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AROMATHERAPY APROPOS OF NORMAL FLORA: FRIEND OR FOE?

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Aromatherapy was practiced since prehistory for alleviating diseases and/or stress relief. Recently, it bloomed after complementary and alternative medicine became popular among individuals seeking homeopathic treatment to evade side effects. Studies revealed that aromatherapy owes its efficacy to complex essential oils that show qualitative and quantitative variabilities depending on plant-related factors. Aromatherapy is delivered through inhalation and dermal contact where volatile oils act locally or penetrate to the circulation to exert systemic effect. Many essential oils possess antibacterial, antifungal, antiviral and/or cytotoxic activities which raises concern against their random use and believing they are completely safe. Also, little evidence exists depicting the selectivity of essential oils towards pathogenic rather than endogenous microbiota. Relevantly, microflora dysbiosis can negatively impact the host's health. Therefore, this article aims to emphasize that long-term studies are required to regulate aromatherapy practice without endangering the body's homeostasis and refute the misleading assumption of its unquestionable safety.

***Keywords**: Aromatherapy; Complementary and alternative medicine (CAM); Microbiota; Essential oils (EO); Dysbiosis*

INTRODUCTION

Complementary and alternative medicine (CAM) is the treatment and diagnostic approaches that take place outside the frame of the standard conventional medical care. They include the historic healing practices and ancient disciplines passed down through generations. Thereby, the concepts and strategies vary between the different cultures in different geographical regions and many have already been included into medical schools curricula and integrated into standard healthcare protocols e.g.: osteopathy and chiropractic that got recognized by the Royal College of General Practitioners in the UK [1]. Whether due to cultural beliefs or actually believing in their effect, many individuals attempt CAM methods in different health conditions, ranging from simple flu or joints stiffness up to cancer support with or without informing their healthcare providers[2,3]. Therefore, the formal and governmental bodies of the modern Western authorities, e.g.: National Health Service (NHS) in the UK and National Institutes of Health NIH and National Center for Complementary and Integrative Health (NCCIH) in the USA, have devised programs to systematically research the different disciplines and their effects alone or in combination with standard medications[1,3–5]. Furthermore, due to the agile and buoyant dynamics of the healthcare systems, new branches and variations are continually evolving that can be classified, according to the NCCIH, into five main domains, as depicted in **Fig.1; 1)** alternative medical systems, 2) biologically-based interventions, 3) energy therapies, 4) manipulative and body-based practices, and 5) mind-body medicine[2,3].

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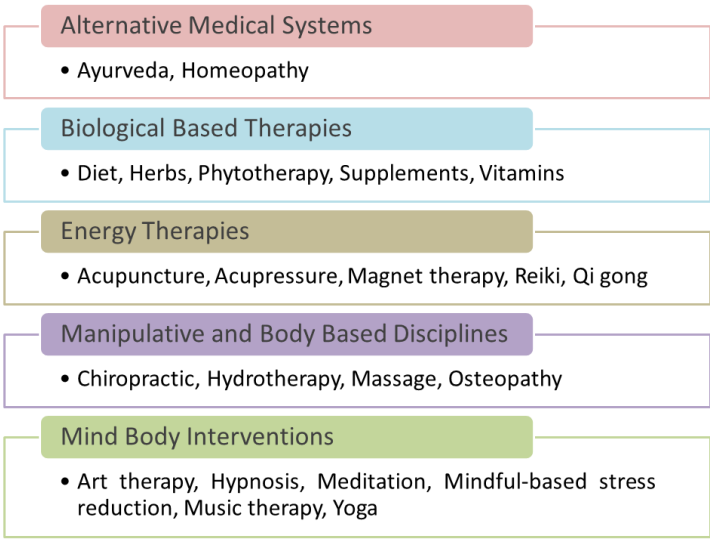

Fig. 1: Main domains of complementary and alternative medicine (CAM) and some of the common examples.

Based on the age, ideologies, education level and access to medical consultation, there are many reasons why patients prefer CAM procedures or seek them as first line of therapy. These include the lower cost, availability in herbal shops, the ease of accessing and communicating with the local practitioners and the notion of their safety and absence of adverse effects (AEs). Furthermore, the act of self-prescription confers a positive psychological impact upon the patients believing that they have control over their own health[3,6,7]. It is imperative here to point out that not only have different CAM interventions been studied as alternative or integrative approaches, but phytotherapy and herbal medicine have also provided basis of developing many active drugs e.g.: aspirin, codeine, digoxin, taxol, etc.[6,8,9].

Aromatherapy as a natural healing practice

Aromatherapy, or essential oil therapy, is a holistic, integral and very popular form of CAM that comprises using essential oils (EO), also known as volatile oils, from different plant parts (e.g.: flowers, stems, leaves, barks and roots of herbs and trees) to improve the emotional, psychological and physiological status[9–11]. More than 3000 EOs have been isolated and identified over the years, out of which almost 300 are commercially important and commonly employed. Aromatherapy has indeed been used since the dawn of time for spiritual and therapeutic healing and re-surfaced in the late 20th century to be widely used alongside mainstream medicine. The main route of administration thereof is inhalation and topical application. Yet, not only local but also systemic medicinal activities have been described. This happens mainly on account of the essential oils olfactory absorption and skin penetrability e.g.: antibacterial, antifungal, antiviral and antioxidant effects, immunomodulation, pain and stiffness relief in musculoskeletal disorders, reduced hypertension, alleviating irritable bowel symptoms, improved sleep quality, relief of migraine, palliative care in cancer patients, etc.[5,9-10,12–17]. Internal use, on the other side, has been cautiously proclaimed. Meanwhile, many official health associations warn against it, due to the high toxicity of EOs upon ingestion, contact with mucosa or even undiluted application to the skin. Hence, they are almost always diluted in carrier oil (vegetable or nut oil) prior to consumption. Higher dilutions (< 2%) are recommended in cases of pregnancy, younger age, underlying diseases (esp. circulatory disorders, asthma and epilepsy) and co-medication[7,10,18]. Other seldom employed routes are intranasal, rectal and vaginal[5,7,10]. Worth mentioning here to point out that this toxicity risk holds no contradiction with the fact that many EOs are designated as GRAS (generally recognized as safe) by the U.S. Food and Drug Administration (FDA) for use as flavors, since they are assessed in extremely low concentration for this purpose.

Besides, they are widely used to enhance the sensory properties of pharmaceutical formulations. EOs have also gained a widespread use in the wake of SARS-COV-2 pandemic due to its effectiveness in alleviating ageusia and anosmia i.e., loss of taste and smell, which are the most common post COVID-19 symptoms[14,19].

Not so long ago, the scientific community has found aromatherapy to be controversial and described it as pseudoscience due to its relevant theoretical ambiguity and the absence of conclusive evidence to support its clinical effectiveness[13,16]. Interestingly, the fragrant nature of essential oils played a big role in this belief as it is difficult to design a blind experiment and provide placebo with a similar characteristic smell, and to oust the psychological factor from assessing the participants' outcome.

Since the late 1970s, there has been an increased public and scientific interest in natural therapies and the popularity has only increased hitherto, influencing the education curricula of healthcare practitioners, the public choices of over-the-counter (OTC) medications and definitely, the scientific attention to investigate, understand and validate the therapeutic value of EOs in order to integrate them in mainstream orthodox medicine[4,10,15].

Historical background of aromatherapy

Aromatics have been employed more than 3500 years BC for different purposes e.g.: medications, perfumes, food additives, and religious rituals. Aromatherapy was first practiced in ancient Egypt as primitive distiller apparatuses were developed for basic crude extraction of oils. Oils, salts, and creams were used for treating several ailments, in addition to preserving the dead corpses before burial. It was believed that the goddess of healing, Sekhmet, mother to Nefertem, the god of incense, fragrant oils and perfumes, used fragrances to bestow health on the living humans and aid the deceased in the next life. The Indian Vedas, written more than 2000 years BC, also documented many plants and extracts that are still in use e.g.: sandalwood, coriander and myrrh. Almost concurrently, the Chinese healing methods exploited the citrus family to achieve the balance between Qi (vital energy), Yin and Yang (negative and positive energies), which was illustrated in the "Internal Medicine" book by the Emperor Huang Ti, along with other medicinal plants and herbal remedies[9,11,20-21].

The Greek physician Dioscorides, father of current herbal textbooks, adapted the plants' application from the ancient Egyptians. Galen's work expanded the Greek knowledge into the Roman culture. Aromatherapy was performed in baths, spas and saunas, and diseases were believed to originate from the imbalance among the four humors (blood, phlegm, yellow bile, and black bile). There was a common trend for *Euporista* instead of physicians i.e.: to adapt easy natural treatments from private farms or gardens. Afterwards, Arabic scientists took over from the previous cultures and developed many of the up-till-now theories and processes. In this era, there was a considerable advancement in *materia medicas*, aromatics and botanical expertise mostly due to Avicenna's efforts[20,21]. The modern concepts of aromatherapy ensued by the French chemist Gattefossé, who created the term *Aromatherapie*, and was followed by Valnet who focused on EO research and included his findings in "The Practice of Aromatherapy" book that illustrated the application in treating wounds, infections, and other ailments.

Nature of essential oils

EOs are secondary metabolites, produced by plants for chemical signaling, cellular repair, insects attraction for pollination and to protect against predators, herbivores and stress conditions e.g.: temperature variations, bacterial or pest infection and draught[11,22]. EOs were reported from several angiosperm families, such as Alliaceae, Apiaceae, Asteraceae, Lamiaceae, Lauraceae, Myrtaceae, Poaceae, Rutaceae, Zingiberaceae, etc. They are categorized, according to fragrances, into the groups; camphorous (e.g.: hyssop, myrtle), citrus (e.g.: lemon, lime, orange), earthy (e.g.: oakmoss, patchouli, vetiver), floral (e.g.: jasmine, lavender, neroli), herbaceous (e.g.: basil, marjoram, rosemary), minty (e.g.: peppermint, spearmint), spicy (e.g. cinnamon, clove, nutmeg) and woody (e.g.: cedarwood, pine, sandalwood)[9,22,23].

The EO composition is undeniably so complex that a single mixture may contain up to 300 single volatile components.

Furthermore, the composition depends on the geo-climatic factors and cultivation conditions i.e., temperature, sun light exposure, soil type, altitude, harvesting time, ripening degree, etc. Besides, postharvest handling of plants is significant to the volatile oils' qualitative and quantitative properties e.g.: storage, cleaning, extraction technique and distilling processes, etc.[5,16,17,24] They are obtained by several methods e.g.: hydro-distillation, organic solvent extraction, mechanical pressure, microwave-assisted extraction, enfleurage, maceration in oil, super critical carbon dioxide extraction, etc.[9,10,17]. They are hydrophobic in nature and the constituents belong to a variety of saturated and unsaturated hydrocarbon compounds from different classes, a few of which are shown in **Fig. 2.** The classes include hydrocarbon terpenes as major components (mono- and diterpenes, biosynthesized via the methylerythritol route, and sesquiterpenes that are obtained through the mevalonate pathway), oxygen-containing terpenoids (phenols, aldehydes, phenyl methyl esters, etc.) via the shikimate pathway, non-terpene hydrocarbons biosynthesized by the phenylpropanoid pathway, in addition to sulfur and nitrogenous compounds[14,17,23].

The importance of normal bacterial flora and how they influence the host's health status

Bacterial flora (also microflora, microbiome, or microbiota and sometimes also referred to as the separate organ or the forgotten organ) is the collective endogenous communities of myriad of microorganisms (bacteria, archaea, fungi, and viruses) that can be found in a specific niche e.g.: human beings, animals, plants, and environmental locations **(Fig. 3 a).** With respect to human beings, they reside on the skin and mucous membranes of different body parts and in several viewpoints, the human body together with the associated microorganisms are perceived as an individual entity, referred to as holobiont under the hologenome concept, due to the interactive and/or symbiotic nature thereof[25–28]. The microbiota linked with an individual primarily follows the rules of genetics and inheritance and evolves with the host during one's life based on the age, lifestyle, diet, surrounding environment, habitat, etc.[28–31].

Microbiota is commensal or mutualistic microorganisms and their positive impact on human health is amply and increasingly recognized, and the conservation of the homeostasis of the holobiont ecosystem is deemed crucial for maintaining the hosts' health. It protects the body against external infectious agents by antagonizing the pathogens and reinforcing the immune system both locally and systemic, exerts sound immunomodulatory effect, and regulates many physiological functions e.g.: response to inflammations, allergies, proper digestion, non-communicable diseases, etc.[25-26,30,32-33]. Furthermore, it is widely premised that the higher the exposure to diverse environmental microbiota, especially in the early age up to 3 years, the more pronounced the health outcomes and sustainment[26]. This is evident by the differences in immune responses and general health conditions among rural and urban children, manual and industrialized societies, or even pets' owners.

As previously mentioned, the microbiota serves as a complex physiological barrier against infectious microbial invasion and other functional disorders and diseases. Hence, changes to the innate holobiont or dysbiosis (via factors like; diet and lifestyle modifications, hygiene and sanitation, prolonged antibiotics use, co-morbidities, immigration, and others) are promptly translated into aberrant host responses e.g.: compromising immunity, proper digestion, gut-brain axis, etc. **(Fig. 3 b).**

Oral microbiome is very diverse, on the one hand due to its anatomy as each of the mucosa, tongue, soft tissue, hard tissue and the teeth surfaces represent distinct niches, and on the other hand due to the hosts oral hygiene, diet, tobacco and alcohol consumption[25-27-34]. The microbes belong mainly to Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes, and Fusobacteria[25,32] where any disruption lead to conditions like; gingivitis, halitosis, periodontitis, etc. Microbiota starts colonizing the skin immediately at birth and intriguingly, the genera in newborns differ according to the birth conditions (i.e.: normal birth or caesarian section, home or hospital birth, breastfed or formula-fed, etc.)[26,33]. Skin microbiota is usually poor in the taxa repertoire due to its nature (acidic pH, sebaceous glands,

moisture), yet it is home to a plethora of microorganisms mounting up to one million per cm^2. The prevalent genera are *Staphylococcus*, *Propionibacterium*, *Corynebacterium*, and *Streptococcus* whose dominance depends on the skin's moisture. Fungi are also strongly represented among skin microbiota especially ascomycetes and *Malassezia*, and to a lesser extent, *Aspergillus* , *Cryptococcus* and *Rhodotorula*[25,26,33]. Disturbance of skin microbiota is associated with alopecia, atopic dermatitis, and other diseases as they control the secretion of antimicrobial peptides by sebocytes and keratinocytes[32]. The upper respiratory tract, principally the nasopharynx region, is inhabited by members of *Corynebacteriaceae* and *Staphylococcaceae* families and less by *Peptoniphilaceae* and *Carnobacteriacea* species namely; *Staphylococcus*, *Corynebacterium*, *Alloiococcus*, *Haemophilus*, *Streptococcus*, *Granulicatella*, and *Moraxella*[25]. Nasopharyngeal microbiota (or airway microbiota) perturbation is manifested by several diseases e.g.: asthma, rhinosinusitis, bronchiolitis, influenza, etc. Gut microbiota (GM), on the other hand, are the most significant, largest, and most versatile microbial community within the human body due to the different physiological conditions along the gastrointestinal tract e.g.: pH, redox state, bile acids, motility, etc. Like other microflora communities, they are also influenced by intrinsic and extrinsic factors e.g.: genetics, age, stress, diet, lifestyle, mode of birth and medications. GM secrete several metabolites that affect many of the hosts' physiological roles e.g.: food digestion, nutrients extraction, xenobiotics processing, immunity, drug assimilation, vitamins biosynthesis, neuronal signaling, hormonal functions, etc.[24,27–31,35]. It is customary to say that GM's taxa assortment and genetic richness are a measure for gut health where the species vary along the gut's length. The most abundant phyla include Firmicutes (*Clostridia*, *Eubacteria*, *Faecalibacteria*, *Lactobacilli*, *Ruminococci*, *Streptococci*), Bacteroidetes (*Bacteroides*, *Prevotella*), and to a lesser extent Proteobacteria (*Desulfovibrio*, *Escherichia*), Actinobacteria (*Bifidobacteria*), Euryarchaeota (*Methanobrevibacter*) and Verrucomicrobia, while the decline thereof could be depicted as disorders of gut-brain axis and neurodegenerative diseases e.g.: Parkinson and Alzheimer's diseases, cardiovascular diseases e.g.: hypertension and atherosclerosis, energy absorption and metabolic distortions e.g.: obesity, dyslipidemia, insulin resistance, inflammatory bowel and fatty liver[24,28,30-31,35].

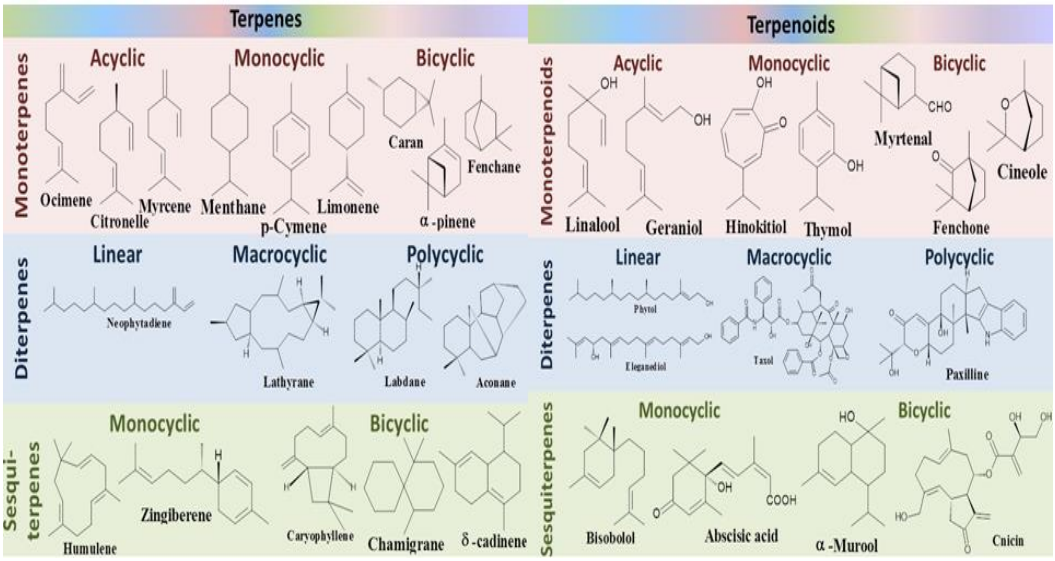

Fig. 2: Examples of essential oils constituents.

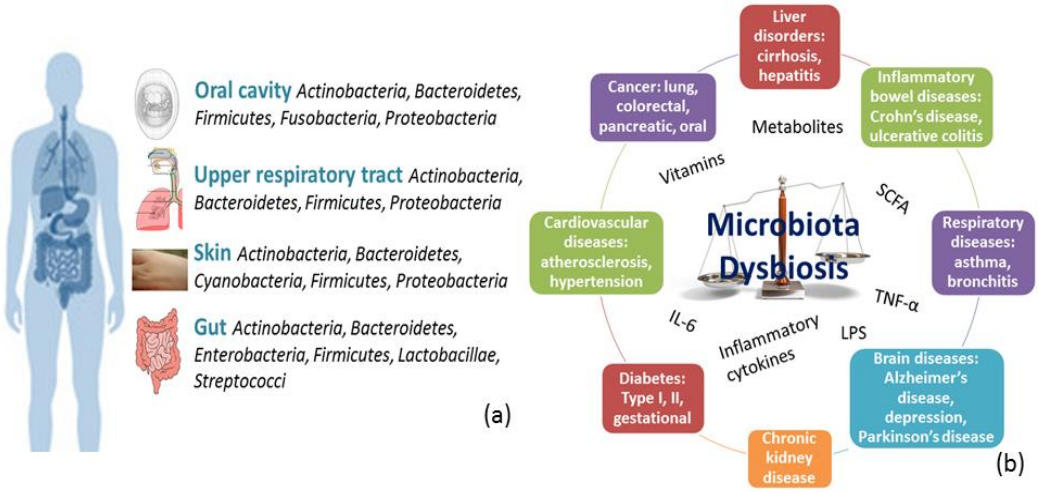

Fig. 3: Human microbiota (a) predominant genera in different locations, (b) diseases related to microbiota dysbiosis; where SCFA stands for short-chain fatty acids; LPS, lipopolysaccharides; TNF-α, tumor necrosis factor alpha; and IL-6, interleukin 6.

How essential oils affect normal bacterial flora

As summarized in the previous section, human microbiota is essential to the metabolic well-being through direct prevention of pathogens, humoral and cellular immunity boosting, energy harvesting, supplying essential nutrients or other physiological processes. For the past few decades, this was strongly emphasized by multi-omics data, including metagenomics and metabolomics analyses and thus, any irregularities are reflected as different pathogeneses. Furthermore, correlations have been established expressing the microbiota dysbiosis during different diseases and interestingly, using them as diagnostic markers or manipulating them for achieving therapeutic targets e.g.: as diet changes, nutraceuticals, via fecal microbial transplantation (FMT), bacterial engineering, or microbiota modulation[24,27–31,35].

Aromatherapy is mainly delivered through inhalation and dermal contact where the volatile oils exert local effect (e.g.: in cases of dermatitis, wound healing, sinus congestion) or penetrates to the circulation to exert systemic effect (e.g.: for improving sleep disturbance, dysmenorrhea, gastrointestinal disorders). EOs' systemic pharmacodynamics is a function of their lipophilic nature that enables permeability through cell walls and cellular lipid membranes to interact with cellular targets, although several reports claim the ambiguity of these targets and the difficulty to specifically assign them due to the complexity of EO's composition and the necessity of the synergistic effects of their components[9,23,36]. Their biological activities are surely versatile and many of them are witnessed in aromatherapy depending on the oil utilized during the intervention e.g.: bergamot, chamomile, geranium, lavender, lemon and neroli oils led to significant decrease in blood pressure when inhaled or massaged[37–39]. Lavender and chamomile oil massage or inhalation has also reduced stress, anxiety and depression, comparable to benzodiazepines, in geriatrics, post-partum cases, hemodialysis and acute coronary patients due to increased serotonin, dopamine and γ-aminobutyric acid neurotransmitter levels[39,40]. Lavender and sweet orange oils aromatherapy could decrease the severity of the pain levels in hemodialysis patients upon inserting the fistula needle by blocking the sodium channels in the pain nerves, as well as inducing the limbic system to secrete endorphins and serotonin [18,22]. Bitter orange, lavender, frankincense and rose oils inhalation were associated with easing the pain of the early natural labor phase in primiparous women and in post-operative pain[22]. Cypress, eucalyptus and fennel oils relieved bronchial and respiratory problems on inhalation[11,22]. Additionally, many of the commonly-used EOs are reported to have strong antibacterial, antifungal, antiviral activities and have therefore been applied for oral hygiene,

treatment of wounds and in food preservation. Broad spectrum antimicrobial activity stems as EOs, especially aldehydic and phenolic ones, enter the cells and work by (i) disintegrating the membrane structure increasing permeation, (ii) depleting ions and cellular molecules, (iii) down-expression of efflux pump genes so the hydrophobic molecules are retained or (iv) even quorum-quenching and (v) biofilm disruption e.g.: carvacrol, eugenol, thymol, and tea tree oil. Other EOs (e.g.: carvone and trans-cinnamaldehyde) are bacteriostatic without disrupting the cytoplasmic membrane or affecting the proton pump or ATP pool[23,34,41]. Ketonic and ester-containing EOs (e.g.: *β*-myrcene and geranyl acetate) have weaker activities while terpenes are inactive. Gram-positive bacteria are more susceptible to EOs, probably due to the outer polysaccharide membrane that surrounds Gram-negative bacteria and filters out or limits the diffusion of the lipophilic molecules[24,41,42]. The antibiotic potential is also reported in fungi, yeast, protozoa, virus, parasites, and larvae[11,23].

Additionally, some evidence for the prebiotic effect of EOs was reported ie: changing the composition of microbiome in favor of beneficial bacteria. EOs are converted by GM into fermentation products (mainly short-chain fatty acids SCFA e.g.: lactic acid, butyric acid, propionic acid) that affect the local pH and hence, the normal flora composition, and get released into the blood circulation to exert both proximal and distant health-boosting effects e.g.: immune, cardiovascular and central nervous systems[43–45]. It is important here to mention that there is no consensus definition for the term "prebiotics" and many revisions took place since it was first described in 1995 yet, it has always been reported as beneficial for the consumer's health [43]. A comprehensive study on the EO of the Chinese herb *Pogostemon cablin* (patchouli), mainly consisting of patchouli alcohol tricyclic sesquiterpene, was conducted. In mice models, patchouli EO significantly increased the beneficial lactic acid-producing *Lactobacilli*, in addition to other SCFA-producing bacteria e.g.: *Anaerostipes butyraticus*, *Clostridium lactatifermentans* while the main G-protein coupled SCFA receptors 41, 43, 109a, that are essential for gut homeostasis, also increased. Harmful bacterial, on the other hand, decreased after the treatment e.g.: *Helicobacter* spp., *Sutterella* spp. Other benefits were also noted post patchouli EO intake including, protection against pathogenic bacteria, colitis, Crohn's disease, inflammation, cancer progress and metastasis via various mechanisms; (i) better gut epithelial lining by increasing mucin, E-adherin, and tight junction proteins Zona occluden-1 and occludin, (ii) decreasing vascular cell adhesion and intercellular adhesion molecules, (iii) increasing the anti-inflammatory M2 macrophages and cytokines IL-4, IL-10 while down-regulating the expression of the pro-inflammatory M1 macrophages and cytokines IL-1β, IL-18, TNF-α, Foxp3[44]. Another study demonstrated that feeding oregano EO (thymol, carvacrol, and terpinene) to ruminant cattle resulted in higher levels of propionate and butyrate, previously described as cellular differentiation promotor, anti-inflammatory, immunity modulator, and anti-cancer. Longer papillae, also attributed to butyrate, were observed which eventually led to improved growth development and carcass weight. Results also proved that oregano EOs decreased the amylolytic in favor of the fibrinolytic bacteria allowing the improved fibers digestion into SCFAs, according with the original prebiotic definition. A significant rise in *Parabacteroides distasonis* was detected enhancing succinate production that regulates glucose metabolism and facilitates propionate biosynthesis. This species also aids in gut wall integrity through tight junction proteins expression leading to efficient absorption capacity and digestion[46]. EOs from *Camelina sativa* (big seed false flax), *Brassica juncea* (brown mustard), and *Lavandula angustifolia* (spicate lavender) also demonstrated prebiotic effects when applied to chicken intestinal model. Lactic acid bacteria and *Bifidobacterium* increased and their acid-producing capacities escalated which ended up in decreasing-to-abolishing lactose-positive bacteria, *Enterococcus*, *E. coli*, and *Proteus*[45].

The hypothesis that aromatherapy is natural and hence, their safety is undeniable is absolutely inaccurate and many side effects were recorded. The most common ones are nausea, allergies, contact dermatitis, and irritation while other more serious AEs depend on the applied EO and may include blisters,

skin necrosis, dyspnea, pulmonary edema, respiratory distress, eczema, convulsions, gynecomastia, etc.[7,47]. Excluding accidental intake reports, AEs can be so severe that they require hospitalization or skin grafts (e.g.: peppermint oil toxicity)[7]. Recently, acute eosinophilic pneumonia cases were confirmed after aromatherapy inhalation by healthy and asthma patients who compliantly administer albuterol and corticosteroids inhalers[47–49]. Yet, under-reporting of AEs remains a significant problem hindering understanding and assessing the true repercussions of aromatherapy and drawing practical instructions for dos and don'ts.

The contribution of aromatherapy to bacterial resistance is amid the less-explored and discussed points especially that they are used in minute doses and thus, the microbial exposure to sub-lethal amounts may trigger resistance due to the complexity of EOs' structure and that several cellular targets are involved[50]. Meanwhile, sufficient evidence is lacking since limited studies were conducted to address this concern, compared to the ones that highlight the potential of EOs and the richness of the phytochemical library. Few examples were documented of EO-induced bacterial resistance *in vitro* which is still quite inconclusive to guide healthcare providers to evidence-based decisions in this regard. Few cases of bacterial resistance were even observed via mechanisms similar to those of synthetic antibiotics i.e., reduced membrane permeability, efflux/influx modulation and chemotaxis-regulated motility e.g.: *Salmonella enterica* developed resistance to basil oil's linalool (*Ocimum basilicum*) after long exposure[36], Becerril and co-workers noticed an increasing resistance to oregano (*Lippia graveolens*) EO (mainly carvacrol) by *Serratia marcescens*, *Morganella morganii* and *Proteus mirabilis*[51], and tea tree oil was linked to cases of methicillin-resistant *Staphylococcus aureus* resistance emergence[50]. The selectivity of EOs to pathogenic microbes over normal flora is also not often discussed, albeit the possible frequent and long use of aromatherapy for mild conditions of sleep disorders, fatigue, pain, etc. Ambrosio and colleagues documented one of the very few relevant studies and showed that the GM *Lactobacillus plantarum* was more susceptible to EOs from *Lippia sidoides* and *Thymus vulgaris* (alecrim-pimenta and thyme, respectively) than to streptomycin standard antibiotic, where *L. sidoides* even inhibited the GM more than the gastroenteritis-causing *Salmonella enteritidis*. In the same study, EOs from *Eucalyptus grandis* and *E. urograndis* (containing allo-ocimene, cineol and α-pinene) selectively inhibited *L. plantarum* while citrus oils, rich in limonene and citrus terpenes, did the opposite[42]. Aires and colleagues also corroborated *in vitro* antibacterial effect of thyme and oregano against normal oral bacteria *Actinomyces viscosus*, *Streptococcus oralis*, *S. salivarius* and others in both planktonic and biofilm forms[34]. Other studies demonstrate how microbiota, *in vitro* or in animal models, is affected upon using EO in phytotherapy, ethnic or even ethnoveterinary medicine, which also suggests emerging imbalance e.g.: for controlling obesity, reduce systemic inflammation, hypocholesterolemia, prebiotic action and increased milk production[24,52–58].

Noteworthy, as well, is that microbiota studies have so far been primarily concerned with the bacterial counterparts while fungi, viruses and other components remain seriously under-studied in health and disease. Therefore, a lot of effort and long-term studies are important to elucidate the limits of xenobiotics administration regimens and the subsequent dysbiosis, as well as observing the *in vivo* consequences under natural conditions.

Conclusion

Despite the great and, yet, increasing popularity of aromatherapy among different socioeconomic classes and in different geographical territories, this practice still relies on societal rituals or oral advice rather than scientific data in most cases. In this regard, a lot is still to be fathomed about the safety, exposure doses, intervention route and other aspects to establish prudent basis. Besides, the chemical variability of essential oils composition (based on climatic, agronomic, or anthropic factors) constitutes a hurdle against standardization of the therapy outcomes without reverting to complicated chemo-typing and analytics by gas chromatography and mass spectrometry. Furthermore, the notion of the absolute benignity of essential oils is quite inaccurate due to their diverse spectrum of biological outcomes, including antimicrobial

activity, which should inevitably influence the hosts' microbiota leading to altered health status. Conclusively, there is an enticing research gap for long-term studies and applying Next Generation Sequencing (NGS) to monitor the effect of the complementary and alternative medicine on microbiota imbalance in health and diseases.

Abbreviations

Adverse effect, AE; Complementary and alternative medicine, CAM; Essential oil, EO; Gut microbiota, GM; National Center for Complementary and Integrative Health, NCCIH; Short-chain fatty acids, SCFA.

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العلاج العطري فى مقابل الميكروبيوم: صديق أم عدو؟

هبة يحيى

قسم كيمياء المنتجات الطبيعية والميكروبية، معهد بحوث الصناعات الصيدلية والدوائية، المركز القومي للبحوث، الدقي ١٢٦٢٢، القاهرة، مصر

يستخدم طب الروائح أو العلاج العطري منذ أزمنة بعيدة لعلاج الأمراض المختلفة أو للاسترخاء و تخفيف التوتر. و قد ازدهر مرة أخرى في العقود القليلة الماضية بعد أن أصبح الطب التكميلي والبديل شائعًا بين الأفراد الذين يسعون إلى العلاج المثلي أو الطب التجانسي للحد من خطورة الآثار الجانبية للعلاج. كشفت بعض الدراسات المنهجية أن فاعلية العلاج بالروائح ترجع إلى الزيوت العطرية أو الزيوت الطيارة ذات التركيب المعقد والتي تختلف خواصها من حيث الكميات و التأثير على حسب العوامل الداخلية والخارجية التي تعرض لها النبات (على سبيل المثال: درجة النضج ودرجة الحرارة ونوع التربة وتقنية الاستخراج). يتم استخدام العلاج بالروائح بشكل أساسي من خلال الاستنشاق والتلامس الجلدي حيث يكون للزيوت الطيارة تأثير موضعي (على سبيل المثال: في حالات التهاب الجلد والتئام الجروح واحتقان الجيوب الأنفية) أو تنفذ إلى الدورة الدموية لإحداث تأثير جهازي (على سبيل المثال: لتحسين اضطرابات النوم وعسر الطمث واضطرابات الجهاز الهضمي). أوضحت العديد من الدراسات أن الزيوت العطرية أو الطيارة تمتلك نشاطًا قويًا كمضادات للبكتيريا والفطريات والفيروسات كما تمتلك تأثيرا سميا على الخلايا مما يثير القلق بشأن استخدامها العشوائي والاعتقاد بأنها خالية من الآثار الضارة. تم توثيق حالات من المقاومة البكتيرية للزيوت العطرية من خلال آليات مماثلة لتلك الخاصة بالمضادات الحيوية مثل: انخفاض النفاذية عبر غشاء الخلايا، وتعديل التدفق لداخل أو خارج الخلايا، وكذلك تغيير الحركة التي ينظمها الانجذاب الكيميائي. بالإضافة إلى ذلك، لا توجد أدلة كافية لتوضيح انتقائية الزيوت الطيارة كمضادة للبكتيريا تجاه البكتيريا المسببة للأمراض بدلاً من البكتيريا المتعايشة أو المجهريات البشرية. في هذا الصدد، يمكن أن يؤدي إختلال الميكروبيوم إلى عواقب سلبية على جميع جوانب صحة الجسم المضيف، مثل: المناعة والهضم السليم و عمل المحور الدماغي المعوي. لذلك، تهدف هذه المقالة إلى تسليط الضوء على أهمية إجراء دراسات طويلة المدى لتنظيم ممارسة العلاج بالروائح دون تعريض توازن الجسم للخطر، ودحض الافتراض المضلل بشأن سلامته التي لا جدال فيها.