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Abstract

Essential oils (EOs) are considered as very interesting and powerful natural products which have a great medicinal value. Therefore, many scientists have recently paid the total attention to the potential role of EOs in paediatry and geriatry.

In the last few years, several preparations applied EOs as a principle ingredient in children therapies, due to a wide range of their uses which are also good documented and well-known in folk medicine. The focus of this review, which comprises the scientific studies mainly from 2000 up to 2015, is directed to show the effect of different EOs in treating or at least reducing the severity of the symptoms of various children's diseases such as, acute respiratory tract infections, meningitis, diarrhea and gastrointestinal infections, infantile colic, cough and bronchitis, epilepsy, attention deficit hyperactive disorder and acute otitis media.

In addition, EOs attracted the attention to deal with older patients, due to their minimum side effects and limited drug interactions. In this review, various EOs offer a potential treatment for several diseases, due to their different biological activities, e.g. anti-diabetic, antihyperlipidemic, anti-osteoporotic, anti-arthritic, antihypertensive, anti-atherogenic and anti-thromobotic activities.

Collectively, the medicinal use of EOs in the pharmaceutical industry has become very popular. Therefore, they are gaining more importance in the future in the treatment of several diseases in paediatry and geriatry.

Zussamenfassung

Ätherische Öle sind als sehr interessant und leistungsfähige natürliche Produkte geworden, die einen großen medizinischen Wert haben. Deshalb haben viele Wissenschaftler vor kurzem die Aufmerksamkeit auf die potenzielle Rolle der Ätherische Öle in Pädiatrie und Geriatrie gemacht.

In den letzten Jahren sind mehrere Präparate der Ätherische Öle bei den Kindertherapien angewandt worden als Hauptbestandteil, weil sie eine breite Palette von deren Anwendungsmöglichkeiten haben, die auch gut dokumentiert und in der Volksmedizin bekannt sind. Der Schwerpunkt dieser Arbeit, in der die wissenschaftlichen Studien von 2000 bis 2015 zussamengefasst worden sind, liegt vor allem auf die Wirkungen verschiedener Ätherische Öle bei der Behandlung oder zumindest bei der Reduzierung der schweren Symptome von verschiedenen Kinderkrankheiten wie, akute Infektionen der Atemwege, Hirnhautentzündung, Durchfall und Magen-Darm-Infektionen, infantile Kolik, Husten und Bronchitis, Epilepsie, Aufmerksamkeits-Defizit-hyperaktive Störung und akute Mittelohrentzündung.

Aufgrund der minimalen Nebenwirkungen und begrenzten Wechselwirkungen der Ätherische Öle mit anderen Medikamenten gewinnen sie derzeit ein größes Intresse für ihre Anwendungen bei der Behandlung von älteren Patienten. In diesem Review bieten verschiedene Ätherische Öle den älteren Patienten eine mögliche Behandlung für verschiedene Krankheiten aufgrund deren unterschiedlichen biologischen Aktivitäten, wie Anti-Diabetes, Hyperlipidämie, Anti-osteoporotische, Anti-arthritische, Antihypertensive, Anti-atherogenen und Anti-thromobotic Aktivitäten.

Zussamenfassend sind die medizinischen Verwendungen der Ätherische Öle in der Pharmazeutischen Industrie sehr populär geworden, daher werden sie in der Zukunft bei der Behandlung von verschiedenen Krankheiten in Pädiatrie und Geriatrie an Bedeutung gewinnen.

Table of Contents

1. Introduction

Since ancient times, essential oils (EOs) are recognized for their medicinal value and they are considered as very interesting and powerful natural products. They continue to exert a paramount importance until the present day. Moreover, EOs and their components have specific biological functions, many of which lend themselves to commercial exploitation. These biological activities attract great interest of many studies suggesting their application in health, agriculture, cosmetics and food industries. In the arena of health and medicine, the diverse array of their biological properties are now being characterized including antimicrobial, anticancer, analgesic, antioxidant, anti-inflammatory, immunemodulatory, antiplatelet and antithrombotic activities. Therefore, many scientists have recently paid the total attention to the potential role of EOs in paediatry and geriatry [1, 2].

2. Role of essential oils on paediatry

Paediatrics is the discipline which deal with all ways of the health of infants, children and adolescents, comprising in the healthy, physically, mentally, and psychological growth and evolution, and their chances to reach as potent agents as same as adults [3]. The age up to eighteen years of age is counted to paediatrics [4]. The paediatrics medical problems vary according to many reasons:

1) Educational, social and cultural considerations,
2) economic disparities,
3) climate and geography,
4) the prevalence and ecology of infectious factors and their hosts,
5) nutritional resources,
6) level of civilization (industrialization and urbanization),
7) the gene frequencies for some disorders,
8) the welfare infrastructure in societies (health and social) [3].

Nowadays several preparations applied essential oils as a principle ingredient in childrens therapies, due to a wide range of its uses which

are also good documented and well-known in folk medicine, e.g. anti-inflammatory, hyperaemic, spasmolytic, carminative ones [5].

In the last few years, herbal constituents have been studied due to their antibacterial, antiviral and antifungal activities [6]. An important factor behind the great interest of herbal remedies and particularly essential oils is the elevated percentage of drug-resistant pathogens [7]. Moreover, the medicinal phenomena of antibiotical resistance recently increased rapidly and raised the mortality infection, especially in developing countries. Therefore, the need to use essential oils as antibacterial and antiviral agents for children and adolescents instead of synthetic antibiotics and antiviral with accompanied side effects is evident [8].

Recently, the use of essential oils is not only limited to traditional and folk uses, but also they participate now as a principle agent in revealing the therapeutical efficacy in many fields, e.g. meningitis, attention deficient hyperactive disorder (ADHD) as well as autistic children [9, 10]. This review will discuss the role of EOs in the treatment or at least in decreasing the severity of the symptoms of various children's diseases.

2.1 Acute respiratory tract infections (ARTIs)

The diseases categorized as ARTIs are worldwide between the most prevalent infections in childhood with elevated incidence among age under 2 years [11]. They are also observed to cause the high risk of morbidity and mortality occupying globally almost 30% of all childhood [12]. Risk factors for these infectious include being male, living in crowded conditions, living far from child care centres and being exposed to passive smoking. However, these factors explain only a fraction of the variation in incidences between children [13]. Infection in the respiratory tract is located either in the upper respiratory tract (URT), e.g. common cold, or in the lower respiratory tract (LRT), e.g. pneumonia, which is always more severe than URT [14]. *Streptococcus pneumonia*, *Haemophilus influenza* followed by *Staphylococcus aureus*

and *Streptococcus pyogenes* give rise to the most popular causes of the ARTI [15].

S. pneumonia caused pneumonia known as LRT that afflicts paediatrics in the whole world. 34 to 40 cases per 1000 is the incidence of pneumonia in children under 5 years [16]. On the other hand, respiratory viruses include respiratory syncytial virus (RSV), influenza virus A and B, human parainfluenza viruses (HPIVs) 1-3, rhinoviruses and adenoviruses representing the major of paediatric ARTI cases (especially the first three viruses) [17, 18]. Moreover, viral RTIs are also implicated in exacerbation of asthma. RSV-infection is the common cause of acute bronchitis [19]. Paediatrics hospitalization is the severe stage of viral infection with influenza, parainfluenza and RSV which can also lead to cardiac disease in children [20].

Almost 99% of all *S. pneumonia* cases were susceptible to treatment with penicillin. Unlike the past decades, however, up to 40 % of clinical isolates have observed to reach already middle or high penicillin and cephalosporin resistance in children [21]. In order to overcome that resistance, usage of essential oils represent a novel strategy against the resistant strains bacteria and viruses causing ARTIs in children [16, 22].

Inouye *et al*. evaluated the activity of some EOs against ARTIs and their major constituents to cure infections by *S. pneumonia* and *H. influenza*. The highest activity against both of them belongs to the EOs of cinnamon bark, lemongrass and thyme. Probably the efficacy is due to the aldehyde constituents which represent the main bioactive constituents in these EOs, (e.g. cinnamaldhyde in cinnamon bark oil). Also TTO, coriander and lavender EOs were investigated to exert moderate inhibition activity which is postulated to be due to the terpene alcohol group as the principle bioactive component (e.g. terpinen-4-ol in TTO) [23]. Lavender oil possesses not enough high capacity of inhibition against ARTIs, but is a useful prophylactic agent when used alone or in combination with other EOs to cure children's diseases [24].

Horne *et al*. tested the potency of 73 EOs against *S. pneumonia* R36A (an encapsulated strain) by using a paper disk diffusion assay. The EOs of oregano, thyme and rosewood oils showed to exert a potent and rapid antibacterial lysis of this resistant strain. These results are confirmed also by broth assay. Thus, the previous mentioned EOs have the potential as an alternative remedy for drug resistant pneumococci [25].

In another study [26], EOs of *Trachyspermum ammi* "ajwain" (Apiaceae) and of *Azadirachta indica* "neem" (*Maliaceae*) showed bactericidal activity against *S. pneumonia*. The inhibition obtained by a minimum bactericidal concentration (MBC) with a dose of 0.25-0.5 µl/ml which confirmed the potent bactericidal activity in ARTIs [26].

Salari *et al*. indicated the potential use of *Eucalyptus globulus* essential oil (EGEO) (Myrtaceae) against pathogenically bacteria isolated from patients with ARTI [27]. Many scientists studied the medicinal properties, especially the antibacterial activity, of Eucalyptus spp.. Therefore, the essential oil was reported consequently to possess a promising bactericidal effect in ARTI of children [28, 29]. The antibacterial activity of EGEO against *S. aureus, S. pyogenes, S. pneumonia* and *H. influenza* isolates obtained from patients with respiratory tract disorders was shown. Minimum inhibitory concentrations (MICs) for these species were 64, 32, 16 and 16 mg/L, respectively; MIC_{90S} were 128, 64, 32 and 32 mg/L, respectively, and MBC_S were 512, 128, 64 and 64 mg/L respectively. Based on these results, it was suggested that EGEO may be used in the treatment of ARTIs, due to its possible therapeutic capacity [27].

A further study [30] investigated the activity of EGEO against *S. pneumonia, S. pyogenes, S. aureus, H. influenza* and more viruses causing viral ARTIs such as *H. parainfluenza*; two viruses; a strain of adenovirus and a strain of mumps virus. The antibacterial activity was evaluated by the Kirby-Bauer-paper method, MIC and MBC of *H. influenza* and *H. parainfluenza* were the most susceptible, followed by *S. pneumonia*. These results emphasized the promising effect of

EGEO in the treatment of ARTIs whatever the causative factor was, bacteria or virus [30].

In a recent study [31], it was investigated that the essential oil of *Cinnamomum cassia* (CCEO) (Lauraceae) possesses a reasonable antiviral activity against the adenovirus (ADV) [31]. ADV is an important etiological agent that can cause ARTIs and may lead to many complications, such cerebral meningitis and infant gastroenteritis [32]. In infants aged six months to three years, ADV cannot only cause viral pneumonia but also it gives rise to long-term lung damage [33]. The main active constituent of CCEO is cinnamaldehyde, which was proved to inhibit the growth of ADV in a concentration-dependent manner. The result of this study proved the value of cinnamon oil in treatment and prevention of ARTIs [31].

Chang *et al*. found that *Zingiber officinale* essential oil "Ginger root" (ZOEO) (Zingiberaceae) is very effective against human respiratory syncytial virus (HRSV), the most common factor in the ARTIs in children [34]. HRSV is a neagative-sense, non-segmented, enveloped RNA virus of *Paramyxoviridae*. HRSV has a single antigenic type, two distinct subgroups and multiple subtypes within each subgroup [35]. ZOEO was proved to be effective against HRSV-induced plaque formation on tracheal epithelium by blocking viral attachment and internalization. These results provide the first evidence to support its possible use to prevent the HRSV infections [34].

Additionally, another study investigated the antiviral effect of the *Lippia graveolens* essential oil (LGEO) "Mexican oregano" (Verbenaceae) against HRSV. The antiviral activity is due to carvacrol, the main bioactive component which is responsible for that antiviral potential. LGEO possesses a significant antiviral effect on HRSV with low risk of cytotoxicity. Therefore, it would be interesting to use rather LGEO in HRSV-diseases of children than ribavirin which is only recommended for special cases involving high-risk in children due to its toxicity [36].

Influenza virus A and B are genus of the *Orthomyxoviridae* family of viruses, influenza A virus is a negative-sense, single-stranded, segmented RNA virus. Both influenza A and B infect human, where influenza B viruses evolve slower than A ones [37, 38]. Several studies tested the effect of EOs of *Allium sativum* "Garlic" and *Allium cepa* "Onion" against influenza A and B viruses which cause ARTIs [39, 40]. Nagai et al. reported also that garlic oil has a useful and a preventive effect against infections with influenza A and B viruses, as well as the *Cumin cyminum* essential oil "Cumin" (Apiaceae) which exerted also a reasonable effect against both viruses [41].

Coming to a conclusion about these previous reports on the role of essential oils and/or their constituents in the treatment of ARTIs in paediatrics (particularly infants): They play an important role and may be an alternative choice to antibiotics in treatment of ARTIs due to their medicinal advantages over synthetic antibiotics.

2.2 Meningitis

Meningitis is a severe acute infectious disease caused by several microorganisms including viruses, bacteria, parasites and fungi. Meningitis incidence rates are correlated with child nationality and vary geographically. Children with a HIV infection have a substantially higher risk of meningitis than those not infected. Fatality rates associated with this disease can be as low as 2 % in infants and children, and as high as 20-30% in neonates [23, 42]. Transient or permeant deafness or other neurological sequelae arise in up to a third of survivors [43]. A wide range of bacteria can cause meningitis. In the neonatal period, which includes premature and term babies up to 3 months of life, group B streptococci cause the most bacterial meningitis-infections in many developed countries [44]. Most cases are caused by subtype III strains and the disease usually arise after the first week of life. Coliform bacilli are the second most common meningeal pathogens in this population, especially strains of *Escherichia coli* possessing K1 antigen. *E. coli* and other Gram-negative enteric bacilli

such as species of *Klebsiella, Enterobacter* and *Salmonella* are the leading cause of meningitis in newborns. *Listeria monocytogenes* is occasionally responsible for a bacterial meningitis; as with group B streptococcal infections, meningeal infections caused by *L. monocytogenes* usually happens after the first week of life also in infants and small children; *S. pneumonia, Neisseria meningitidis* and *H. influenza* type B are the most common meningeal pathogens. Children older than 5 years or older are almost exclusively affected by *S. pneumonia* and *N. meningitidis* [45].

Meningitis usually follows an invasion of the bloodstream by organisms that have colonised mucosal surfaces. In the neonatal period, pathogens are acquired mainly, although not exclusively during birth by contact and aspiration of intestinal and genital tract secretions from the mother. In infants and children, meningitis usually develops after encapsulated bacteria that have colonised the nasopharynx which disseminated in the blood. Viral infections of the upper respiratory tract commonly precede invasion of the bloodstream and may develop into meningitis [46].

Imelouma *et al.* studied the antimicrobial activity of *Lavandula dentate* essential oil (LDEO) (Lamiaceae), collected on eastern Morocco, against 22 bacteria strains including *N. meningitidis, H. influenza, S. pneumonia* which are the main bacteria causing meningitis in infants and children and also including *E. coli, Klebsiella, Enterobacter*, *Salmonella* and *L. monocytogenes* which are the leading cause of meningitis in newborns. LDEO was suggested to exert a potential antimicrobial activity as it exhibited the highest bacterial inhibitory effect against Gram-negative bacteria *E. coli*, *N.meningitidis* and also *Klebsiella* at the same range 0.041 mg/ml, followed by *H. influenza* at 0.16 mg/ml (MIC). The results indicated that LDEO may find its application in the future research in treating meningitis and play an important role in the pharmaceutical industry [45, 47].

Another study [48] discussed the antibacterial activity of essential oil of *Ocimum gratissimum* (OGEO) (Lamiaceae) against *L. monocytogenes* which is a Gram-positive bacterium, resistant against

deleterious effects of freezing, drying and heat. Therefore, it causes easily meningitis in new-borns, as their immune system is not enough able to defend bacteria. It attacks infants in a form of influenza-like symptoms and finally leads to meningitis or meningoencephalitis [48, 49]. OGEO inhibited progressively at concentration from 20 to 250 µg/µl the bacterial growth of *L. monocytogenes*. As a result, OGEO is capable of suppressing these heat resistant organisms and might be widely used as effective agent against resistant meningitis [50].

Recently, Hong *et al*. revealed the potential biological effects of the EO of *Pinus densiflora* (PDEO) (Pinaceae) and *Chamaecyparis obtuse* (COEO) (Cupressaceae). The meningitis inhibitory effect is due to β-thujene and bornyl acetate, respectively. This inhibition effect by both PDEO and COEO against *L. monocytogenes* was found to be 45.9 % and 50 % respectively [51].

Silva *et al*. investigated the great role of coriander EO (Apiaceae) against both Gram-positive and Gram-negative bacteria and showed that coriander oil inhibited *Klebsiella* at a concentration of 0.2% (v/v), which proved the potent bactericidal activity of coriander oil due to its membrane permeability which is noteworthy and justifies the use of the herbal essential oils in the antibiotics field [50].

Diallyl trisulphide and diallyl tetrasulphide, the major bioactive constituents of garlic EO revealed in vitro antibacterial activity against *K. pneumonia* and its multiple resistant bacteria strains. Therefore, the garlic oil has enough potency to treat nosocomial infections manifested by meningitis [52].

2.3 Diarrhea and gastrointestinal disorders

During the last decade, diarrhea infections have threatened the life of millions of people around the world [53]. It is estimated that one in five children die before his fifth birthday due to diarrhea in developing countries [54]. This situation has been connected with the increase of the development of antimicrobial resistance and the high cost of current antimicrobials [55]. Further, diarrhea is a complex disease that may

have viral, bacterial or even parasitic backgrounds [56]. Thus, alternative treatments using EOs with wide antimicrobial/or antiviral activity against diverse agents of diarrhea is advantageous [57].

Mostly infectious diarrhea is self-limiting and only requires supportive management. Viral agents are increasingly recognized as causative agents of epidemic and sporadic diarrhea [58]. One of the most common cause of gastroenteritis in children worldwide and its resultant diarrhea is the human rotavirus (HRV) which may cause morbidity and mortality. The HRV is a non-enveloped virus with a double strand RNA segmented genome that allows segment change among viruses and generating diversity [59]. Therefore, a vaccine against rotavirus has the potential to save millions of children daily [58].

Pilau *et al*. reported that the *Lippia graveolens* essential oil (LGEO) "Mexican oregano" (Verbenaceae) exhibited a great inhibitory effect *in vitro* on HRV by suppressive activity against the organisms causing diarrhea as *Salmonella enterica* and *E. coli*, that might be due to its bioactive alcohol, carvacrol. LGEO represents a promising alternative agent against diarrhea HRV in children in comparison with other synthetic antivirals [36, 60].

Somie *et al*. examined the anti-diarrheal activity of *Lippia javanica* essential oil (LJEO) (Verbenaceae) against gastrointestinal disorders and intestinal parasites. LJEO was found to be effective against almost all diarrhea-causing bacteria such as *Bacillus* and *E. coli* (at 6mg/ml), *Shigella* and *Enterococcus fecalis* (at 3mg/ml), as well as *Salmonella* (at 1.5 mg/ml). [55]. Moreover, the EOs of *Pouzolia mixta* (Urticaceae) and *Mucuna Coriacea* (Fabaceae) were used over the decades as traditional healers as a result of their curing effects on gastrointestinal tract problems and have found to be very effective [55].

One of the most popular and effective EOs used in diarrhea is chamomile essential oil (*Matricaria recutita* L. Asteraceae). Chamomile oil is commonly used for many ailments [61]. As an apple pectin-chamomile extract may help to shorten the course of diarrhea in

children, as well as relieve symptoms associated with the conditions [62]. Two clinical trials have evaluated the efficacy of chamomile oil for colic treatment in children. In these trials, chamomile oil was combined with other EOs of different herbs (liquorice, fennel) for administration. The first trial indicated the elimination of colics in 57% of children compared to 26% in placebo group after 7 days of a treatment course by a double-blind, randomized study [63]. Another study, announced the safety profile of chamomile, because it was used in children aged from (0.5-5.5) years, and it relieves the infantile colic disorders without side effects [64].

The anti-diarrheal activity of *Santalum album L*. EO (SAEO) "East Indian Sandelwood" (Santalaceae) was studied by Guo *et al*. in castor oil-induced diarrhea mice. SAEO is a medical plant which possesses anti-diarrheal and antibacterial activities. At doses of 200, 400 and 800 mg/kg, SAEO showed significant anti-diarrheal activity against castor oil-induced diarrhea as compared with control. These findings confirmed that SAEO exerts a spasmolytic role in gastrointestinal motility which is probably mediated by inhibition of muscarinic receptors, 5-HT receptors and calcium influx. All the previous results provide a pharmacological basis for its clinical use in treatment of diarrhea as well as gastrointestinal disorders [65].

Further investigations proved that also peppermint EO (Lamiaceae) may be used as a therapeutic agent against gastrointestinal disorders in children. A double-blind controlled trial was carried out on 42 children with gastrointestinal disorders such as irritable bowel syndrome (IBS) which is characterized by a chronic abdominal pain and a predominant diarrhea or constipation [66]. IBS is considered as one of the functional gastrointestinal disorders which has no known organic cause. Children who have a history of recurrent abdominal pain are at increased risk of IBS during adolescence and young adulthood [67]. After 2 weeks of treatment with enteric-coated peppermint oil capsules or placebo, 75% of those who received peppermint oil showed a reduction in the severity of pain associated with IBS. These findings

proved that peppermint EO may play an important role in treatment of gastrointestinal disorders in children in the future [66].

Another important factor which plays a great role in occurrence of diarrhea in children is the food safety, as food safety is a fundamental concern of both consumers and the food industry, especially as the number of reported cases of food-associated infections continues to increase and is rapidly modified [68]. Food processors, food safety scientists and regulatory agencies have been increasingly concerned with the growing number of food-borne illness outbreaks caused by some pathogens and/or their enterotoxins *E. coli*, *S. aureus*, *Salmonella* spp. and *Clostridium* spp. which are responsible for many cases of intestinal disorders, causing vomiting and diarrhea [69]. Increased use of antibiotics, along with over-prescribing and/or poor patient compliance, has led to the development of bacterial resistance to antibiotics. Therefore, research into more effective antimicrobial food agents, in particular natural antimicrobials, such as EOs has received attention in the past decade. As a result, EOs nowadays could be widely used as food flavors and preservatives to prevent growth of food-borne bacteria and molds and thus extended the shelf life of processed foods [70].

Orrojalian *et al*. analysed the antibacterial activity of EOs of three Apiaceae species including *Bunium persicum, Cuminum cyminum* and *Carum copticum*. The antibacterial effects of the EOs were assessed on several food-borne pathogens causing diarrhea in children, namely *S. aureus*, *Bacillus cereus*, *E. coli*, *Salmonella enteritidis* and *L. monocytogenes*. The results indicated that the ranges of MIC of these EOs were found to be 0.03-0.5, 0.18-3 and 0.37-3 mg/ml, respectively, for *C. copticum*, *B. persicum* and *C. cyminum*. Notably, *C. copticum* EO exerted the strongest antibacterial activity against tested food-borne bacteria, possibly related to the presence of high amount of thymol and γ-terpinene which have been reported to possess antibacterial properties [69, 71]. *C. copticum* EO used as a carminative for children and as an anti-cholera remedy in India, Pakistan and Egypt [72]. Moreover, the combination of *B. persicum* and *C. cyminum* EOs was believed to be

useful in treating diarrhea, dysentery and for curing stomach ailments, as this combination of both EOs exerts a synergistic activity against the pathogens. According to these results, it was suggested that the EOs of these three Apiaceae species have noticeable anti-diarrheal activity and potential application in food industry [69].

Rahman *et al*. evaluated in vitro the anti-listerial potential of *Piper chaba* essential oil (PCEO) (Piperaceae). *L. monocytogenes* is believed to cause gastroenteritis and more importantly listeriosis, a serious disease with high mortality rate in immune compromised people, unborn, children and neonates. It is also regarded as one of the most important food-borne pathogens of the recent years, and numerous food-borne outbreaks and sporadic cases of listeriosis have been reported [73, 74]. Most reports associate listeriosis with the consumption of contaminated ready-to-eat food, such as dairy products, processed or cured meat and poultry, salads, sea food and uncoated eggs [75]. PCEO was proved to exert a great potential anti-listerial effect against all five strains of *L. monocytogenes* ATCC 19111, 1911, 19118, 19166 and 15313. Moreover, it also shows a strong inhibitory effect on the viable cell count of the tested *Listeria* spp. In conclusion, PCEO might be suitable for using in food industries as a preservative to control or at least reduce food-borne pathogens [68].

The long history of using *Psidium guajava* "Guava" (Myrtaceae) has led modern-day scientists to study the effect of Guava EO against diarrhea. Guava EO is traditionally used against diarrhea, gastroenteritis and other digestive complications, as it was validated in different clinical studies, as it helps to inhibit the intestinal transit and delayed gastric emptying [76]. Another study investigated the antimicrobial effects of guava EO on diarrhea causing bacteria. Guava EO containing preparations, like tea, are commonly used as a medicine against gastroenteritis and child diarrhea by those who cannot afford or do not have access to antibiotics. The results of this study screened that Guava EO is very active against *S. aureus* and *Salmonella* spp. as well as its good curative effect on infantile rotaviral enteritis, thus making

up an important potential source of new antimicrobial compounds [57, 77].

2.4. Infantile colic

Infantile colic (also known as baby colic) is defined as episodes of crying for more than three hours a day for more than three days a week for three weeks (Wessel criteria) in an otherwise healthy child between the ages of two weeks and four months [78]. Infantile colic is a self-limiting condition of undetermined etiology and is one of the most common problems within the first three months. Various mechanisms of colic exist including food allergies, formula intolerance, immaturity of the gastrointestinal tract, excessive gas formation and intestinal cramping have been hypothesized, but none of them proven. It is possible, that the etiology of colic is multifactorial. Since colic does not carry a biological marker, diagnosis of colic is clinical and is usually made when an infant meets the Wessel criteria. Wessel criteria remains the most-widely-used measure to diagnose colic.

Infantile colic is considered to be a frequent cause for visits to a paediatrician and to the emergency room. Despite its benign, natural course, colic carries a substantial psychological, emotional and physical burden for parents [79]. Various carminative plants have been used to relieve infantile colic, including catmint, chamomile, lemon balm, dill, caraway and fennel. Among these plants, fennel is the most frequently recommended. A clinical study demonstrated that *Foeniculum vulgare* essential oil (FVEO) (Apiaceae) is effective in reducing the intensity of infantile colic. The therapeutic effect of FVEO may be secondary to a spasmolytic action. The spasmolytic action of FVEO may be explained by the similarity of the chemical structure of anethole (the main ingredient in FVEO) to dopamine. This similarity may result in the binding of anethole to dopaminergic receptors [79].

Another study examined the effectiveness of aromatherapy massage using lavender EO as a possible treatment for infantile colic [80]. Nowadays lavender EO is used widely in the aromatherapy for

treatment of many diseases [81]. In the previous study, a group of 40 infants between 2 and 6 weeks of age with a gestational age of 38-42 weeks and normal development and growth were examined. Infants in the treatment group received abdominal massage by their mothers using lavender oil, while those in the control group were not subject to an intervention. The infants in both control and treatment groups were attended once a week, in total five times. The effect of the massage was measured in terms of changes on the length of time the infants cried per week. The result of these findings concluded that the use of an aromatherapy massage using lavender oil was found to be very effective in reducing the symptoms of infantile colic [80].

Savino *et al*. evaluated the anticolic effect of the EOs of three different herbs, *Matricariae recutita* L. "chamomile" (Asteraceae), *Foeniculum vulgare* "fennel" (Apiaceae) and *Melissa officinalis* "lemon balm" (Lamiaceae) on breastfed colicky infants [82]. It is known that chamomile extract has an important antispasmodic activity on the smooth muscle of intestine, as well as its sedative action [83]. Additionally, fennel EO shows anti-flatulent and antispasmodic properties, as well as inhibition of the intestinal fermentation, so this oil is currently used as a spasmodic remedy for digestive alterations [84]. Moreover, lemon balm EO is believed to possess an antispasmodic activity on the smooth muscle in the intestine and its mechanism of this antispasmodic action can be explained by phosodiesterase inhibition [85].

2.5 Cough, bronchitis and pertussis

The cough is a protective reflex mechanism that removes foreign materials and secretions from the bronchi and bronchioles of the airways (foreign objects, catarrhs of the respiratory system, etc.). It is inappropriately stimulated in various situations like inflammations of the respiratory tract or neoplasia [86]. Cough is the most common problem managed by general practitioners (GPs) in the developed countries, as it is more common in pre-school children than in any other

age group. Two out of three children aged between 0 and 4 years visit their GP at least once a year with an acute respiratory infection and up to three-quarters of these are suffering from having cough. Most coughs in pre-school children are caused by RTIs, with about 7% caused by asthma and chronic obstructive pulmonary disease (COPD) which is characterized by airway obstruction and hypersecretion of mucus, additionally causing symptoms like wheezing or dyspnoea. Therefore, this type of cough is considered as a chronic cough [87]. Antitussive agents are used mainly to suppress dry, painful and patient-disturbing coughs; the use of this group of drugs suppresses only one symptom without influencing the underlying condition. Administration of such drugs in cough associated with bronchiectasis or chronic bronchitis should be prevented because of possible harmful sputum thickening and retention [86]. Moreover, chronic cough, defined as daily cough for more than 4 weeks, considered trivial to some health professionals, is associated with significant morbidity, and a burden to parents, as it is most common in childhood. Also chronic cough may be reflective of an underlying serious disorder and delayed diagnosis (e.g. foreign body) may cause chronic respiratory morbidity in children [88]. Many adverse effects of the antitussive drugs like depression of the respiratory centre, decreased secretion in the bronchioles and inhibition of ciliary activity, increased sputum viscosity, decreased expectation acts as limitation to the therapy. Therefore, the use of herbal drugs and their EOs is increasing all over the world for various ailments including antitussive activity as they are mostly safe and devoid of adverse effects. They are considered as an important source for the discovery of novel bioactive compounds, which have served and continue to serve as lead molecules for the development of new drugs [86].

Pertussis (whooping cough) is another frequent and important infectious disease of the respiratory tract, mainly caused by the Gram-negative rod bacterium *Bordetella pertussis*. It is frequently believed that pertussis is exclusively a childhood disease, but it is the most serious in young infants [89], a highly contagious bacterial disease. Initially symptoms are usually similar to those of the common cold which than is followed by weeks of severe coughing fits. Following a

fit of coughing a high-pitched whoop sound or a gasp may occur as the person breathes in. The coughing may last for more than a hundred days or ten weeks. Children less than one year old may have little or no cough and instead have periods where they do not breathe. The incubation period is usually seven to ten days. Nearly 2 % of infected children less than a year of age die [90]. Manifestations of *B. pertussis* infections vary by magnitude of the bacterial inoculum, age, immune status and probably further yet unidentified individual factors. They can range from asymptomatic, apnoea and uncharacteristic cough by typical coughing spells with posttussive phlegm and/or vomiting and duration also varies between a few days and several months [89].

Several studies investigated the traditional use of the EO of *Thyme vulgaris* L "Thyme" (Lamiaceae) in treatment of respiratory conditions including cough and bronchitis. Thyme essential oil used widely in folk medicine for many years for its expectorant, antitussive, antibronchitic properties, as well as its potential effect in the treatment of whooping cough [91, 92]. Its spasmolytic and antitussive activities have historically been attributed to thymol and carvacrol, the main active components. *In vitro*, it was proved that thyme oil exerts relaxing effect on tracheal and ileal smooth muscle by inhibiting phasic contractions. Regarding these results, thyme oil can be used as a monotherapy for many specific respiratory indications or in combination with other EOs for treatment of cough and bronchitis. Moreover, the German expert panel and the commission E have approved thyme for use in bronchitis [93].

Shah *et al*. studied the antispasmodic and bronchodilatory activities of the essential oil of *Artemisia maritima* (AMEO) (Asteraceae), it is an European species of wormwood known as sea wormwood [94, 95]. AMEO contains 1,8-cineole, thujone and camphene as active constituents. The previous study revealed that AMEO exhibited spasmolytic and bronchodilator activities mediated possibly by dual blockade of calcium channels and phosphodiesterase (PDE) which provides the pharmacological basis to the medicinal use of AMEO in treatment of cough, bronchitis and possibly asthma [94].

Another study by Gilani et al. investigated the role of the essential oil of *Nepeta cataria* (NCEO) (Lamiaceace) in the treatment of respiratory disorders [96]. Medicinally, NCEO is used in respiratory hyperactive disorders such as cough, asthma and bronchosis. The bronchodilatory properties of NCEO is attributed to the presence of 1,8-cineole, α-pinene, α-humulene and geranyl acetate, as its four major components. These data indicate that NCEO possesses spasmolytic and myorelaxant activities mediated through dual inhibition of calcium channels and PDE, which may explain its traditional use in cough and asthma [92, 97, 98].

Zingiber officinale "Ginger" (ZOEO) (Zingiberaceae) essential oil was also proved to be safe, efficient and potent in treatment of cough and bronchitis [99]. ZOEO was screened for *in vitro* antibacterial activity against bacteria isolated from children by disc diffusion method. ZOEO showed highest significant effect against *B. pertussis* and other isolated bacteria at 25 μg/ml [100]. The antimicrobial activity of ginger may be attributed to the fact that it contains antimicrobial substances such as zingiberol, zingiberine and bisabolene [101]. The results of the previous studies emphasize the usefulness of ginger oil in the treatment of whooping cough as well as different respiratory and throat bacterial infections [100].

Additionally, various EOs extracted from different aerial parts of herbs also exhibit a potent bronchodilatory effect and are popular remedy for cough, bronchitis. The essential oil of *Eugenia caryophyllus* "Clove" (ECEO) (Myrtaceae) is believed to fight germs, viruses and bacteria and encourages also the lessening of phlegm from the respiratory system. Eugenol represents 60 to 90 % of the clove oil constituent’s index which is known as a sedative compound. It is also often used in herbal remedies for whooping cough due to its sedative effect [99].

Moreover, *Allium sativum* essential oil "Garlic" (Amaryllidaceae) is used as expectorant. Syrup of garlic oil is a valuable medicine for asthma, hoarseness, coughs, difficulty of breathing, and being of particular virtue in chronic bronchitis and an account of its powers of

promoting expectoration. Therefore, it possesses an anti-asthmatic and broncholytic activity [99, 102]. Although eucalyptus oil and peppermint oil are well known because of their bronchodilatroy effects, they are not used in children and infants, because the ingestion of both oils caused significant morbidity in infants and young children, so they should not be recommended for children [99, 103].

2.6 Epilepsy and paediatric seizures

Epilepsy is a chronic disease that often requires lifelong treatment [104]. It is a disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomena with and without loss of consciousness [105]. 10.5 million children worldwide are estimated to have active epilepsy. Epilepsy is the second most common chronic neurological condition seen by neurologists. Over the past 15 years, syndrome-oriented clinical and EEG diagnosis, and better aetiological diagnosis, especially supported by neuroimaging, has helped to clarify the diversity of epilepsy in children, and has improved management.

Perinatal and post infective encephalopathy, cortical dysplasia and hippocampal sclerosis account for the most severe symptomatic epilepsies. Ion channel defects can underlie both benign age-related disorders and severe epileptic encephalopathies with a progressive disturbance in cerebral function. However, the reasons for age-related expression in children are not understood [106]. Several new epileptic drugs have been recently introduced but have provided limited therapeutic benefits, as nearly 15 % of childhood epilepsy cases are resistant. The efficacy of new antiepileptic drugs are usually evaluated in short trials as add-on therapy in refractory epilepsy [107]. In developing countries, economic factors make it necessary to consider drug price; herbal drugs are normally cheaper and are usually more accepted among the general population [104].

Kangralkar *et al*. evaluated the anticonvulsant activity of the essential oils of both *Cyperus esculentus* (CEEO) and *Cyperus*

rodundus (CREO) (Cyperaceae). Their anticonvulsant property was assessed by their ability to protect against maximal electroshock (MES) induced convulsions. MES induced tonic seizures can be prevented either by drugs that inhibit voltage dependent Na^+ channels such as phenytoin, valproate, felbamate and lamotrigine or by drugs that block glutaminergic excitation mediated by the n-methyl-D-aspartate (NMDA) receptor, such as felbamate. The CEEO and CREO are estimated to follow any of the above mechanisms. These data postulated that both EOs were found to possess a potent anticonvulsant activity. A significant reduction in MES induced convulsions compared to control in a dose-dependent manner [105].

Several investigations indicated the antiepileptic effect of the essential oil of *Rosa damascena* (RDEO) (Rosaceae) [104, 108]. RDEO contains several components such as geraniol, citronellol, farnesol, nerol, eugenol, citral, linalool and myrcene. Therefore, it is suggested that these compounds might be responsible for the hypnotic effect of EORD [109]. Previous experimental studies on the effect of this purified oil showed that doses of 500 and 750 mg/kg have antiepileptic effects on PTZ-induced seizures in rats [108, 110]. Moreover, it is believed that geraniol possesses methoxyphenol forms in its structural pathway, which is considered to exert hypnotic and anticonvulsant properties according to the various behavioural studies. Therefore, it is conceivable that geraniol may be at least partially responsible for the antiepileptic effects of RDEO by the GABA-system. On the basis of these observations, it is concluded that RDEO shows anticonvulsant effects and can improve seizures in children who are resistant to synthetic antiepileptic drugs [104].

Nigella sativa essential oil "Black cumin" (NSEO) (Ranunculaceae) has been known for its anticonvulsant effects due to thymoquinone as its major component [111]. The anticonvulsant and antioxidant effects of NSEO against PTZ-induced arousal in mice were investigated. As a result, this study clearly demonstrated a potent anticonvulsant property of NSEO against the development of arousal consequences in PTZ-agitated mice, and it was more potent as an

anticonvulsant agent than valproate, as a major antiepileptic drug, when they were compared. On the basis, NSEO showed antiepileptogenic properties as it reduced the sensitivity of agitated mice to the convulsive and lethal effects of PTZ. The mechanism of the anticonvulsant effects seems to be correlated with the antioxidative effects, because it is suggested that the neuroprotective action of NSEO may correlate with its ability to inhibit not only excessive ROS formation but also seizures generation [112]. Furthermore, Akhondiary *et al*. investigated the effect of NSEO on intractable seizures of children, with the goal of reducing seizures frequency as well as antiepileptic drug dosage. This study was assessed by a double-blind clinical trial and compared the results with those of placebo. The results showed that NSEO may alter the monoamine level in the CNS and these changes inhibited the epileptic activity of patients. This warrants the antiepileptic effects of NSEO in children with refractory seizures which was attributed mainly to thymoquinons [111, 113].

The monoterpenoid alcohol terpinen-4-ol (T-4-ol) is a bioactive constituent of many EOs of several plants such as *Alpinia zerumbet*, *Tanacetum cademum*, *Melaleuca alternifolia* and others [114, 115, 116]. The anticonvulsant activity of T-4-ol was investigated in a study by De Sousa *et al.*. The treatment of mice with T-4-ol (200 mg/Kg) caused a significant decrease in the spontaneous motor activity at 30, 60 and 120 min. after administration. T-4-ol (100 and 200 mg/kg) also produced a significant dose-dependent increase in the duration of sleeping in mice. Pre-treatment of mice with T-4-ol at doses 100, 200 and 300 mg/kg significantly increased the latency of PTZ-induced seizures of picrotoxin (PIC). In another model, T-4-ol decreased the tonic hind convulsions percentage at the dose of 300mg/kg [117]. T-4-ol is also considered as a potent anticonvulsant, as it inhibits chloride ion channels activated by γ-amino-butyric acid (GABA) receptors. Furthermore, it decreases the sodium current through voltage dependent sodium channels and thus its anticonvulsant effect can be also related to changes in neuronal excitability [118]. From the overall results it was concluded that T-4-ol shows a depressant effect on the CNS and significant anticonvulsant activity [117].

Quintans-Junior et al. also examined the anticonvulsant potential of the essential oil of *Cymbopogon winterianus* "Lemon grass" (CWEO) (Poaceae) [119]. CWEO is an important essential oil yielding aromatic grass and it is rich in citronellal, geraniol and citronellol [120]. In Brazilian folk medicine CWEO is used for treatment of epilepsy and anxiety. A behavioural screening demonstrated that CWEO (100, 200 and 400 mg/kg) caused depressant activity on CNS. When administered concurrently, it reduced the number of PTZ- and PIC- induced seizures to 50 % of the experimental animals, besides, it significantly increased the latencies of chronic seizures induced by strychnine. These data lead to the conclusion that CWEO exerts a CNS depressant activity in addition to anticonvulsant properties due to the reduction of neuronal excitability mainly by means of the voltage-dependent Na^+ channels and by facilitation of the inhibitory synaptic input by simply activating $GABA_A$. This mechanism explains the role of citronellol in CWEO [119].

2.7 Attention deficit hyperactive disorder (ADHD)

ADHD is a common childhood disorder that has been estimated to affect 8-12 % of school-age children; with boys outnumbering girls 3:1. Recent studies have shown that ADHD is associated with significant impairment in multiple domains of functioning, including a high frequency of psychiatric comorbidity with disruptive mood and anxiety disorders, poor educational attainment, lower IQ and low occupational performance. ADHD is also associated with maladaptive interpersonal interactions and low self-esteem [121]. ADHD is a neurodevelopmental psychiatric disorder in which there are significant problems with executive functions (e.g. attention control and inhibitory control) that cause attention deficits, hyperactivity or impulsiveness which is not appropriate for person's age. These symptoms must begin by age six to twelve and persist for more than six months for a diagnosis in childhood continue to have symptoms into adulthood [122]. A collective study indicated the great role of EOs in the management of ADHD, when used concomitantly with other supporting strategies, such as relaxation and

mindfulness techniques, cognitive behavioural therapy and counselling, particularly where co-morbidities are present, e.g. anxiety, depression, low self-esteem and restlessness [123].

The use of EOs in ADHD children was investigated by several scientists to prove the influence of EOs on cerebral activity, especially with in the limbic region (e.g. the pituitary gland, the hypothalamus, amygdale and hippocampus, which influence mood, emotion, behaviour, memory and hormonal activity) [124, 125]

Table 2.1 Different EOs and their potential influence on the limbic system (adapted and newly drawn from H. Godfrey) [123].

Organ	**Essential oils of**
Pituitary gland	Jasmin, patchouli, clary sage, Ylang-ylang.
Thalamus	Grapefruit, rose, jasmine, clary sage.
Hypothalamus	Frankincense, geranium, rosewood, bergamot.
Amygdale/Hippocampus	Peppermint, rosemary, lemon, black pepper.

Tisserand *et al*. recommended that EOs of nutmeg, rosemary, peppermint and eucalyptus may also benefit due to their cephalic stimulating activity. However, he also pointed out, because of potential sensitivity traits amongst individuals with ADHD, that rosemary and peppermint oils be regarded with caution and administration in low dosage. Significantly, it was reported that massaging with EOs of eucalyptus, geranium, lavender and peppermint into the soles of an autistic child produced a great benefit, stating that treatments *"helped reduce the hyperactivity and increase his attention span"* [126]. Furthermore, there is a risk that the recipient may develop an allergic reaction to certain EOs or may become sensitized to others very

quickly. Paradoxically, however, EOs can also be of value for some of the sensitivity conditions, such as eczema, sleep disturbances and emotional vulnerability [123].

Moreover, it was found that using one drop of a blend of *Bosswellia carteri* "Frankincense" (Burseraceae), *Anthemis nobilis* "chamomile roman" (Asteraceae) or *Lavandula angustifolia* "Lavender" (Lamiaceae) and *Citrus bergamia* "Bergamot" (Rutaceae) or *Citrus reticulata* "Mandarin" (Rutaceae) on a tissue and inhaling helped to quell panic attacks and feelings of anxiety in an ADHD client. Additionally, using EOs for psycho-emotional conditions in small amounts are very effective. Direct inhalation of EOs requires limited amounts (half to one drop) to procure a significant response [123]. Sorensen *et al*. also emphasized the direct chemical influence of EOs on cephalic function, especially with in the frontal lobe and limbic area of the brain, stimulating or balancing hormonal/dopaminergic activity, positively influencing memory, mental alertness, clarity and attention, co-ordination, response time, motion and behaviour [124]. In addition, another scientific report by Miyazaki *et al*. found that the inhalation of orange oil increased activity of the parasympathetic nervous system [127]. Another similar study revealed that the odour of bitter orange affected the cortex and inhibited the excitement of the CNS including sedative effects [128].

According to another finding, it is suggested that the EOs derived from woods and roots appear to have a significant "grounding" or "earthing" on anxious or hyperactive clients. *Boswellia carteri* essential oil for example, appears almost to immediately slow or deepen the breathing of patients. Adding *C. aurantium* essential oil or *C. reticulata* or *C. bergamia* to a "grounding" blend as a complement, appears to uplift and lighten the clients mood. On this basis, managing anxiety in individuals with ADHD, which is often a consequence of their hyperactivity, aids their ability to slow down, stop and think, and find their locus of control [123, 129]. EOs may be applied in combination with relaxation and mindfulness techniques or behavioural therapy. They may be employed for their chemical influence on the above

processes, or used to reinforce positive memory cues. They may be applied in combination with massage techniques, where self-esteem may be improved and hyperactivity temporarily quelled [130].

In conclusion, the chemical qualities and therapeutic versatility of EOs appear ideal when managing the complexity of symptoms presented by ADHD. EOs are suggested to inspire significant benefits in terms of exerting a positive psycho-emotional and physiological influence within the recipient, especially in terms of supporting the co-morbidities of depression, anxiety, low self-esteem and sensitivity. EOs can be used concomitantly alongside other supporting strategies such as relaxation, cognitive behavioural therapy and counselling. Based on the previous results, EOs can be employed to support the symptoms (rather than the cause) of ADHD and may be used potentially in management and/or treatment of ADHD in children [123].

2.8 Acute otitis media

Acute otitis media (AOM) is one of the most common diseases of childhood and is the leading indication for prescription of antibiotics to children [131]. It has a peak of incidence between six and 18 months, although ear infections are common from four months to four years [132]. These years 50-84% of children experience at least one episode of AOM. Recurrent otitis media is also common; 10 to 19% of children suffer 3 or more episodes during the first year alone [133]. AOM is defined as:

1) History of acute onset of signs and symptoms,
2) presence of middle-ear effusion, and
3) signs and symptoms of middle-ear inflammation.

The main pathogens in this disease are *S. pneumonia* and *H. influenza*. Due to concern over antibiotics resistance in these bacteria and the high spontaneous resolution rate (80% within three days), the American Academy of Paediatrics (AAP) recommended the initial watchful waiting of children with AOM and during this times, families often seek alternative treatments [132]. Therefore, complementary and alternative

medicine (CAM) used in paediatric patients remains relatively common. Herbal remedies were used by 40 % of those families that reported use of CAM modalities. CAM approaches are also often used for treatment of recurrent AOM [134]. Treatment of the ear pain early using CAM decreases both parental anxiety and the child's discomfort and accelerates the healing process [135].

The essential oil of *Ocimum basilicum* "Sweet basil" (OBEO) (Lamiaceae) exerts an antimicrobial activity and a recent study clearly demonstrated the rapid bactericidal effect that the vapors from these oils have [23, 136]. Because the tympanic membrane is not considered to be permeable to antimicrobial agents in liquid form, treatment of AOM through the external ear canal is not advised. However, the vapors of EOs can diffuse from the external ear canal into the middle ear in quantities that are sufficient to produce an antimicrobial effect on AOM. The antimicrobial effect of the introduction of OBEO into the external ear canal of rats with experimental AOM caused by *S. pneumoniae* or *H. influenza* was evaluated. According to the results of this study, it was concluded that the treatment with OBEO was effective, as it cured or healed 56 to 81% of rats infected with pneumococci, compared with 5.6 to 6% of rats in the placebo group. Thus, OBEO and its bioactive constituents (thymol and carvacrol) placed in the ear canal can provide an effective treatment of AOM, then a significant advance can be made in the treatment of AOM in children [131].

There is some evidence that in the management of ear pain the topical administration of a combination of herbal medicines (e.g. Otikon otic solution containing EOs of garlic bulb (*Allium sativum*), marigold (*Calendula flores*), mullein flower (*Verbascum Thapsus*) and St. John's wort (*Hypericum perforatum*) in olive oil is as effective as orally administered amoxicillin and topical anaesthetics (e.g. ametocaine® and phenayonein®) due to its antimicrobial, anti-inflammatory, immunostimulating effects and good penetration through the tympanic membrane [135, 137]. The dosage for this previous phytotherapeutic drug to children can be estimated for

children under 4 years of age with 1/3 of the dosage for adults. Moreover, the EO of mullein flower (*Verbascum spp.*, Scrophulariaceae) is known to be effective as a topical ear oil for otitis externa, due to its great effect to unlock the Eustachian tube and to decrease the inflammation [132].

Additionally, aromatherapy with lavender, chamomile, cajuput, evening primerose oils has been also used to treat AOM. Chamomile oil may be used for children with otitis media who are very irritable, in great pain and inconsolable. Furthermore, the eucalyptus oil can be usually administered by steam inhalation and used mostly late in the course of AOM. Another EO that can be definitely applied for treatment of AOM is *Aconitum napellus* (Ranunculaceae). It can be given against throbbing ear pain that comes on suddenly after exposure to cold or wind and in children with higher fever and whose ears are bright red or tender to the touch. It may be better used in the intial stage of an ear infection [132].

3. Essential oils in geriatry

A geriatric patient is a biologically elderly patient who is at acute risk of loss of independence due to acute and/or chronic diseases (multiple pathology) with related limitations in physical, psychological, mental and/or social functions. The abilities to perform the basic activities of independent daily living are diminished or lost. Patients suffer from multiple pathologies which seriously impair their independence [138].

For this EOs attracted the attention to deal with older patients, and especially when EOs are administered as great pharmacy with various options to treat those patients with minimum side effects and limited drug interactions. EOs could replace the current polypharmacy of the elder patient to offer a potential treatment for diabetes, hypertension, cardiac diseases, cancer, arthritis and psychiatric disorders.

3.1 Anti-diabetic activity

Diabetes mellitus (DM) is a complex metabolic disorder characterized by high blood glucose level due to defects in insulin secretion, insulin action or both, it affects the metabolism of carbohydrate, fats, proteins and electrolytes in the body. Type I diabetes (DM1) or insulin-dependent DM occurs due to the immunological destruction of pancreatic ß-cells and consequent insulin deficiency. Type II diabetes (DM2) or non-insulin-dependent diabetes mellitus (NIDDM) is characterized by impaired insulin secretion or insulin resistance [139]. Resistance to insulin impairs the sensitivity of the main target organs (muscle, liver and adipose tissues) to hormones, which increase circulating free fatty acids (FFA) concentrations, inhibit muscle cells glucose uptake and enhance glucose production by the liver. These conditions are considered as DM hallmarks [140].

New researches have focused on the essential oil efficacy on the enzymes and transporters which control the balanced insulin-glucose relationship such as:

a) Glucose kinase (GCK) which is stimulated by insulin and its activation increases glucose utilization and its uptake by

the liver. Therefore, efforts are exerted to discover and develop GCK activators as a novel therapy in type 2 DM.

b) Phosphoenolpyruvate carboxykinase (PEPCK) is a key enzyme which is suppressed by insulin. It controls hepatic gluconeogenesis and glucose output in the liver.
c) Glucose transporter type 4 (GLUT4) it is a target for antidiabetic agents, as it stimulates glucose uptake by adipose tissues and muscles.
d) Peroxisome-proliferator activated receptor (PPAR) is a receptor which controls many genes expression involved in glucose and lipids metabolism. [141-144].

Currently, the range of medication is limited. None of the available options is able to enhance vigorously insulin secretion and simultaneously sensitivity [145]. Many recent studies on the treatment of type 2 diabetes have focused on the potential use of plant constituents with hypoglycaemic and hypolipidaemic effects. Consequently, there has been a growing interest in essential oils, due to their anti-oxidative and hypolipidaemic activities [146]. Several plants EOs have been implicated in insulin signalling pathways modulating glucose transport and glucose-metabolism related enzyme activation, PPAR activation and all of which play roles in diabetes [147-149].

Cinnamon essential oil (CVEO), *Cinnamomum verum* (Lauraceae), showed to possess antidiabetic activity due to its main constituent (75%) cinnamaldahyde, which is responsible for almost all biological activities of it. CVEO exerts a potential anti-hyperglycaemic pharmacological cascade which leads finally to lower blood glucose level and protects the body organs from diabetic complications [150].

Khan *et al* [151], demonstrated that intake of CVEO *in vivo* reduces serum glucose level in people with type 2 diabetes and suggests that cinnamon oil also reduced the risk factors associated with diabetes and cardiovascular diseases. CVEO revealed an increase *in vitro* glucose uptake and glycogen synthesis and an increase of phosphorylation of the insulin receptor as well [152]. In this study [151] it was found that CVEO increased glucose uptake and also the insulin

sensitivity by inhibition of dephosphorylation of insulin receptors, leading to maximal phosphorylation of the insulin receptors, thereby increasing the insulin sensitivity. These results were confirmed by his *in vitro* study on 60 people with type 2 diabetes for 40 days followed by 20 days washout-period and they have been divided into cinnamon group and placebo group. In the cinnamon group the reduced fasting serum glucose (18%-29%) and no significant change in placebo group was obvious [151].

Cao *et al*. confirmed the anti-hyperglycaemic effect of CVEO by means of enhancing the glucose uptake by stimulating the glucose transporter type 1 (GLUT1) in the cultured adipose tissues.

The reduction in postprandial blood glucose level after CVEO administration in the postprandial phase (15, 30, 45 min.) was explained by reduction also in the gastric emptying rate, which plays an important role in carbohydrates delivery in small intestine. Therefore, CVEO showed to suppress the insulin resistance in high-fructose diet fed rats by enhancing the insulin signalling by nitric oxide pathways in skeletal smooth muscles [153, 154].

Jia *et al*. reported that the oral administration of CVEO in streptozotocin-induced diabetic rats at doses 100, 200 and 300 mg/kg over 14 days resulted in decrease in blood glucose level by 11.1 %, 22.5% and 38.7% respectively. In conclusion, it is obvious that CVEO plays an anti-diabetic role *in vivo* and *in vitro* due to its anti-hypoglycaemic activity and due to the insulin-like action or by increasing the sensitivity of body tissues to insulin [155].

Capparis spinosa essential oil (Capparaceae) (CSEO) is an oil from a native fruit in circum-Mediterranean countries, and possesses a sweet and showy fragrant. It possesses reasonable amounts of volatile aldehydes and monoterpene hydrocarbons which play an important role in its antihyperglycaemic activity [156]. CSEO exerted a significant and potent antihyperglycaemic activity in streptozotocin-diabetic rats. It was demonstrated that repeated oral administration of CSEO for two weeks was accompanied by an important improvement in glucose

tolerance and a strong decrease of body weight in highly glucose tolerant of high fat diat mice which is considered as the adequate model for studying pathophysiology of human type 2 diabetes. Obesity is associated with insulin resistance and cardiovascular diabetes risk factors. Thus, insulin resistance in obese type 2 diabetic patients is significantly worse than in non-obese diabetic patient. Therapeutic agents with both anti-diabetic and anti-obese effects are therefore particularly beneficial [157]. Another possible action of CSEO to exert its postprandial hypoglycaemic effects is located in the gastrointestinal tract where it slows the digestion of food and thus decreases the rate of carbohydrate absorption and clearing the postprandial glucose load with no effects on basal plasma insulin concentrations in both normal and diabetic rats. Therefore, the hypoglycaemic activity of this oil is due to the inhibition of hepatic glucose production and/or stimulation of glucose utilization by peripheral tissues especially muscles and adipose tissues and could also act as inhibitor of tubular renal glucose re-absorption [158].

Nigella sativa oil (Ranunculaceae*)*, NSO contains volatiles compounds mainly monoterpenoids and their oxygenated derivatives [159]. Thymoquinone (TQ) is the major compound of NSO and it is responsible for almost all of its biological activities [160]. Most importantly, NSO activates the adenosine mono-phosphate-activated protein kinase (AMPK) in the liver and muscles to improve glucose metabolism. NSO mediates its action by stimulating the AMPK. It also reduces the enzymatic pathway involved in increasing fatty acid production by the liver (ACC=Acetyl-CoA-carboxylase); thus, it increases the sensitivity of insulin. The activation of AMPK inhibits the pathway of gluconeogenesis in liver. In muscle, NSO activates AMPK towards allowing the increased synthesis and translocation of GLUT4 and consequently increases the glucose transport. NSO also acts in pancreas by augmenting the secretion of insulin. As a result of these previous mechanisms, NSO increases the circulating insulin and enhances the sensitivity of peripheral tissue to the insulin [159].

Farah *et al*. investigated the insulinotropic properties in diabetes type 2-like model. The result demonstrated significant decrease in blood glucose level together with significant increase in serum insulin level after treatment of streptozotocin-induced diabetic rats with NSO. It was also suggested that this action is due to decrease in hepatic gluconeogenesis and on the other hand, NSO stimulates regeneration of β-cells and incites insulin secretion from them [160]. Another finding reports that using of NSO increased the serum insulin and lowered serum glucose levels without causing and evidence of histopathological damage in liver via increase of Serum-Glutamat-Pyruvat-Transferase (SGPT) [161].

Oxidative stress is involved in the origin of type 1 diabetes, especially via the apoptosis of pancreatic ß-cells, as well as insulin resistance in type 2 diabetes. It was also determined that a stress could participate potentially in development of hyperglycaemia by setting of sympathetic system, activation of corticotrope function, secretion of growth hormone with the increase of hepatic production of glucose and reduction of its peripheral clearance and by liberating of endorphins inhibiting the secretion of insulin [162]. NSO seems to protect β-cells against oxidative stress, as well the majority of Langerhans islets and also attenuates the damage of ß-cells of the pancreas following exposure to toxic elements such as cadmium, because NSO prevents lipid peroxidation and increases anti-oxidant deficiency system activity. NSO and its volatile monoterpenoids compounds play an emphasized role in neuron protection via inhibiting significantly some of Mitogen-Activated Protein Kinase (MAPKs) which is responsible for the neurodegeneration in type 1 diabetes [161].

In conclusion, it appears that the antidiabetic activity of NSO is mediated by multiple modes of actions, which indicates that NSO exerts promising reducing effects *in vivo* and *in vitro* with highly safe parameters.

Lemon balm essential oil LBEO *Melissa officinalis* (Lamiaceae) is a well-known herbal component species used in perfumes and shows to have a strong anti-diabetic activity either due to its direct mechanism

on diabetes pathways or by reduction the oxidative stress [146]. De Sousa *et al*. demonstrated that the LBEO revealed a strong anti-oxidant activity without any toxicity and without induction of a liver damage but it also decreases plasma transaminases which are a cause and a result for DM [163]. LBEO decreases glucose concentration by stimulating glucose kinase (GCK) activity and inhibiting glucose 6-phosphatase (G6Pase) activity in liver. Hepatic GCK activity was increased significantly and in contrast to G6Pase and phosphenolpyruvate-carboxykinase (PEPCK) were decreased by the LBEO group compared with control group. Accordingly, LBEO treatments appear to improve glucose metabolism by an increase in GCK activity and a decrease in gluconeogenic enzyme activity (i.e. G6Pase and PEPCK) [162].

In conclusion, LBEO is a safe antidiabetic agent with double edged merits, the antihyperglycemic activity and the antioxidant activity, thus, LBEO should be considered as one of the strongest antidiabetic agent with two different mechanisms of action.

3.2 Antihyperlipidemic activity

Hyperlipidaemia is a disorder, where the serum and hepatic lipids ratio are not in balance, due to various medical and biological reasons. Hyperlipidaemia is an important factor to induce metabolic syndrome such as obesity, diabetes and cardiovascular diseases. Recently, some antihyperlipidaemic agents from herbal medicines have been in the spotlight in medical science field due to their potent efficacy and the high safety profile in comparison to synthetic chemical agents [164].

M. officinalis essential oil (Lemon balm), LBEO contains the oxygenated monoterpenes geranial, neral and geranyl acetate as main constituents of this oil and it revealed to have a hypolipidemic effect [165]. Jun *et al*. found that the plasma triglycerides (TG) concentrations were significantly reduced in apolipoprotein E2 (APOE2) mice which were orally administrated with LBEO. In the same study, it was known that cellular TGs and

cholesterol concentrations were also significantly decreased in a dose- and time-dependent manner in HepG2 cells stimulated with LBEO compared with control and this was due to the reduction of the rate of fatty acid synthesis. Additionally, LBEO stimulation in HepG2 cells induced bile acid synthesis and reduced the nuclear form of sterol-regulatory element-binding protein **(**SREBP-2), a key transcription factor in hepatic cholesterol synthesis with no side effects or symptoms of toxicity [165]. These findings suggest that the intake of LBEO plays a great role in controlling the dyslipdemia.

Curcuma essential oil (CLEO) "Turmeric" *Curcuma longa L.* (Zingiberaceae) which contains an essential oil with a potential hypolipidemic effect. The major components of CLEO are ar-d-tumerone and α/β-tumerone [166]. Singh *et al*. investigated the potent antihyperlipidemic activity of this essential oil in hamsters. CLEO significantly reduced plasma total cholesterol, LDL-cholesterol and TGs, in addition to increasing the HDL-cholesterol when compared with control group. This effect is exerted by more than one mechanism: CLEO treats the hyperlipidaemia via:

a) Increasing the hepatic expression of PPARα, LXRα and LPL accompanied by reduced SREBP-2 and HMGCR expression,
b) attenuating hyperlipidaemia-induced oxidative stress,
c) the protective effect of CLEO on hyperlipidaemia induced endothelial dysfunction, and via
d) favouring biliary and faecal cholesterol excretion [166].

As a summary, the above results indicated that CLEO shows to be a potent antihyperlipidemic agent in the future.

Coriander *Coriandum sativum* (Umbelliferae), it is a well-known carminative whose EO showed to have a hypoglycaemic effect due to the volatile constituents, e.g. linalool, geraniol and terpinen-4-ol. Lal *et al*. found that coriander EO reduced the cholesterol and TGs in induced-hyperlipidaemia rats. It can be assumed that coriander EO exerts a therapeutic effect by reducing the high lipids levels by increasing their catabolism and eventual excretion [167]. Dhanapakim *et al*. reported

also the antihyperlipidemic effect of coriander EO via the increase in HMG-CoA reductase [168].

Hibiscus *Hibsicus sabdariffa* L. (Malvaceae). HSEO was shown to lower the plasma lipids and reduce the liver damage. Yang *et al*. indicated that the decrease in the lipid content of hepatocytes is due to the activation of AMP-activate protein-kinase (AMPK) and reduction of SREBP-1, thus inhibiting the expression of fatty acid synthase and HMG-CoA reductase. It was discovered also, that linalool and α-terpineol are responsible for the hypolipidemic effects and its putative mechanism on liver. In conclusion, HSEO is worthy of being further investigated and could be developed as an adjunct for hepatic lipid control and hyperlipidemic therapy [169].

Pinus koraiensis (Pinaceae) essential oil (PKEO) with α-pinene and α-terpineol as main constituents, revealed to be a potent pharmaceutical agent for the treatment of hyperlipidaemia via the following mechanisms:

a) Up-regulation of LDL-receptors at the mRNA level as well as suppression of the expression of fatty acid synthase (FAS) and glycerol-3-phosphate acyltransferase which are involved in lipid metabolism in Hep G2 cells,
b) attenuation the expression of FAS and activation of LDL receptors at the protein level in the cells, and
c) reduction of LDL oxidation [164].

Satureja khuzestanica essential oil (Lamiaceae) (SKEO) possesses antioxidant properties and thus it seems to be useful in diseases related to oxidative stress such as diabetes and hyperlipidaemia. Ghanbari *et al.* indicated that SKEO exerts a great influence on metabolic parameters of hyperlipidemic patients via decreasing the total lipid profile LDL, VLDL, TAG and total cholesterol due to its antioxidative activity and due to its monoterpene contents (carvacrol and thymol) which adjust the lipid picture. Therefore, it proposed that SKEO can be used as a potent hypolipidemic agent with several antioxidative properties [170].

3.3 Anti-osteoporotic activity

Osteoporosis is a skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. The WHO provided a practical definition of osteoporosis as a bone mineral density (BMD) of greater than 2.5 standard deviation (SD) below the young normal mean. The etiology of osteoporotic fracture is complex [171]. Also it results from low bone mass (osteopenia) due to excessive bone resorption. Sufferers are prone to bone fracture from already relatively minor traumata. Agents including selective estrogen receptor modulators (SERMs), bisphosphates and calcitonin are frequently used to prevent bone loss [172]. Currently, there is no cure for osteoporosis and treatment is focused on reducing the risk for fracture.

Chamomile EO (Asteraceae) was evaluated for its ability to stimulate the differentiation and mineralization of osteoblastic cells. Chamomile EO was shown to stimulate osteoblastic cell differentiation and to exhibit an anti-estrogenic effect, suggesting an estrogen-receptor related mechanism [172].

Cumin cyminum EO "Cumin" (Apiaceae) is currently under active investigation for its role in estrogen-related disorder and it is able to be used as possible in treating postmenopausal osteoporosis soon. Shrike *et al*. deals with CCEO to evaluate the anti-osteoporotic activity of it in a phytoestrogen-rich plant. An anti-osteoporotic effect by comparison between bone and ash densities was found. CCEO showed greater bone and ash densities and improved microarchitecture of bone in SEM analysis. Unlike estradiol it did not affect body weight gain and weight of atrophic uterus in OVX-animals. CCEO prevented ovariectomy-induced bone loss in rats with anabolic effect on atrophic uterus. The osteoprotective effect was comparable with estradiol. Thus, CCEO is regarded as a promising agent in prevention and treatment of osteoporosis [173].

3.4 Anti-arthritic activity

Arthritis means joint inflammation, it is a chronic, progressive and disabling auto-immune disease. The disease mostly affects the aging population. Arthritis can progress very rapidly causing swelling and damaging cartilage and bone around the joints, commonly the hands, feed and wrists, but it is a systematic disease which means that it can affect the whole body and internal organs (lungs, heart and eyes). Arthritis can cause severe and ultimately disability to carry out everyday tasks. Any part of the body can become inflammed or painful from arthritis.

The two most common types of arthritis are osteoarthritis (OA) and rheumatoid arthritis (RA). OA is a degenerative joint disease, resulting from the wear and tear from day to day life. It leads to pain, tenderness, swelling and decreased functions of joints namely, knees, hips, hands and spine. RA is an autoimmune disease that occurs when the body's own immune system mistakenly attacks the synovium (cell lining inside the joint). It causes joint pain, stiffness, swelling and loss of joint function. Fortunately, nature has a remedy for these conditions and there are a number of herbs and their EOs that work synergistically to reduce chronic joint inflammation, such as OA and RA. EOs could be of great value when used in a program of health care and highly effective preventive medicine when compared to expensive synthetic drugs [174].

Piper aleyreanum essential oil (Piperaceae) PAEO showed to play a role against formalin-induced inflammation and pleurisy rats' models. β-pinene (9%), camphene (5.2%) were the major oil constituents. The oral administration of PAEO significantly inhibits the neurogenic and inflammatory phases of formalin-induced licking in the formalin test. These results support the widespread use of PAEO in popular medicine and demonstrate that this plant has therapeutic potential for the development of EOs with antinociceptive, anti-inflammatory [175].

Litsea cubeba EO "May Chang" (Lauraceae) was found to exert a preventive efficacy in the treatment of the RA using CFA-induced arthritis in rat model. Lin et al. indicated that LCEO significantly attenuates adjuvant arthritis in rats by decreasing the level of the TNF-α, IL-1β and IL-6 and increasing of IL-10 in serum as well as it downregulates the level of inflammatory enzymes such as COX-2 and 5 LOX. Therefore, it suppressed the paw swelling and arthritis score on CFA-induced model rats and all these notifications are confirmed by histopathological improvement in joint architecture in rats treated with LCEO [176].

Permna serratifolia essential oil (Verbenaceae) is known because of its anti-arthritic activity, the main constituents are linalool and 3-hexenol which are responsible for the anti-arthritic activity. Rajendran *et al.* validated the ethno-pharmacological of PSEO anti-arthritic activity by Freund's adjuvant induced arthritis model. PSEO inhibited the rat paw edema by 68.3 % and the anti-arthritic effects were confirmed by various biochemical parameters such as Hb content, total WBC, RBC, erythrocytes and SR. This current result showed that PSEO possesses a significant anti-arthritic activity may be due to its linalool content [177].

3.5 Cardiovascular activity

3.5.1 Antihypertensive activity

Hypertension (HTN) is the medical term for high blood pressure (BP), it is a chronic medical condition in which the BP in the arteries is elevated. It is classified as either primary (essential) or secondary. About 90 % to 95 % of cases are termed primary HTN, which refers to high blood pressure for which no medical cause can be found. The remaining 5 to 10 % of cases called secondary HTN, are caused by other conditions that affects kidneys, arteries, heart or endocrine system [178].

As an alternative to drug therapy, it is desirable to change the dietary style and use medicinal plants agents for the prevention and

treatment of HTN and thereby to avoid the adverse effects of organically synthesized drugs as well as the high cost of drug therapy [179].

Nigella sativa volatile oil (Ranunculaceae) showed to be a potent antihypertensive agent due to its active constituent thymoquinone (TQ) and cymene P. NSVO exerts a potent hypotensive effect and reduced both the systolic (SBP) and diastolic (DBP) blood pressure compared to the placebo group with no side effects [179]. El Tahir *et al*. investigated the role of TQ in NSVO and its influence on arterial blood pressure in a dose-dependent manner and that effect was antagonized by cyproheptadine, hexamethonium atropine and spinal pithing. Moreover, NSVO-induced cardiovascular depressant effects which were significantly antagonized by atropine and cyproheptadine [180]. In conclusion, the NSVO-induced hypotension was mediated mainly centrally via indirect and direct mechanisms that involved both 5-hydroxytryptaminergic and muscarinic mechanisms. At last, NSVO seemed to be a potent centrally antihypertensive agent.

Carum copticum essential oil (Apiaceae) contains mainly thymol as the main constituent of this oil which might be the key of its hypotensive activity. Gilani *et al*. investigated the inhibitory effect of CCEO on K^+ induced contraction and confirmed that Ca^{+2} channel blocking leads to a dose-dependent fall in arterial blood pressure in anaesthetized rats. This confirmed the CCEO blood pressure lowering effect which is mediated partially by means of cholinergic mechanism. The spasmolytic effect (calcium antagonist) was observed at relatively low doses in rabbit jejunum, aorta and guinea-pig trachea and is probably responsible for the hypotensive and bronchodilator activities of the oil [181]. These results indicated the presence of calcium antagonists in CCEO thus providing a sound mechanistic basis for some of their folkloric uses.

Essential oil of *Mentha x villosa* (Lamiaceae) MVEO possesses a hypotensive effect in deoxycorticosterone acetate (DOCA)-salt-hypertensive rats. DOCA is injected to rats as a resembled analogue to humans with HTN. Lahlou *et al*. studied the effects of chronic treatment

with DOCA-salt on cardiovascular responses to injection of MVEO in conscious rats. MVEO (i.v) bolus injection decreased mean arterial pressure (MAP) and heart rate (HR) in a dose-dependent manner without affecting bradycardia. These results confirmed that (i.v) treatment with MVEO decreases blood pressure in conscious DOCA-salt-hypertensive rats dose-dependently and that this action is enhanced when compared with un-nephrectomized controls. This enhancement could be related mainly to an increase in MVEO-induced vascular smooth muscles relaxation, rather than to enhanced sympathetic nervous system activity in this hypertensive model [182].

Another study concerned with EO of *Alpinia zerumbet* (Zingiberaceae) AZEO which is a potent hypotensive agent due to its terpinen-4-ol content which is a bioactive monoterpenoid alcohol. AZEO decreased the mean arterial pressure (MAP) and heart rate (HR) after treatment of deoxycorticosterone acetate (DOCA)-salt conscious rats. The decreased BP is due to the terpinen-4-ol-induced vascular smooth muscle relaxation. Also it enhanced the sympathetic nervous system activity in a dose-dependent manner. These data support the hypotensive activity of both AZEO and its alcohol in hypertensive cases [183].

Essential oil of *Croton nepataefolius* (Euphorbiaceae) CNEO is used as an alternative treatment for HTN with minimal side effects. The hypotensive effect of CNEO resulted from its direct vasodilatory action via vascular smooth muscles. MAP reduction achieved via i.v. bolus of CNEO without bradycardia in a dose-dependent behaviour. In an isolated thoratic aorta preparations of CNEO induced a concentration-dependent reduction of phenylephrine (PE) induced contraction and the arteries of DOCA rats showed increased sensitivity to CNEO. All these results postulated that CNEO exerts its vasodilatory effect via vascular smooth muscles dilatation resulting in reduction in MAP and HR [184].

Interaminense *et al*. corroborate the antihypertensive effects of essential oil of *Ocimum gratissimum* (Labiatae) OGEO via the vascular effects by its active constituent eugenol. OGEO relaxed the PE-induced

contractions and the vasorelaxant effects of OGEO were significantly altered by removal of the vascular endothelium. In a calcium-free medium the $CaCl_2$ induced contractions were significantly reduced and even abolished by OGEO. These data suggest that the OGEO hypotensive effect is due to an active vascular relaxation which is partly dependent upon the integrity of the vascular endothelium and seems predominantly mediated by inhibition of plasmalemmal Ca^{+2} influx rather than Ca^{+2} induced release from the sarcoplasmic reticulum [185].

The bark essential oil of *Aniba canelilla* (Lauraceae) ACEO performs its hypotensive activity through two different mechanisms. Normotensive rats got (i.v.) injected ACEO, which lead to hypotension and bradycardia. However, both ACEO-induced hypotension and bradycardia were significantly reduced by pretreatment with methylatropine. These data show that treatment of rats with ACEO induce dose-dependent hypotension and bradycardia. The relaxation seems partly mediated by an endothelial L-arginine/nitric oxide pathway via peripheral muscarinic receptor activation (endothelium-dependent relaxation) and on the other hand predominantly by means of inhibition of calcium inward current (endothelium-independent-relaxation). ACEO shows a potent hypotensive effect in normotensive rats with 2 mechanism dependently or independently of endothelium relaxation [186].

3.5.2 Anti-atherogenic activity

Atherosclerosis is a process in which deposits of plaque builds-up in the innermost layer of the artery, the intima plaque can eventually significantly reduce blood flow, leading to serious health problems. Increased concentrations of oxidatively modified LDLs in cholesterol play a substantial role in disease initiation. Atherosclerosis can therefore be slowed down or inhibited by preventing the oxidation of LDLs [2]. Atherosclerotic index indicates the deposition of foam cells or plaque, fatty infiltration or lipids in heart, coronaries, aorta, liver and kidney. The higher the atherosclerotic index the bigger is the risk of these organs for oxidative damage [187].

Tea tree oil (Myrtaceae) (TTO) is rich of monohydrocarbon alcohols and particularly terpinene. γ-Terpinene and terpinen-4-ol are found to be potent anti-atherogenic agents due to their role in LDL oxidation inhibition. TTO inhibits the LDL oxidation in the propagation phase with an antioxidative effect on the Cu^{+2}-induced and AAPH-induced oxidation of human LDL *in vitro*. Thus, TTO is a promising safe anti-atherogenic agent which already is added to the food and beverage to protect it against oxidation and thus reducing the plaque formation of a wide range [188].

Salvia miltiorrhiza essential oil (Lamiaceae) is widely used traditionally agent in cardiovascular diseases. 1,8-Cineole, camphor and α-pinene are the major constituents which are responsible for the anti-atherogenic activity. Ling *et al*. reported that SMEO inhibits TNF-α induced expression of intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) in vascular endothelial cell. This can attenuate the platelet-derived growth factor (PDGF)-induced proliferation of vascular smooth muscle cells, exerting an anti-atherogenic action with that mechanism [189].

Syzygium aromaticum essential oil "clove" (Myrtaceae) is shown to possess anti-atherogenic activity due to inhibition of protein glycation in hypercholesterolemic animals and human models. Jin *et al*. investigated the anti-atherogenic activity of clove oil *in vitro* and *in vivo* using the hypercholesterolemic zebrafish. It was reported that clove oil is a potent inhibitor of copper-mediated LDL-oxidation and LDL phagocytosis by macrophages. Clove oil also possess a potent cholesteryl ester transfer protein (CETP) inhibition activity in a concentration-dependent manner, it decreases the serum cholesterol and TGs levels by 68% and 80%, respectively. As a summary, clove oil possess potent activity to suppress the incidence of atherosclerosis via effective antioxidant potential, prevention of Apo A-I glycation and LDL-phagocytosis, inhibition of CETP and hypolipidemic activity. These previous mechanisms and results represent one of the promising cardioprotective agents with herbal background [190].

Citrus aurantium essential oil (Rutaceae) is known for its aromatic constituents limonene, α-terpineol and terpinyl-acetate to be a natural anti-atherogenic agent. Liu *et al*. demonstrated the mechanism of CAEO to inhibit plaque formation. CAEO enhanced the adiponectin transcript in differentiated 3T3-L1 cells, it induced peroxisome proliferator-activated receptor (PPAR), γ-controlled luciferase expression in a dose-dependent manner and up-regulated the adiponectin expression in adipocytes which spot a highlight on the molecular explanation for the anti-atherogenic effect of CAEO, with the expectation to have in the next few years a promising safe, cheap and effective anti-atherogenic agent [191].

3.5.3 Anti-platelet and antithromobosis activity

Thrombosis is usually associated with platelet activation and the release of eicosanoids which contribute to initiation and aggravation [2]. Activation of blood platelets plays a crucial role not only in haemostasis but also in pathological development of several arterial disorders, including strokes and myocardial infarction. There is increasing evidence that acute clinical manifestations of coronary atherosclerotic diseases are caused by plaque disruption and subsequent platelet-thrombus formation, it is also documented that platelets participate in tumor progression allergic inflammation and non-allergic responses by producing inflammatory substances, such as cytokines and eicosanoids [192].

The antiplatelet agents currently used for this purpose are effective in the prevention of thromboembolic disease, but many have side effects such as gastric erosions (e.g. Aspirin®), agranulocytosis (e.g. tricolopidine) or show poor separation between therapeutic efficacy and haemorrhagic complication [2]. Therefore, there is resurgent interest in exploring the anti-platelet activity of medicinal plant extracts (essential oil) because these are cost effective, easily available form of indigenous resources and are comparable to synthetic blood thinner in this prospective [193].

Garlic leaf EO (Amaryllidaceae). GLEO are showed to possess a potential inhibition properties of platelet aggregation. These effects are due to the aroma volatile compounds diallyl trisulfide, diallyl disulfide and methyl allyl trisulfide. GLEO showed to exert an anti-platelet aggregation activity by inhibiting thromboxane A_2 (TXA_2) synthase, to block the TXA_2/PGH_2 receptor and lowering the TXB_2 levels. It also penetrates the membrane of intact platelets and reduces the viscosity of the inner part of the lipid bilayer, they also interfere with the expression of fibrinogen receptor at the cell surface, thereby inhibiting fibrinogen binding. They inhibit also the platelet aggregation via suppressing the formation of TXA_2 by altering arachidonic acid metabolism. Moreover, they inhibit platelet aggregation induced by adrenaline, collagen, adenosine diphosphate and calcium ionophore A23187. Furthermore, polysulphides, particularly dimethyl sulphide and diallyl trisulphides found to possess inhibitory effect on the thromboxane synthesis itself in platelets. In conclusion, GLEO postulated to be the most effective natural agent that inhibit platelet aggregation and may be a more potent than synthetic blood thinners [2, 194].

Lavender essential oil (Lamiaceae) showed a broad spectrum of antiplatelet effects and was able to inhibit platelet aggregation induced by arachidonic acid ADP, collagen and the stable thromboxane receptor agonist with no prohemorrhagic properties. It is thought that all effects are due to linalyl acetate, the main bioactive constituent of lavender oil [2].

Ecodia rutaecarpa essential oil (Rutaceae) showed to exert anti-platelet activity *in vivo* due to the aromatic constituents linalool, γ-terpinene and β-thujene which are the bioactive substances by inhibition of phospholipase captivity, leading to reduced phosphoinositide breakdown followed by the inhibition of thromboxane A_2 formation. Moreover, EREO prolongs the occlusion time of thrombus formation, and it is more potent than heparin in preventing the ADP-induced thromboembolic death. Therefore, EREO is a promising natural anti-thrombotic agent [195].

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5. CURICULUM VITAE

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Work Experience

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Mary's Pharmacy, Hurghada, Egypt
Community Pharmacist
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Training Experience

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Available on request.

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