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“Essential Oils and Drugs: Interactions”

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Abstract

The essential oils and their constituents have been used and applied for a long time in the treatment in a lot of diseases, and their uses and applications are in an increasing growth and due to their increasing importance more and more scientific studies were conducted to investigate their effects on other drugs under the title of essential oil-drug interactions. Also many studies are conducted to investigate the effects of essential oils and their constituents on sensory functions like smelling and tasting ability. The aim of this article is to summarize the literature on this topic published in the period 1990-2014. The major interactions discussed are the interactions between essential oils and prescribed drugs like: Aspirin®, ACE-inhibitors, beta-blockers, calcium channel blockers, anti-depressants, antiepileptic drugs, benzodiazepines and analgesics.

One chapter discusses the actions of essential oils on olfactory and gustatory systems.

Key words: Essential oils, Aromatherapy, Essential oils-drugs interactions, Olfactory and gustatory disorders, Essential oils sensory effects.

Zusammenfassung

Schon seit jeher wurden ätherische Öle und deren Bestandteile in der Behandlung von vielen Krankheiten. Deren Verwendung und Bedeutung steigt beständig, sodass auch eine große Zahl an wissenschaftliche Studien mit dem Titel „Wechselwirkungen zwischen ätherischen Ölen und Arzneimittel “ durchgeführt werden, um deren Wechselwirkungen mit anderen Arzneimitteln zu untersuchen. Ebenfalls widmeten einige Studien ihre Aufmerksamkeit der Frage, wie ätherische Öle und deren Bestandteile auf den Riech- und Geschmackssinn einwirken. Das Ziel dieses Artikels ist, die zwischen 1990 und 2014 veröffentlichte Literatur zu diesem Thema zusammenzufassen. Die Hauptwirkungen zwischen den ätherischen Ölen und Arzneimitteln, die hier beschrieben werden, sind: Aspirin®, ACE-Inhibitoren, Betablocker, Kalziumkanalblocker, Antidepressiva, antiepileptische Arzneimittel, Benzodiazepine und Analgetika. Ein Kapitel konzentriert sich auf die Wirkung der ätherischen Öle auf den olfaktorischen und gustatorischen Sinn.

Contents:

1. Introduction.

The co-administration of herbal drugs which contain essential oils with other drugs may lead to drug interactions which can increase or decrease the efficacy and adverse and side effects of both of drug and herb.

These interactions may occur through different mechanisms, physiological and pharmacological ones.

A) Physiological interactions:

They are interactions by which herbal drugs and essential oils act by different mechanisms and on different receptors and/or enzymes other than the prescribed drug to produce the same physiological effects of the drug which may lead to the need to decrease the prescribed drug dose to avoid the expected side and adverse effects due to synergism between essential oils and drugs.

These interactions may also lead to antagonistic actions of the prescribed drug which means decreasing the efficacy of the drug which may lead to the demand to increase the drug dose to avoid the expected therapeutic failure.

This type of interactions is the most common type of essential oil-drug interactions because every essential oil has its own characteristic pattern of constituents which cause the biological and physiological effects which are the reason to be used in complementary therapies.

B) Pharmacological interactions:

These types of interactions may be:

1) Pharmacokinetic interactions:

Here essential oils interfere with the pharmacokinetic characters of the drug. The drug passes through four main pharmacokinetic steps which are:

absorption, distribution, metabolism and excretion. Essential oils may affect any of these steps changing the bioavailability and efficacy of the drug.

It may increase or decrease absorption, distribution, or elimination of the drug leading to the need to increase or decrease the dose or the dose interval of the drug according to the type of interaction.[1] Some essential oils like peppermint oil in a dose of 90 mg and caraway oil in a dose of 50 mg show an antispasmodic effect [2], also it was reported that lavender essential oil in a dose of one to four drops daily, usually placed on a sugar cube[3], has also an antispasmodic action and an inhibitory effect on the intestinal smooth muscles movement.[4] It is also reported that *Rosa damascena* Mill flower, known as damask rose, essential oil and as well the single fragrance compounds, e.g. geraniol and citronellol oil in a dose of 1-2 g into 200 ml water[5] have an inhibitory effect on the ileum smooth muscles. [6]

All these effects decrease the gastrointestinal motility which is an important factor that controls and regulates the absorption and the bioavailability of most of orally administered drugs. The oil constituents will increase the contact time between the drug and the surface of stomach and intestine available for absorption which will lead to increase the absorption and bioavailability of the drugs, but severe inhibition of gastrointestinal tract motility leads to the opposite result and can decrease the absorption and bioavailability of the orally administered drug. [7]

Also some other essential oils are reported to have an effect on hepatic microsomal cytochrome P-450 enzymes which may affect the metabolism of other drugs. Induction of hepatic microsomal cytochrome P-450 enzymes means an increase of the rate of metabolism of the drug and a decrease of its effects which may lead to the need to increase the dose of the drug or change the dose interval to avoid the expected therapeutic failure. But inhibition of hepatic microsomal cytochrome P-450 enzymes leads to a decrease of the rate of metabolism of the drug and thus increases its effects which may lead to the need to decrease the dose of the drug or

increase the time interval of the drug dose to avoid the expected side effects and toxicity.[8]

Some essential oils and their constituents are considered as inducers of some hepatic microsomal cytochrome P-450 enzymes, such as: [8]

Isozyme	Inducer-Essential oil or constituents and the dose
CYP1A1	Rosemary oil (5 g/kg for 2 weeks). Bergapten (2.5 g/kg for 6 weeks). β-Myrcene (1g/kg for 1 day). 1,8-Cineole(800mg/kg/day for 3 days).
CYP1A1/2	Myristicin (96 mg/kg). Eugenol (1 g/kg/day for 10 days).
CYP1A2	Rosemary oil (5 g/kg for 2 weeks). Diallyl sulfide (0.2% for 13 days). Diallyl disulfide (0.2% for 13 days).
CYP2B1	Hinoki wood oil (300 mg/kg/day for 5 days). Hibawood oil(300 mg/kg/day for 5 days). 1,8-Cineole (300 mg/kg/day for 5 days). Cadinene (300 mg/kg/day for 5 days). α-Pinene (300 mg/kg/day for 5 days). Borneol (300 mg/kg/day for 5 days). Limonene (5% w/w for 2 weeks). β-Myrcene (1 g/kg/day for 10 days).

CYP2B1/2	Rosemary oil (5 g/kg for 2 weeks). Farnesol (1 g/kg/day for 4 weeks). Myristicin (96 mg/kg). α-Ionone (300 mg/kg). β-Ionone (300 mg/kg). 1,8-Cineole (400 mg/kg/day for 3 days). Diallyl sulfide(0.2% for 13 days). Diallyl disulfide (0.2% for 13 days). Eugenol (1 g/kg/day for 10 days).
CYP2B2	Limonene (5% w/w for 2 weeks).
CYP2E1	Myristicin (96 mg/kg).
CYP3A1/2	Farnesol (1 g/kg/day for 4 weeks). 1,8-Cineole (800 mg/kg/day for 3 days).
CYP3A2	Hinoki wood oil (300 mg/kg/day for 5 days). Hibawood oil (300 mg/kg/day for 5 days). Cadinene (300 mg/kg/day for 5 days). 1,8-Cineole (300 mg/kg/day for 5 days).
CYP4A1	Citral (1.5 g/kg/day for 5 days).
CYP4A1-3	Farnesol (1 g/kg/day for 4 weeks).
CYP4A2	α-Pinene (300 mg/kg/day for 5 days).
CYP19	Farnesol (1 g/kg/day for 4 weeks).

Some essential oils and their constituents are considered as inhibitors of some hepatic microsomal cytochrome P-450 enzymes, such as: [8]

Isozyme	Inhibitor-Essential oil or constituent and the IC_{50}
CYP1A1	Bergamottin (0.057 μM). Isopimpinellin (1.36 μM). Angelicin (11.7 μM).
CYP1A2	Chamomile (blue) oil (1.59 μg/mL). (*E*)-Spiroether (0.47 μM). (*Z*)-Spiroether (2.01 μM). Chamazulene (4.41 μM). Safrole (5.7 μM).
CYP1B1	Perillyl alcohol (1.5 μM).
CYP2A6	Bergamot oil. Lime oil. (6*R*)-(+)-Menthofuran. Safrole (12.0 μM).
CYP2B1	(-)-α-Pinene (0.087 μM). (+)-α-Pinene(0.089 μM). β-Myrcene (0.14 μM). (+)-Limonene (0.19 μM). α-Terpinene (0.76 μM). Citral (1.19 μM). Citronellal (1.56 μM). Camphor (7.89 μM). β-Ionone (0.03 μM). 1,8-Cineole (4.7 μM). (-)-Menthol (10.6 μM). α-Terpinol (14.8 μM).

CYP2B6	Citral (6.8 μM). Geraniol (10.3 μM). Borneol (9.5, 22 μM). Isoborneol (5.9, 26 μM).
CYP2C9	Chamomile (blue) oil (14.3μg/mL). α-Bisabolol (46.1 μM). Chamazulene (59.3 μM). Farnesene (73.1 μM).
CYP2D6	Chamomile (blue) oil (8.49 μg/mL). Chamazulene (1.06 μM). α-Bisabolol (2.18 μM). Farnesene (4.80 μM). (*E*)-Spiroether (34.8 μM). (*Z*)-Spiroether (57.6 μM). Safrole (110 μM).
CYP2E1	Tangerine oil. Bergamot oil. Mandarin oil. Petitgrain oil. Lemon oil. Orange oil. Grapefruit oil. Lime oil. Neroli oil. Garlic oil (500 mg/kg for 1-3 days). Diallyl sulfide (0.2% for 13 days). Diallyl disulfide (0.2% for 13 days). Safrole (1.7 μM).

CYP3A	Oxypeucedanin (1.8 μM). Isopimpinellin (1.9 μM). Bergapten (3.1 μM). Psoralen (5.1 μM). Bergamottin (22 μM).
CYP3A4	Chamomile (blue) oil (4.97 μg/mL). (*Z*)-Spiroether (6.13 μM). (*E*)-Spiroether (7.14 μM). Chamazulene (7.58 μM). α-Bisabolol (15.8 μM). Farnesene (38.1 μM). Peppermint oil. (-)-Menthol. (-)-Menthyl acetate. DHB (1.2 μM). Bergamottin (4.5 μM). Bergaptol (77.5 μM). Bergapten (19 μM). Psoralen (116 μM). Safrole (43.5 μM).

Essential oil constituents also bind to plasma proteins which interfere with the drugs distribution and activity. [8] Most essential oil constituents have properties that favor binding to plasma protein [9]. 97% of any given dose of β-elemene was reported to be bound with plasma protein [10], 98.5% of any given dose of bergaptene and 77.5% of any given dose of methoxalen became reversibly bound to serum proteins, principally albumin. [8] Binding to human serum albumin has also been demonstrated for borneol, safranal, and thymoquinone. [11, 12,13]

2) Pharmacodynamic interactions:

Additive, synergistic or antagonistic effects of combinations of drugs are possible with any type of drugs, including essential oils. Therefore, essential oil constituents can act as sedatives, anticoagulants, anti-hypertensives which will increase the effect of conventional drug taken for the same purpose and also these constituents counteract the effects of other drugs.

As an example, an essential oil constituent which has a hypotensive action will potentiate the effect of co-administered drug, which is used in treatment for hypertension and will counteract the effect of a co-administered drug, which is used in treatment against hypotension.

These types of interactions differ from physiological interactions because the two interacting drugs produce the same or the opposite effects by acting on the same pathway, like on the same receptor or enzyme.

The clinical importance of this type of interaction has not yet been properly evaluated, because there is a lack of the sufficient pharmacological studies for the single fragrance compound which will not help in finding out the possible pharmacodynamic interaction between the essential oil and the drug. [1]

2. The influence of essential oils and single fragrance compounds on other drugs.

2.1. Essential oil interactions with Aspirin® and other non-steroidal analgesics.

Aspirin® or acetyl salicylic acid is an analgesic, antipyretic and anti-inflammatory drug. A non-steroidal anti-inflammatory drug which acts by inhibition of cyclo-oxygenase enzymes to produce effects which also include the known anticoagulant effect. [14, 15]

Interactions have been reported between essential oils whose actions involve the production of prostaglandins and/or thromboxanes, such as essential oil constituents of *Eucalyptus citriodora* in a dose of 72 µg/ml or *Ocimum gratissimum* in a dose of 125 µg/ml [16] and the non-steroidal anti-inflammatory drugs and analgesics. It was also reported that Aspirin and other NSAIDs show a high plasma protein binding which will create a source of interactions with other essential oil constituents which also show a high plasma protein binding, such as β-elemene, bergaptene and methoxalen, causing interactions at the distribution level. [17]

It was discovered that the essential oil of *Cinnamomum osmophloeum* twigs at a concentration of 10 µg/ml as well as trans-cinnamaldehyde, (*L*)-borneol, caryophyllene oxide and other constituents, such as (*L*)-bornyl acetate, β-caryo-phyllene, eugenol, (*E*)-nerolidol, and cinnamyl acetate, have excellent anti-inflammatory character [18] which potentiates the anti-inflammatory activity of Aspirin® and other NSAIDs.

It has been reported that aromatherapy with lavender essential oil, with or without massage, at a dose of 1-4 drops of the drug daily or by boiling 10g of the drug in 2 liters water to be added to the bath [3], can reduce the perception of pain and the need for conventional analgesics like Aspirin® in both adults and children. [4]

Ginkgo containing ginkgolides, which are unique terpene lactones, act as specific platelet-activating factor antagonists and have been associated with spontaneous bleeding which may potentiate the bleeding tendency side effect of Aspirin® [1] as reported in a case of an elderly man already taking Aspirin® at a dose of 325 mg Aspirin® daily after a surgery in the coronary artery, which produced continuous bleeding in the eye which blocked the normal ability to see when he began to use ginkgo at a dose of 40 mg tablet concentrated as 50:1 two times daily. The bleeding stopped after cessation of ginkgo. [19]

It was reported that some essential oils and their constituents inhibit platelet aggregation and blood coagulation such as cold-pressed garlic oil (18 mg/day for four weeks), onion essential oil constituents such as diallyl

sulfide, diallyl disulfide and diallyl trisulfide show dose-dependent inhibition of ADP-induced aggregation of isolated human platelets in-vitro at 5-10 μM.[20]

In a report of the in-vitro anti-platelet activity of some essential oils and their constituents such as the oil of *Ocotea quixos* (a non-commercial oil containing 27.8% cinnamaldehyde and 21.6% methyl cinnamate), *Artemisia dracunculus* (70% estragole) and *Foeniculum vulgare* (75.8% (*E*)-anethole), *Origanum vulgare* (54.4% carvacrol and 14.3% thymol), and *Thymus vulgaris* (8.0% carvacrol and 6.8% thymol) were the most potent inhibitors of arachidonic acid-induced platelet aggregation with IC50 values of 1.9 and 4.7 μg/mL.[21]

The essential oil of *Foeniculum vulgare* and the single fragrance compound (*E*)-anethole both demonstrated significant antithrombotic activity in vivo in mice at oral doses of 30 mg/kg/day for five days. [20]

Inhibition of platelet aggregation has been confirmed for cinnamaldehyde, (E)-anethole, estragole, eugenol, carvacrol and thymol and dose-dependent antiplatelet activity, due to an anti-prostaglandin action, was demonstrated by eugenol and isoeugenol, which were both as potent as indomethacin, while myristicin, elemicin and safrole were 100 to 1,000 times less potent.[20] There are some essential oils, such as essential oils of birch (sweet), garlic, onion, and wintergreen are contraindicated to be used in combination with anticoagulant drugs such as Aspirin®, heparin and warfarin because they are known to inhibit blood coagulation. Other essential oils which must be used cautiously if they are co-administered with other anticoagulant drugs, because they inhibit platelet aggregation based on in-vitro data either for the oil or a major constituent are anise, atractylis, basil, cassia, chervil, cinnamon (bark and leaf), clove (bud, leaf and stem), fennel, lavandin, oregano and thyme oil. [20, 21, 22, 23, 24]

It was also reported that essential oils and their constituents of birch tar, buchu (pulegone ct, at a dose of 18 ng/mL) and pennyroyal could exacerbate glutathione depletion which will increase the risk of the hepatotoxicity caused by N-acetyl-para-benzoquinone imine, a hepatic-

toxic metabolite of acetaminophene “paracetamol”, which is considered as a non-opioid analgesic. [8, 25, 26]

The essential oil from the leaves of *Cryptomeria japonica*, whose major costituents are terpinene-4-ol and elemol, produces a strong inhibitory activity on ulceration induced by HCl/ethanol and water immersion stress at a dose of 455 mg/kg in rat and also shows a strong inhibitory activity on ulceration induced by HCl/Aspirin® and pylorus-ligation at a dose of 228 mg/kg in rat.[27] So that it can be useful to use this essential oil with Aspirin® and other NSAIDs to decrease the gastric ulceration caused by their use.

It was also reported that the daily pharmacological dose of garlic essential oil (8 mg/day) [28] should be avoided by anticoagulated patients, like patients who administered Aspirin®, due to an interference with thromboxane synthesis and decreasing platelet aggregation. [29]

It is also known that the hepatic microsomal enzyme CYP2C9 is involved in the metabolism of Aspirin® [30] and it was reported that some essential oils and single fragrance compounds, such as chamomile (blue) oil (14.3µg/mL), α-bisabolol (46.1 µM), chamazulene (59.3 µM), farnesene (73.1 µM) act as CYP2C9 enzyme inhibitors [8, 31], which inhibit the metabolism of Aspirin® and prolong and potentiate its effects and increase the risk of Aspirin® toxicity and side effects. [8]

2.2. Essential oil interactions with angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers and other drugs acting on cardiovascular system.

Angiotensin-converting enzyme inhibitors are agents which inhibit this converting enzyme in order to inhibit the activation of angiotensin I to angiotensin II, an action which leads to hypotensive effects. They are used in the treatment of hypertension, heart failure, following myocardial infarction and diabetic nephropathy. [32, 33]

Beta-blockers are agents which block beta-adrenergic receptors to prevent the effect of endogenous catecholamines on these receptors producing a hypotensive effect. They are used mainly in the treatment of hypertension, angina pectoris, cardiac dysrhythmias, thyrotoxicosis and anxiety. [34, 35]

It is reported that essential oil of lavender, which contains linalool, linalyl acetate, 1,8-cineole, β-ocimene, terpinen-4-ol and camphor [36], at a dose of one to four oil drops/ day may be placed on a sugar cube[3] acts via an increase in intracellular cAMP. This action on capillary smooth muscles leads to vasodilatation and is responsible for the hypotensive action of lavender [4], which potentiates the hypotensive effects of ACE-inhibitors, beta-blockers, calcium channel blockers and other hypotensive drugs and increases the risk of their side effects creating the need to adjust the dose and the dose-interval of these hypotensive drugs.

The essential oil of *Cymbopogon winterianus*, which consists of citronellal, (+)-limonene, citronellol, geraniol and cubenol [37, 38], is discovered to cause severe decrease in blood pressure combined with an increase in the heart rate and this oil is also reported to have an ability to block calcium channels which will lead to interactions with other calcium channel blockers such as nifedipine, amlodipine, diltiazem and verapamil, and it was also reported that the essential oil of *C. winterianus* at the dose of 20 mg/kg induces transient brady-arrhythmias. Furthermore, it leads to a vasodilatation in rat mesenteric artery, which appeared to be mainly mediated by an inhibition of the Ca^{+2} influx. [39]

Thus interactions with beta-blockers and calcium channel blockers are possibly due to the different and opposite effects of these essential oils on the heart rate at different doses.

Interactions have been reported between nicardipine, a calcium channel blocker, and some essential oils and their constituents. Nicardipine is metabolized by CYP3A2 [40] and some essential oils and their constituents, such as farnesol (1 g/kg/day for 4 weeks), 1,8-cineole (800 mg/kg/day for 3 days), hinoki wood oil (300 mg/kg/day for 5 days) , hibawood oil (300 mg/kg/day for 5 days), cadinene (300 mg/kg/day for 5 days), induce

CYP3A2, which leads to an induction of nicardipine metabolism, while other essential oil constituents, such as oxypeucedanin (1.8 μM), isopimpinellin (1.9 μM), bergapten (3.1 μM), psoralen (5.1 μM), bergamottin (22 μM), inhibit CYP3A2 , thus inhibiting the metabolism of nicardipine.[8]

The inhaled mixture of the essential oils of lavender, ylang-ylang, marjoram and neroli when they are blended at a 20 : 15 : 10 : 2 ratio was reported to cause significant decrease in ambulatory daytime blood pressure with no difference on night time blood pressure and to cause a decrease in salivary colistrol concentrations [41]. This action which interferes with antihypertensive drugs at specific part of the day (day time) with no effect on the other part of the day (night time), which creates therapeutic disturbance and a need to adjust the dose or the time interval of the antihypertensive drug during the same day.

Essential oil of black pepper, which contains mainly camphene, limonene, α-pinene, β-pinene, geraniole, 1,8-cineole, linalool, borneol, terpinen-4-ol [42], is reported to have an inhibitory effect on angiotensin-I converting enzyme activity in a concentration of 50 mL/L[43], an action which is a direct pharmacodynamic synergism with all ACEIs and a physiological synergism with all other antihypertensive drugs affecting their potency and efficacy. [43]

Many essential oils like essential oils of araucaria, pungent basil, blue cypress, emerald cypress, and jade cypress lower blood pressure [44], which create interactions with anti-hypertensive drugs.

Hepatic microsomal cytochrome P-450 enzymes, isozymes like CYP1A2 and CYP2D6, are involved in the metabolism of some beta-blockers like propranolol [45], so that the essential oils or their constituents which induce CYP1A2, like myristicin (96 mg/kg), eugenol (1 g/kg/day for 10 days), rosemary oil (5 g/kg for 2 weeks), diallyl sulfide (0.2% for 13 days), diallyl disulfide (0.2% for 13 days), also induce the metabolism of propranolol decreasing its effects. Other essential oils and single fragrance compounds which inhibit CYP1A2 like chamomile (blue) oil (1.59 μg/mL),

(*E*)-spiroether (0.47 μM), (*Z*)-spiroether (2.01 μM), chamazulene (4.41 μM) and safrole (5.7 μM) and also essential oils which inhibit CYP2D6 like cypress (blue) oil and sandalwood oil inhibit the metabolism of propranolol leading to an increase of its effects. [8, 31, 46, 47]

A study conducted at Yale University proved that the aromas of spiced apple have a vasodepressor effect and can decrease the stress, [48] which create a physiological interaction with ACEIs. Lemon aroma caused an increase in heart rate, whereas rose aroma leads to a decrease in the heart rate [48], an action which interacts with the effects of beta-blockers. Also sweet orange aroma caused significant increase in heart rate after inhalation. [48]

2.3. Essential oil interactions with antidepressants, anticonvulsants, anti-anxiety drugs and other drugs acting on the central nervous system.

There are a lot of drugs that act on the central nervous system. Two major categories of these drugs are anti-depressants and benzodiazepines. Anti-depressants which may be selective serotonin re-uptake inhibitors (SSRIs), tri-cyclic antidepressants (TCAs), mono-amine re-uptake inhibitors, mono-amine receptor blockers, and mono-amine-oxidase enzyme inhibitors (MAOIs). These drugs are used mainly in treatment of depression and they may be also used in the treatment of obsessive compulsive disorder, panic disorder, bulimia nervosa and neuropathic pain. [49, 50]

Benzodiazepines are agents which potentiate the GABA-effect on its receptors producing an anxiolytic effect on small doses and a sedative hypnotic effect in high doses. These drugs used mainly in the treatment of anxiety, insomnia and can be used also in the treatment of some types of epilepsy. [51, 52]

The exposure to the essential oil of orange (*Citrus sinensis*), which consists mainly of limonene, citral, citronellal, sinesal, n-nonanal, n-decanal, linalyl

acetate and geranyl acetate [53], could reduce anxiety and improve the mood at a dose of 0.25 ml corresponding to five drops twice daily [54], which will lead to a potentiation of the effects of ant-depression and anti-anxiety drugs.

The essential oil of *Artemisia dracunculus L.*, which contains chavicol methyl ether, ocimene, myrcene, α-pinene, camphene, limonene, and linalool [55], has the ability to block both clonic seizures induced by PTZ at an ED50 of 0.26 ml/kg and tonic seizers induced by MES at an ED50 of 0.84 ml/kg. This leads to an interaction and potentiation of other anti-epileptic drugs like phenytoin, valporate, felbamate, and lamotrigine, thus inhibiting the voltage dependent Na^{+} channels and exerting an anti-epileptic effect against MES-induced tonic seizers or interactions with drugs, like ethosuximide which reduces T-type Ca^{+2}-currents and shows the same activity against PTZ-induced clonic seizers or potentiates the anti-convulsing effect of benzodiazepines. [56]

Also eugenol, the major component of clove oil, was reported to have the same anticonvulsant activity and the same synergism with anti-epileptic drugs. [56]

It was reported that the brain waves in the EEG of subjects exposed to four types of aroma, i.e., eucalyptus, lavender, spiced apple, and an odorless solvent as a control, were associated with different α-wave and theta-wave distributions with these previously mentioned aroma. Spiced apple odor was the most effective in stimulating α-wave activity which elicits a relaxing effect of the odor. [48] Other studies used changes of the EEG as indices for the measurement of the effect of aromas. The aromas of lavender, cineole, jasmine, α-pinene and sandalwood were examined. [48, 57, 58] An elevation in the value of α-waves, which means relaxation, was demonstrated after the application of lavender, cineole, α-pinene and sandalwood. While an elevation in the value of the β-waves, which means stimulation, was demonstrated after the application of jasmine aroma. [48, 57, 58] All these relaxing and stimulating effects on brain waves will interact

positively or negatively with other anti-epileptic drugs and benzodiazepines.

The essential oil from *Citrus aurantium* is discovered to have anxiolytic and sedative effects at a dose of 0.5-1 g/kg in adult male mice and can be used in treatment of insomnia, anxiety and some types of epilepsy, which creates an enhancement of the effect of the anti-epileptic drugs and benzodiazepines. [59]

A study was carried out to find out the essential oils producing an anti-conflict effect according to specific test called Geller-type conflict test. It was found that diazepam, a benzodiazepine, elevated the response rate within the alarm period, which means that it exerts an anti-conflict effect, but the 5-HT1A partial agonist, buspirone, did not. Frankincense oil at a dose of 1600 mg/kg in mice decreased the response rate within the safe-period producing an opposing effect to diazepam. While, on the other side, lavender oil produced the same action as diazepam, which will lead to potentiating diazepam effect. [60] Also the essential oil of *Corton zehntneri*, a popular plant in Brazil, used to treat nervous disturbance, is discovered to have an anti-anxiety and anti-depressant effect at a dose of 10 µl/kg in rat. [61]

In general, it was shown that a lot of essential oils used in aromatherapy, exhibit an anti-anxiety effect and sedative effect even with high stressed patients like patients in intensive care units. [62] These actions have direct effects on other anxiolytic-sedative hypnotic drugs.

Some essential oils, if taken orally, can cause convulsions in vulnerable persons. People with epilepsy who are taking suppressant medications may be lower vulnerable that non-epileptics. Some essential oils and their constituents may lead to a therapeutic failure of other anti-epileptic drugs. They are known as convulsing compounds, such as thujone (0.1 mg/kg), pinocamphone (0.1 mg/kg), β-pulegone (0.5 mg/kg), camphor (2 mg/kg), and methyl salicylate (5 mg/kg). [63]

There are also other essential oils and fragrance compounds, which show sedative effects like anise oil (50 mg/kg in mouse), basil oil (50 mg/kg in mouse), fennel oil (50 mg/kg in mouse), lavender oil (ED50 248 mg/kg in mouse), citronellal (100-400 mg/kg in mouse), marjoram oil (50 mg/kg in mouse), (*E*)-anethole (300-400 mg/kg in rat), 1,8-cineole (100-400 mg/kg in mouse), citral (100-200 mg/kg in mouse), linalool (200 mg/kg in mouse), linalyl acetate (100 mg/kg in mouse), myristicin (20 mg/kg in mouse), cis-jasmin, menthol and borneol. [63, 64, 65, 66] They all have a CNS-depressant effect and some of them, namely anise oil, lavandin oil, bergamot oils, citronellal, eugenol, linalool, thymol [63], borneol [64], cis-jasmin [65] and menthol [66] potentiate the GABAA receptor-mediated responses which reflect direct potentiating of the effect of benzodiazepines.[63]

Also the essential oils of basil, cinnamon, clove bud, leaf and stem, parsnip and pimento leaf have shown drug interactions with MAOIs, a class of anti-depressants. Constituents of these oils (myristicin as an example at a Ki value of 26 μM), inhibit MAO enzymes, exerting a direct pharmacodynamic potentiating of the effect of MAOIs and thus affect blood pressure and cause tremors and confusion, especially if they are co-administered with MAOIs. [8, 67, 68] They also show interactions with pethidine, an opioid analgesic, because of potentiating the serotonin causing agitation, delirium, headache and convulsions. [8, 69]

These previously mentioned essential oils and their constituents show interactions with SSRIs because they potentiate CNS serotonin levels which may cause the serotonin syndrome, a syndrome due to accumulation of serotonin or potentiating serotonin effects, its symptoms are increased heart rate, shivering, sweating, tremors, hyperthermia and high blood pressure. [8, 70] Also essential oils that induce or inhibit the hepatic microsomal cytochrome P-450 enzymes lead to a direct interaction with the effect on CNS-acting drugs due to their direct induction or inhibition of the metabolism process. [8]

3. The effect of essential oils on smelling and tasting ability.

3.1. Physiology of normal smelling and tasting senses:

3.1.1. Olfactory sensation:

Humans can distinguish 2000 to 4000 (even up to 10.000) different odors. Olfactory mucosa acts as the receptor organ for the smelling process. The olfactory receptor cells, which are between 10 to 20 million cells, are found to be surrounded with a thin layer of mucus, where any molecule to be smelled must be dissolved in. Neural connections, afferent and efferent, found to be between the receptor cells and a specific part of the brain called olfactory bulb. [71]

Olfaction sensory specifity: Olfactory sensor cells recognize a very specific structural feature of the odorant molecules. The cloned receptor 17 of the rat, for example, reacts with the aldehyde n-octanal but not to octanol or octanoic acid. One sensor recognizes if the compound is ortho, meta or para-substituted, while another detects the length of the substituent regardless of where this is located on the ring. [72]

The olfactory system is connected directly to the fore brain. It can also show interaction and distributions to other senses like taste and hearing, [73, 74] and the term "smound" express the interaction between olfaction "smell" and hearing "sound". [75, 76]

3.1.2. Gustatory sensation:

Taste buds, which are specific G-protein coupled receptors, are responsible for tasting process, they are found to be at the surface of the tongue and the substances to be tasted can enter to the taste bud through taste pore. [78, 79]

Taste buds are responsible for the sensation of the major five modalities of taste, which are bitter, sour, sweet, salty and umami. [80] Also taste buds

can recognize and taste the fatty substances. [81] It was also discovered that some receptors for bitter taste founded to be in lung tissues which can cause relaxation to the respiratory tract upon exposure to a bitter substance which can play a role in treatment of pulmonary diseases like COPD and asthma. [82] The sense of taste has a protective function as spoiled or bitter tasting food is often poisonous. [82]

3.2. Types of different smelling and tasting disorders:

3.2.1. Smell disorders:

Smell acuity reflects the ability to detect and recognize vapors. There are a vast variety of vapors to which the olfactory system can respond. Smell acuity can best be evaluated clinically by standard techniques inclusive the measurement of thresholds, magnitude estimation and hedonics.[83] Abnormalities in smell acuity have been categorized clinically, these categories are useful to define treatment modality and predict therapeutic efficacy.

Hyposmia: Is a general term describing decreased smell acuity and is the most common smell change which occurs following drug treatment.

Hyposmia composed of three types:

Type I hyposmia: Is the inability to recognize vapors of any concentration at the primary olfactory area.

Type II hyposmia: Is a quantitative decrease in ability to detect and/or recognize vapours. This defect is the most common form of hyposomia observed following drug treatment.

Type III hyposmia: Reflects a decrease in magnitude estimation, with maintenance of normal detection and recognition thresholds. [83, 84]

Anosmia: Is the inability to detect or recognize vapors either at the primary or accessory areas of olfaction. This type of loss is relatively rare. [83]

Dysosmia: Is the general term describing distortion of smell function. [83, 85, 86] It is subdivided into two major types: Aliosmia and phantosmia. [83, 84] Aliosmia can be subdivided into specific categories which include: (i) Cacosmia, the unpleasant, decayed smell associated with vapors of normally pleasant smells; (ii) torquosmia, an unpleasant chemical burned smell associated with normal pleasant vapors; (iii) a mixed smell combining both cacosmia and torquosmia; and (iv) parosmia, a distorted , but not necessary an unpleasant, smell sensation.[83,84]

Phantosmia is the presence of a smell in the nasal cavity without the presence of external stimuli and is commonly referred to an olfactory hallucination. [83, 85]

Treatment for olfactory problems is based on the determination of a diagnosis. Any organ-based etiology should be treated by the appropriate specialist, also medical and surgical correction of nasal disorders and the use of nasal steroids show some success. The presence of a systemic disease, medications, environmental toxins and neurological disorders should be concerned during treatment. [86]

3.2.2. Taste disorders:

Taste acuity reflects the ability to detect and recognize tastants, commonly exemplified by salt, sweat, sour, bitter and umami. [83] Abnormalities in taste acuity have been clinically categorized by degree of impairment of detection, recognition and/or magnitude estimation. [87]

Hypogeusia: Decreased ability to detect or recognize any stimuli which are subdivided into:

Type I hypogeusia: Is the inability to recognize any tastant. [83, 84]

Type II hypogeusia: Is a quantitative decrease in the ability to detect and/or recognize tastants. This defect is the most common of hypogeusia observed following drug treatment. [83, 84]

Type III hypogeusia: Reflects decrease in magnitude estimation with maintenance of normal taste detection and recognition thresholds. [84]

Ageusia: Is the total inability to detect or recognize tastants in oral cavity. [84]

Dysgeusia: Is the general term which describes distortion of taste function. [84, 88] It is subdivided into two major types: Aligeusia, the unpleasant taste of foods and drinks usually pleasant [83] and phantogeusia, an unpleasant taste produced endogenously not associated with the presence of foods and drinks in oral cavity. This is commonly labeled as a gustatory hallucination. [83, 84, 88, 89] Aligeusia can be subdivided into several specific categories of distortion: (i) Cocageusia, is the unpleasant, rotten, decayed taste associated with the intake of food or drink normally considered as pleasant; (ii) torquogeusia, a chemical, salty, bitter, metallic taste associated with the oral introduction of food or drink; (iii) a mixed taste, combination between cocageusia and torquogeusia; (iv) parageusia, an unusual, but not necessary an unpleasant taste, associated with oral intake of foods and drinks.[83,84,88]

Phantogeusia is taste extinction in the rapid and complete loss of taste following normal appreciation of the initial taste of food or drink. It can also be subdivided into cocageusia, torquogeusia or mixed components. [87]

The success of treatment for gustatory problems depends upon the etiology. An orofacial source of a taste problem can usually be treated by dental professionals. Another cause for a taste problem may be psychological or behavioral which can be handled by a specialist in stress management. On the other side, taste problems may appear as a side effect after administration of a specific drug which creates huge stress on the patient. Moreover, patients need to be advised on nutrition and appetite issues to prevent nutritional deficiencies. The effect of zinc supplementation for chemosensory deficiencies is controversial but probably not harmful. [90] Finally, supplementation of food with taste and smell, like herbs and spices or with other stimulants, such as crunchy, smooth or fizzy improves palatability and flavor as well as the desirability of eating. [90]

3.3. Sensory effects of essential oils.

Taste-aroma interactions:

The sensation of flavor is elicited by a combination of nasal and oral stimulation. A lot of aromatic substances, such as lemons, apples and oranges can be identified only depending on their aroma, but enhancement to the flavor occur upon ingestion by sweetness or sourness, and many odor or taste compounds also elicit pungency, cooling or heat which also affects the tasting ability. [91]

Odor and taste interactions may result from physical, physiological, cognitive or psychological effects. [89] The minty, bitter and cooling, sensations of menthol can show odor and taste interactions in form of competitive antagonism at the receptors level. [91]

Many psychological factors influence odor and taste perception and their interactions. Specific combinations of tastants and odorants influence the definition and the discrimination of individual sensations, which affect their integration or separate perception. [91]

An orally ingested substance while the nose is closed will block the olfaction process because it will not allow the aromas to reach the olfactory receptors. An experiment was done on a specific ester called "ethyl butyrate" it was reported that when this ester is sipped while the nose is blocked, 80% of the taste disappeared. This gives us an example on the effect of aroma on tasting ability. [91]

After the introduction of a mixed solution between citral and salt or sucrose, it was found that the odor intensity of citral is not affected by any change or increase in the concentration of salt or sucrose, while a marked elevation in the taste intensity of both salt and sucrose is reported after increasing citral concentrations, which gives us an idea about the effect of odors on taste intensity. [91]

It was reported that the peanut butter aroma does not have the ability to increase the taste intensity of sweet sensation, while the aroma of

strawberry have this ability, which can be used as an evidence that the enhancement of taste intensity is due to some types of interactions between taste and aroma not due to the different composition of the aromas. [91]

Cinnamon oil aroma exhibits a pleasing warm spicy after taste which may interfere with the taste of other substances. [92]

Odorants effect on olfactory system:

It was proved that different aromas and volatiles can compete with each other at the receptor level as agonist and antagonists. [93]

It was reported that stored eugenol, an essential oil constituent naturally detected in clove oil and mace oil, has an antagonistic effect on an olfactory receptor "mOR-EG", which leads to direct olfactory disturbances. This action is done by a derivative to isoeugenol produced during the storage process as a result of oxidation reactions and act as a strong competitive blocker to this olfactory receptor. [93]

The medical and toxicological literature is replete with reports of smell loss or distortion in humans after acute or chronic exposure to a number of volatiles. It was reported that smell dysfunction occurs after exposure to some volatiles like menthol and furfural [94], the later is considered as oily liquid with the odor of almonds found in corncobs and wheat bran. [95]

Saturation, adaption and cross-adaption of odorants:

Adaption or cross-adaption may occur during continuous exposure to specific odorants. A study reported that self adaption occurs to sweaty-smelling 3-methyl-2-hexenoic acid as the magnitude estimates were greatly reduced relative to initial estimates. Significant cross-adaption occurs between the ethyl esters and 3-methyl-2-hexenoic acid was noted only for EE 3-M-2-H, and that means that a larger amount of odorants is required to produce sensory effects due to adaption or cross-adaption between odorants sharing common sensory channels due to the partial overlap. The exact mechanism is unknown but it may be due to receptor down regulation or receptor competition. [96]

4. Conclusion.

Due to the ascending importance of essential oils and their constituents, it is very important to study and summarize the possible interactions between essential oils and other prescribed drugs, which leads to potentiating of drug effects and increases the risk and the possibility of toxicity and side effects, and may lead to therapeutic failure of the drug, especially with widely prescribed drugs which are used in treatment of chronic diseases like: Aspirin®, analgesics, angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, anti-depressants, anti-epileptics and benzodiazepines.

A lot of interactions between essential oil constituents and these drugs were reported either physiologically or pharmacologically. These interactions must be well clarified and illustrated, not only to the physician, but also to the patients. They can purchase herbal drugs and essential oils without prescriptions and they use these natural products every day in their normal life, so they also should inform the physician which herbal products they intake, which can show serious interactions with the prescribed drugs.

Also interactions between essential oils and the sensory system were reported either by interference with tasting ability, affecting olfactory function or adaption and saturation of the sensory receptors.

The effects of essential oils on olfactory and gustatory functions must be illustrated and studied, because they affect the patient's acceptance and interfere with the normal life style of the patients, which may interfere with patient's ability to continue administration of the herbal drug or the co-administered prescribed drug.

In this overview, references on these possible interactions and sensory effects have been summarized.

5. References.

1. Williamson Elizabeth M. (2003) Drug interactions between herbal and prescription medicines. Drug safety. 26 (15): 1075-1092.

2. Georg K.J.,Spilker Th. (2003) Effect of peppermint oil and caraway oil on gastrointestinal motility in healthy volunteers ; a pharmacodynamic study using simultaneous determination of gastric and gall-bladder and orocaecal transit time. Aliment Pharmacol. Ther. 17: 445-451.

3. English Lavender in: PDR for herbal drugs. (2000) Medical economics company, Inc. at Montvale. Page: 278.

4.Cavanagh H.M.A., and Wilkinson J.M. (2002) Biological activities of lavender essential oil. Phytotherapy research. 16: 301-308.

5. Damask Rose in: PDR for herbal drugs. (2000) Medical economics company, Inc. at Montvale. Page: 644.

6.Sadraei H., Asghari G., Emami S. (2013) Inhibitory effect of *Rosa damascena* Mill flower essential oil, geraniol and citronellol on rat ileum contraction. Res. Pharm. Sci. 8 (1): 17-23.

7. Michaelle Clark A., Richard Finkel, Jose Rey A., Karen Whalen, Richard Harvey A. (2012) Lippincott's illustrated reviews : Pharmacology, fifth edition, Lippincott William and Wilkins , Florida, China. Page: 8.

8. Tisserand Robert, Young Rodney, and Williamson Elizabeth M. (2014) Essential oil safety: A guide for health care professionals: Chapter 4: Kinetics and dosing. Elsevier Publisher. Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, and Toronto. Page: 40-66.

9. Florence A.T., Attwood D. (1998) Physiochemical principle of pharmacy.Third edition, Pharmaceutical press, London.

10. Wang K., Su C.Y. (2000) Pharmacokinetics and disposition of β-elemene in rats. Yao Xue Xue Bao. 35: 725-728.

11. Kanakis C.D., Tarantilis P.A., Tajmir-Riahi H.A., et al. (2007) Corcetin, dimethylcorcetin and safranal bind human serum albumin in: Stability and antioxidative properties. J. Agric. Food. Chem. 55: 970-977.

12. Hu L., Chen D.Y. (2009) Application of headspace solid phase micro extraction for non-covalent interaction of borneol with human serum albumin. Acta.Pharmacol. Sin. 30: 1573-1576.

13. Lupidi G., Scire A., Camaioni E., et al., (2010) Thymoquinone, a potential therapeutic agent of *Nigella sativa* binds to site I of human serum albumin. Phytomedicine. 17: 714-720.

14. Rang H.P., Dale M.M., Ritter J.M., Flower R.J. and Henderson G. (2012) Rang and Dale's Pharmacology, seventh edition; Elsevier Churchill Livingstone Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, Toronto. Page: 318-335.

15. Michaelle Clark A., Richard Finkel, Jose Rey A., Karen Whalen, Richard Harvey A. (2012) Lippincott's illustrated reviews : Pharmacology, fifth edition, Lippincott William and Wilkins , Florida, China. Page: 525-548.

16. Sahouo Bedi G., Tonzibo Z.F., Chopard C., Mahy J.P. and Guessan T.N. (2003) Anti-inflammatory and analgesic activities: chemical constituents of essential oils of *Ocimum gratissimum*, *Eucalyptus citriodora* and *Cymbopogon giganteus* inhibited lipoxygenase L-1 and cyclooxygenase of PGHS. Bull. Chem. Soc. Ethiop. 17 (2): 191-197.

17. Abebe W. (2002) Herbal medication: Potential for adverse interactions with analgesic drugs. Journal of clinical pharmacy and therapeutics. 27: 391-401.

18. Yu-Tang Tung, Meng-Thong Chua, Sheng-Yung Wang, Shang-Tzen Chang. (2008) Anti-inflammatory activities of essential oil and its constituents from indigenous cinnamon (*Cinnamomum osmophloeum*) twigs. Bioresource technology. 99: 3908-3913.

19. Rosenblatt M., Mindel J. (1997) Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract. N. Engl. J. Med. 338: 1108.

20. Tisserand Robert, Young Rodney, and Williamson Elizabeth M. (2014) Essential oil safety: A guide for health care professionals: Chapter 7: The cardiovascular system. Elsevier Publisher. Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, and Toronto. Page: 111-118.

21. Tognolini M., Barocelli E., Ballabeni V., et al., (2006) Comparative screening of plant essential oils: Phenylpropanoid moiety as basic core for anti-platelet activity. Life Sci. 78: 1419-1432.

22. Hsu H.C., Yang W.C., Tsai W.J., et al. (2006) α-bulnesene, a novel PAF receptor antagonist isolated from *Pogostemon cablin*. Biochem. Biophys. Res. Community. 345: 1033-1038.

23. Huang J., Wang S., Luo X., et al. (2007) Cinnamaldehyde reduction of platelet aggregation and thrombosis in rodents. Tromb. Res. 119: 337-342.

24. Tsai Y.C., Hsu H.C., Yang W.C., et al. (2007) α-bulnesene, a PAF inhibitor isolated from the essential oil of *Pogostemon cablin*. Fitoterapia. 78: 7-11.

25. Swales N.J., Caldwell J. (1992) Cytotoxixity and depletion of glutathione (GSH) by cinnamaldehyde in rat hepatocyte. Hum. Exp. Toxicol. 10: 488-489.

26. Choi J., Lee K.T., Ka H., et al. (2001) Constituents of the essential oils of the *Cinnamomum cassia* stems bark and the biological properties. Archives of pharmaceutical research. 24: 418-423.

27. Takayuki M., Chika H., Toru K., Hideyo S., Haruo S., Tadashi S., Rihei T., Hideko T., Toshiyuki M., and Takeshi A. (2000) Isolation of the anti-ulcer compound in essential oil from the leaves of *Cryptomeria japonica*. Biol. Pharm. Bull. 23 (5): 595-598.

28. Garlic in: PDR for herbal drugs. (2000) Medical economics company, Inc. at Montvale. Page: 329.

29. Boullata Joseph I. Nace Angela M. (2000) Safety Issues with herbal medicine. Pharmacotherapy. 20 (3): 257-269.

30. Nami S.P., Seung-Hyun K., Young H.N., Young-Min Y., and Hae-Sim P. (2011) Polymorphisms of aspirin-metabolizing enzymes CYP2C9, NAT2 and UGT1A6 in aspirin-intolerant urticaria. Allergy Asthma Immunol. Res. 3 (4): 273-276.

31. Ganzera M., Schneider P., Stuppner H. (2006) Inhibitory effects of the essential oils of chamomile (*Matricaria reculita L.*) and its major constituents on human cytochrome P-45o enzymes. Life Sci. 78: 856-861.

32. Rang H.P., Dale M.M., Ritter J.M., Flower R.J. and Henderson G. (2012) Rang and Dale's Pharmacology, seventh edition; Elsevier Churchill Livingstone Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, Toronto. Page: 270-276.

33. Michaelle Clark A., Richard Finkel, Jose Rey A., Karen Whalen, Richard Harvey A. (2012) Lippincott's illustrated reviews : Pharmacology, fifth edition, Lippincott William and Wilkins , Florida, China. Page: 198,199.

34. Rang H.P., Dale M.M., Ritter J.M., Flower R.J. and Henderson G. (2012) Rang and Dale's Pharmacology, seventh edition; Elsevier Churchill Livingstone Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, Toronto. Page: 174-189.

35. Michaelle Clark A., Richard Finkel, Jose Rey A., Karen Whalen, Richard Harvey A. (2012) Lippincott's illustrated reviews : Pharmacology, fifth edition, Lippincott William and Wilkins , Florida, China. Page: 90-93.

36. Robert Shellie, Luigi Mondello, Philip Marriott, and Giovanni Dugo. (2002) Characterization of lavender essential oil by using gas-chromatography-mass spectrometry with correlation of linear retention indices and comparison with comprehensive two dimensional gas-chromatography. Journal of Chromatography. Volume 970, Issues 1-2, Pages: 225-234.

37. Eduardo C., and Vargas Rubem M.F. (2006) Experiments and modeling of the *Cymbopogon winterianus*: Essential oil extraction by steam distillation. J. Mex. Chem. Soc. 50 (3): 126-129.

38. Simic A., Rancic A., Sokovic M.D., Ristic M., Grujic-Jovanovic S., Vukojevic J., and Marin P.P. (2008) Essential oil composition of *Cymbopogon winterianus* and *Carum carvi* and their antimicrobial activities. Pharmaceutical Biology. Volume 46, No. 6, Pages: 437-441.

39. Jgor A., Italo M., Jose P., Arie B., Angelo A., Lucindo Q. Junior, and Marcio S. (2010) Cardiovascular effects induced by *Cymbopogon winterianus* essential oil in rats: Involvement of calcium channels and vagal pathway. Journal of pharmacy and pharmacology. 62: 215-221.

40. Shinozukak K., Umegaki K., Kubotay Y., et al. (2002) Feeding of *Ginkgo biloba* extract (GBE) enhance gene expression of hepatic cytochrome P-450 and attenuate the hypotensive effects of nicardipine in rats. Life. Sci. 70 (23): 2783-2792.

41. In-Hee K., Chan K., Kayeon S., Myung-Haeng H., Heon M.L., and Myeong S.L. (2012) Essential oil inhalation effect on blood pressure and salivary colistrol levels in pre-hypertensive and hypertensive subjects. Evidence-based complementary and alternative medicine. Article I.D. 984203, 9 Pages.

42. Jirovetz L., Buchbauer G., Beniot Ngassoum M., and Geissler M. (2002) Aroma compound analysis of *Piper nigrum* and *Piper guineese* essential oils from Cameroon using solid-phase micro-extraction gas chromatography, solid-phase micro-extraction gas-chromatography mass-spectrometry and olfactometry. Journal of chromatography A. 976: 265-275.

43. Ganiyu O., Ayokunle O.A., Oluwatoyin V.O., and Ifeoluwa A.A. (2013) Anti-oxidative properties and inhibition of key enzymes relevant to type-2 diabetes and hypertension by essential oils from black pepper. Advances in pharmacological sciences. Article ID 926047, 6 Pages.

44. Tisserand Robert, Young Rodney, and Williamson Elizabeth M. (2014) Essential oil safety: A guide for health care professionals. Elsevier Publisher. Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, and Toronto. Page: 658.

45. Masubuchi Y., Hosokawa S., Horie T., Suzuki T., Ohmori S., Kitada M., and Narimatsu S. (1994) Cytochrome P-450 isozymes involved in propranolol metabolism in human liver microsomes. The role of CYP2D6 a ring-hydroxylase and CYP1A2 as N-desisopropylase. Drug metabolism and disposition. Vol. 22, No. 6, Pages: 909-915.

46. Debersac P., Heydel J.M., Amiot M.J. et al. (2001) Induction of cytochrome P-450 and/or oxidation enzymes by various extract of rosemary: description of specific patterns. Food Chem. Toxicology. 39: 907-918.

47. Ueng Y.F, Hsich C.H., Don M.J., et al. (2005) Inhibition of human cytochrome P-450 enzymes by the natural hepatotoxin safrole. Food Chem. Toxicology. 43: 707-712.

48. Hongratanaworakit T. (2004) Physiological effects in aromatherapy. Songklanakarin J. Sci. Technol. 26 (1): 117-125.

49. Rang H.P., Dale M.M., Ritter J.M., Flower R.J. and Henderson G. (2012) Rang and Dale's Pharmacology, seventh edition; Elsevier Churchill Livingstone Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, Toronto. Page: 564-583.

50. Michaelle Clark A., Richard Finkel, Jose Rey A., Karen Whalen, Richard Harvey A. (2012) Lippincott's illustrated reviews : Pharmacology, fifth edition, Lippincott William and Wilkins , Florida, China. Page: 151-159.

51. Rang H.P., Dale M.M., Ritter J.M., Flower R.J. and Henderson G. (2012) Rang and Dale's Pharmacology, seventh edition; Elsevier Churchill Livingstone Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, Toronto. Page: 533-534.

52. Michaelle Clark A., Richard Finkel, Jose Rey A., Karen Whalen, Richard Harvey A. (2012) Lippincott's illustrated reviews : Pharmacology, fifth edition, Lippincott William and Wilkins , Florida, China. Page: 112-114.

53. Sweet orange in: PDR for herbal drugs. (2000) Medical economics company, Inc. at Montvale. Page: 748.

54. Lehrner J., Christine E., Walla P., and Pötsch G. (2000) Ambient odor of orange in a dental office reduce anxiety and improve mood in female patients. Physiology and Behavior. 71: 83-86.

55. *Artemisia dracunculus* in: PDR for herbal drugs. (2000) Medical economics company, Inc. at Montvale. Page: 320.

56. Mohammad S., Leila N., and Mohammad K. (2004) Anticonvulsant activity of chemical composition of *Artemisia dracunculus L.* essential oil . Journal of Ethnopharmacology. 94: 283-287.

57. Manley Charles H. (1993) Psycho physiological effect of odor. Critical reviews in food science and nutrition. 33 (1): 57-62.

58. Ryoko M., Tamiko M., Yoshiaki K., Yoshifumi M., Koichi I., Hajime H., and Testsu K. (2000) Effects of inhalation of essential oils on EEG activity and sensory evaluation. Journal of physiological anthropology and applied human sciences. 19 (1): 35-42.

59. Maria I.R., and Mirtes C. (2002) Anxiolytic and sedative effects of extracts and essential oil from *Citrus aurantium*. Biol. Pharm. Bull. 25 (12): 1629-1633.

60. Toyoshi Umezu. (2008) Behavioral effects of plant-derived essential oils in the Geller-type conflict test in mice. Jpn. J. Pharmacol. 83: 150-153.

61. Lazarini C.A., Uema A.H., Brandao G.M.S., Guimaraes A.P.C., and Bernardi M.M. (2000) *Corton zehntneri* essential oils: effect on behavioral models related to depression and anxiety. Phytomedicine. 7 (6): 477-481.

62. Mi-Yeon Cho, Eun Sil Min, Myung-Haeng Hur, and Myeong Soo Lee. (2013) Effects of aromatherapy on the anxiety, vital signs, and sleep quality of precutaneous coronary intervention patients in intensive care units. Evidence-based complementary and alternative medicine. Article ID. 381381, 6 Pages

63. Tisserand Robert, Young Rodney, and Williamson Elizabeth M. (2014) Essential oil safety: A guide for health care professionals: Chapter 10: The nervous system. Elsevier Publisher. Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, and Toronto. Page: 131-146.

64. Granger R.E., Campell E.L., and Johnston G.A. (2005) (+) and (-) Borneol: efficacious positive modulators of GABA actions at human recombinant alpha-1 beta-2 gamma-2l GABAA receptors. Biochem. Pharmacol. 69: 1101-1111.

65. Hossain S.J., Aoshima H., Koda H., et al. (2004) Fragrances in oolong tea that enhance the response of GABA receptors. Biosci. Biotechnol. Biochem. 68: 1842-1848.

66. Hall A.C., Turcotte C.M., Betts B.A., et al. (2004) Modulation of human GABAA and glycine receptors currents by menthol and related mono-terpenoids. Eur. J. Pharmacol. 506: 9-16.

67. Huong D.T.L., Jo S.Y., Lee M.K., et al. (2000) Monoamine oxidase inhibitors from cinnamomi cortex. Natural product sciences. 6: 16-19.

68. Tao G., Irie Y., Li D.J., et al. (2005) Eugenol and its structural analogs inhibit monoamine oxidase A and exhibit anti-depressant like activity. Bioorg. Med. Chem. 13: 4777-4778.

69. Reynolds, J.E.F. (Ed.). (1993) Martindale: The extra pharmacopeia. The pharmaceutical press, London.

70. Izumi T., Iwamoto N., Kitaichi Y., et al. (2006) Effects of co-administration of a selective serotonin reuptake inhibitor and monoamine oxidase inhibitor on 5-HT related behavior in rats. Eur. J. Pharmacol. 532: 258-264.

71. Rodney Rhodase, George A.Tanner. (2003) Medical physiology. Lippincott Williams and Wilkins. Part 2 chapter 4, page: 87, 88.

72. Agamemnon Despopulos, Stefan Silbernagl. (2003) Color Atlas of physiology, 5th edition, chapter 12, and page: 340.

73. Masaoka Y, Satoh H, Akai L, and Homma I. (2010) Expiration: the moment we experience retronasal olfaction in flavor. Neurosci Lett. 473(2): 92-96.

74. Doty Richard L. (2001) Annual review of psychology. 52(1): 423-452.

75. Wesson D.W., Wilson D.A. (2010) Smelling-sounds: olfactory-auditory convergence in the olfactory tubercle. J. Neurosci. 30(8): 1021-3013.

76. Peeples, Lynne. "Making scent of sounds". Scientific American. February 2010.

77. Wikipedia, The free encyclopedia. Available:

http://en.wikipedia.org/wiki/olfactory_sense. (19.Mai 2014).

78. Agamemnon Despopulos, Stefan Silbernagl. (2003) Color Atlas of physiology, 5th edition, chapter 12, and page: 338.

79. Bachman, A.A. and Beachamp G.K.. (2007) Taste receptor genes. Annu.Rev.Nutr. 27:389-414.

80. Rodney Rhodase, George A.Tanner. (2003) Medical physiology. Lippincott Williams and Wilkins. Part 2 chapter 4, page: 87, 85.

81. Laugerette, Fabienne, Patricia Passillly, Bruno Patris, Isabelle Niot, Maria Febbraio, Jean-Pierre Montmayeur, Philippe Besnard. (2005) CD 36 involvement in oro-sensory detection of dietary lipids, spontaneous fat preference and digestive secretions. 115 (11): 3177-3184.

82. Wikipedia, the free encyclopedia. Available at:

http://en.wikipedia.org/wiki/taste.

83. Henkin R.I. (1993) Evaluation and treatment of human olfactory dysfunction In: Otolaryngology.vol2.Philadelphia: Lippincott. Page: 1-86.

84. Henkin R.I. (1994) Concepts of therapy in taste and smell dysfunction: repair of sensory receptor functions as primary treatment. In: Kurihara K., Suzuki N. and Ogawa H., editors. Olfaction and taste. Tokyo: springer Verlag. Page: 568-73.

85. Henkin R.I. (1994) Drug-induced taste and smell disorders: incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. Drug safety. 11 (5): page: 323-325.

86. Ship Johnathan A., and Chavez Elisa M. (2001) Special senses: Disorders of taste and smell .In: Sol Silverman, L.Roy Eversole, Edmond L.; editors. Essential of oral medicine. London. page: 281.

87. Henkin R.I. (1994) Drug-induced taste and smell disorders: incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. Drug safety. 11 (5): page: 322.

88. Henkin RI. (1991) Salty and bitter taste. JAMA. Page: 265-576.

89. Henkin RI. (1992) Phantogeusia. In: Taylor RB. Editor. Difficult diagnosis II. Philadelphia: WB sounders co. Page: 348-56.

90. Ship Johnathan A., and Chavez Elisa M. (2001) Special senses: Disorders of taste and smell .In: Sol Silverman, L.Roy Eversole, Edmond L.; editors. Essential of oral medicine. London. Page: 286.

91. Noble A.C. (1996) Tate-aroma interactions. Food Sci. and Technol. 7: 439-444.

92. Can Baser Hüsnü K. and Buchbauer Gerhard. (2010) Handbook of essential oils: Science, technology and application: Chapter 7: Safety evaluation of essential oils. Taylor and Francis Group. New York. Page: 186-205.

93. Yuki Oka, Akio Nakamura, Hidenori Watanabe, and Kazushige Touhara. (2004) An odorant derivative as an antagonist for an olfactory receptor. Chem. Senses. 29: 815-822.

94. Doty Richard L. and Hastings Loyl. (2001) Neuro-toxic exposure and olfactory impairment. Neurotoxicology. Volume 1, No. 3, Page: 547-575.

95. Wikipedia. The free encyclopedia. Available at:

http://www.en.wikipedia.org/wiki/furfural. at 05.08.2014.

96. John D. Pierce, Xiao-Nong Zeng, Evgueny A. Arnovo, George Preti and Charles J. Wysocki. (1995) Cross-adaption of sweaty-smelling 3-methyl-2-hexenoic acid by a structurally similar, pleasant smelling odorants. Chem. Senses. 20 (4): 401-411.

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