes [114], human lymphocytes and in mouse bone marrow [115,116]. Trans-anethole oxide and trans-asarone oxide, were genotoxic and induced liver and skin cancers [117]. Terpineol, cinnamaldehyde, carvacrol, thymol, carvone and eugenol have mutagenic effects [118-120]. Therefore, the importance of essential oils as mutagen used in anti-cancer therapy and destroys cancer cells to reduce the side effects of the chemotherapy and radiation therapy.

Cytoplasmic Mutagenicity

We mentioned before for mutagen which induced genetic damages resides in the DNA of the nucleus. Without knowing the biological consequences of cytoplasmic damage (cytoplasmic genes) "cytoplasmic genes": DNA-containing bodies in the cell but external to the nucleus meaning that cytoplasmic mutagenicity occurs in cytoplasmic organelles such as mitochondria and chloroplasts or from cellular parasites like viruses or bacteria.

Scientists have learned from the yeast to prove the relationship between the deterioration of mitochondria and essential oils, where they observed immediate changes of respiratory metabolism after treatment of yeast cells (*Saccharomyces cerevisiae*) with the tea tree essential oil [121], and the treatment of the yeast cells with essential oils of cinnamon, clove, garlic, onion, oregano and thyme led a delay in ethanol production [122]. In plants, treatment of plants with essential oils leads to mitochondrial damage including mitochondrial membranes and DNA and thus the formation of mutations (respiratory deficient cytoplasmic petite mutants). But the treatment of α-pinene prevents these mutations [122]. In the bacteria and mammals, cells damage occurs in the respiratory system and thus cell death.

Carcinogenicity of the Essential Oils

A carcinogen is any substance that causes cancer because of its ability to damage the genome or destroy the cellular metabolic processes and induces the uncontrolled, malignant division, leading to the formation of tumors. However, severe DNA damage leads to apoptosis, but if the programmed cell death pathway is damaged, then the cell cannot prevent itself from becoming a cancer cell [123]. Therefore, cancer is a disease in which normal cells are damaged and do not undergo programmed cell death as fast as they divide via mitosis [123]. Co-carcinogens are chemicals does not cause cancer on its own but promote other substances carcinogens to cause cancer [123].

Most of essential oils are cytotoxic without being mutagenic, but they are carcinogenic after metabolic activation [124]. As an example, *Salvia sclarea* essential oil stimulates estrogen secretions and then induces estrogen-dependent cancers.

Some essential oils contain photosensitizing molecules that cause skin cancer. Of these oils is the *Citrus bergamia* (*Citrus aurantium* ssp. bergamia) essential oil containing psoralen which a photosensitizing molecule that induce skin cancer after formation of covalent DNA adducts under ultraviolet A or solar light [125]. In *Sassafras albidum* essential oil, safrole compound induces carcinogenic metabolites in rodents [126,127]. Similarly, limonene, compound found in the citrus essential oil, was carcinogenic in male rats [126]. Estragole, found in the essential oils of *Ocimum basilicum* and *Artemisia dracunculus* have carcinogenic properties in rat and mouse [127,128]. However, pulegone component from mint essential oils, induce carcinogenesis [129].

Antimutagenic Properties of Essential Oils

Mutations are implicated in many important human diseases, including atherosclerosis, autoimmune and neurodegenerative diseases, some types of diabetes and cancer. There are evidences that essential oils act as inhibitors of mutagenesis and carcinogenesis [130,131]. For many years and still more studies on the detection of the role of volatile oils as antimutagenic properties. The efforts of the scientists succeeded in this, where the results indicated that essential oil of sage (*Salvia officinalis*) possess antimutagenic potential against mutations [132]. Also, sage essential oil has an inhibitory effect on chromosome aberrations in mice [133].

The previous studies showed that the effectiveness of essential oils as anti-mutagenic properties may be due to inhibition of penetration of the mutagens into the cells [134,135], inactivation of the mutagens by direct scavenging, antioxidant capture of radicals produced by a mutagen or activation of cell antioxidant enzymes [136-138], inhibition of metabolic conversion [139], or activation of enzymatic detoxification of mutagens. The essential oil may be promoted to repair the DNA with an unknown possibility [140,141].

Essential oil of *Origanum compactum*, *Melaleuca alternifolia*, *Lavandula angustifolia*, *Helichrysum italicum*, *Ledum groenlandicum* and *Ravensara aromatica* has antimutagenic properties [142-144]. Hernandez-Ceruelos et al. [145] demonstrated that essential oil of *Matricaria chamomilla* has the potential as antimutagenic effect and Gomes-Carneiro et al. [142] attributed this action to α-bisabolol component. Also Vukovic-Gacic et al. [136] showed that antimutagenic effect of *Salvia officinalis* essential oil is due to thujone, 1,8-cineole, camphor and limonene compounds. They also revealed that menthol, α-pinene, α-terpinene, α-terpineol, 1,8-cineole, limonene, camphor, citronellal and citral compounds have antimutagenic effect.

So now it has become acceptable that prooxidant activities can induce apoptosis and necrosis [146-148], and may damage cellular membranes, and finally leads to cell death, at least in mammalian cells [149,150], hence the importance of volatile oils as antioxidants and its role as antimutagenic.

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