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CNS EFFECTS OF *HOMALOMENA AROMATICA* BASED ON LINALOOL CONTENT: A REVIEW

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Abstract:

The rhizome of Homalomena aromatica Schott. (Family: Araceae) is used by the local people throughout the north-eastern states of India to treat skin diseases, jaundice, diarrhea, stomach pain and as an insect repellent. Present research on Homalomena aromatica is only concentrated on these aspects of the plant based on the above mentioned ethnomedicinal uses. Linalool, the chief constituent of the essential oil portion of rhizome of Homalomena aromatica is a monoterepene alcohol having tremendous effect on the central nervous system. A detail review has been done on the effects of linalool on central nervous system namely in anxiety, convulsion, pain, sedation as well as in neurodegenerative disorders such as Alzheimer's disease. This review provides a basis for further research on Homalomena aromatica to treat different diseases associated with central nervous system.

Keywords: Linalool; Anxiety; Convulsion; Pain; Sedation; Alzheimer's disease.

Introduction

Homalomena (Family:Araceae) is an important genus of plant in the ethnomedicinal practices of the people of South-east Asia. Two species of *Homalomena* are reported; *Homalomena pendula* (Blume) Bakh. f. which is also known as *H. rubescens* (Roxb.) Kunth. This species is found in Meghalaya and Sikkim (The Wealth of India, 1988). The other known species is *H. aromatica* Schott. which is commonly also known as "*Sugandhmantri*" or "*Sugondhi-kachu*" or "*Gandhuri*" or "*Ganchana*". *H. aromatica*, a rhizomatous perennial herb is found in Assam, Arunachal Pradesh, Nagaland, Mizoram, Manipur and Tripura of India and Chittagong hill of Bangladesh (Barua *et al* 2014). Traditionally, *H. aromatica* is common as an ingredient in food habits of many tribes of north-east India, petiole of the plant is used in curry as spice and condiment for the pleasant odour whereas the leaves are also cooked as vegetable which is good in digestive disorders. The aroma of the rhizomes of *H. aromatica* is traditionally used for treating common cold of infants. In the state of Tripura, the fresh rhizomes of *H. aromatica* are crushed and paste is applied on body to treat inflammation (Majumdar

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and Datta 2007). The therapeutic potential of the essential oil from the rhizomes of *H. aromatica* is not reported extensively but it has tremendous potential as a prospective herbal remedy for different diseases. The reported therapeutic indications of *H. aromatica* are given in Table 1.

Table 1: Therapeutic indications of *Homalomena aromatica.*

Sl. no.	Therapeutic indication	References
1.	Antifungal	(Policegoudra *et al* 2012; Singh *et al* 2000; Singh *et al* 2002)
2.	Larvicidal	(Chungsamarnyart, Jiwajinda, and Jansawan 1991; Komalamisra *et al* 2005)
3.	Insecticidal	(Singh *et al* 2000)
4.	Insect-repellent	(Hazarika *et al* 2012)
5.	Acaricidal	(Chungsamarnyart, Ratanakreetakul and Jansawan 1994)
6.	Antibacterial	(Laishram *et al* 2006)
7.	Hepatoprotective	(Dutta *et al* 2013)
8.	Ulcerprotective	(Chandana *et al* 2014)

The essential oil has been principally isolated and characterized by gas chromatography-mass spectrum (GC-MS) analysis. Linalool (LL) (**1**) was reported to be the chief constituent of the essential oil but the concentration varies according to two researchers. Shukla and his co-workers reported the concentration of LL to be 32.45 % whereas, Policegoudra and his co-workers have reported it to be 62.5 % in the rhizome of *H. aromatica* (Shukla *et al* 2015; Policegoudra *et al* 2012; Sung *et al* 1992). Other chief constituents of essential oil in rhizomes of *H. aromatica* are terpene-4-ol (**2**), δ-cadinene (**3**), α-cadinol (**4**), M-cymene (**5**), T-muurolol (**6**), viridiflorol (**7**) and α-selinene (**8**) (Shukla *et al* 2015; Policegoudra *et al* 2012). Three sesquiterpene alcohols, 1-β, 4-β, 7-α- trihydroxyeudesmane, homalomenol A and homalomenol B were also isolated from the roots of this plant (Sung *et al* 1992).

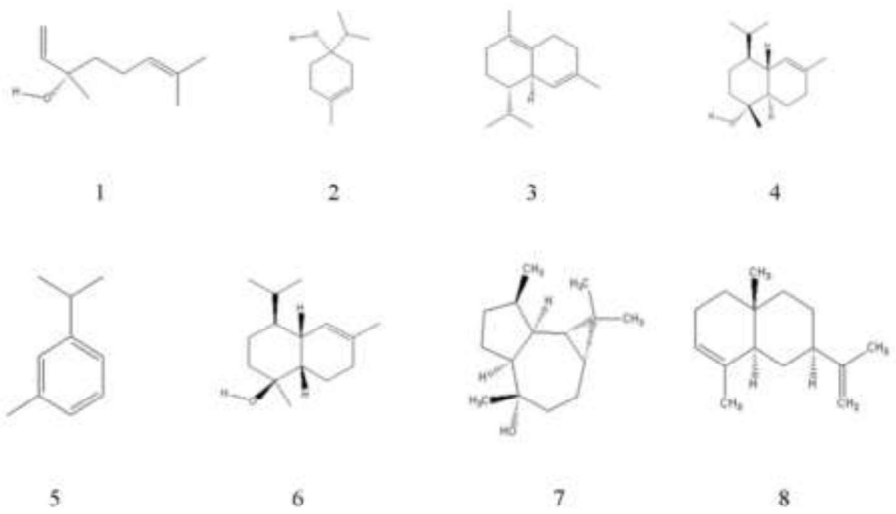

Figure 1: Structures of major essential oils (**1-8)** present in *Homalomena aromatica*.

Traditional medicinal systems throughout the world uses LL producing plant species for a number of disorders chiefly in disorders associated with central nervous system (CNS). *Aeollanthus suaveolens* Spreng. (Family: Lamiaceae) is used as a homemade anticonvulsant remedy in the Brazilian Amazon whereas *Cissus sicyoides* is used as a diuretic, anti-inflammatory and as an anti-diabetic in Dominican Republic (Elisabetsky *et al* 1995; Elisabetsky and Setzer 1985; Kainer and Duriea 1992; Toledo *et al* 1983; García *et al* 2000). *Citrus bergamia* Risso, *Melissa officinalis* L., *Rosmarinus officinals* L., *Cymbopogon citratus* DC. and *Mentha piperita* L. are all LL containing plants used traditionally as analgesics, sedatives, hypnotics and anxiolytics (Elisabestky, Marschner and Souza 1995). LL is an optically active compound but evidence suggest that (-)-LL is more medicinally active then (+)-LL. So during the course of this study the therapeutic potential of (-)-LL is only been reviewed.

Pharmacokinetics of Linalool

The water solubility of LL is found to be poor, which might be the reason behind its poor bioavailability (Shi *et al* 2016). In a dermal study to determine the pharmacokinetic parameters of LL, the peak plasma concentration of LL was reached by 19 min with a mean plasma concentration of 100 ng/ml. It was also found that LL disappeared from the blood in 90 min with biological half lives of 14 min (Jager *et al* 1992). In an inhalation study, almost consistent pharmacokinetic parameters were obtained even when the environment of exposure to LL was different. Serum LL levels in mice were

found to be 7–9 ng/ml after a 1 h inhalation to 5 mg/l LL (Buchbauer *et al* 1991). In a separate experiment when the mice were subjected to 5 mg/l of LL by inhalation for 1 hr, the serum LL levels were found to be 8 ng/ml (Jirovetz *et al* 1990). The results for both the experiments were found to be almost similar. LL on account of being a tertiary alcohol is metabolized primarily through conjugation with glucouronic acid and excreted through urine and to a very lesser extent as feces (Williams 1959). Some substituents might undergo oxidation and form polar metabolites, this is meditated by cytochrome P-450 dependant mono-oxygenases (Chadha and Madyastha 1984; Joint Expert Committee on Food Additives, WHO 1999). The metabolic fate of LL was studied in mammals, Rats were administered ^{14}C- labeled dose of 500 mg/kg of LL and various parameters were studied after 72 h of dose administration. 55 % of LL was excreted in urine, 23 % was excreted in air while only 15% was excreted as feces. The highest percentage (1.2%) of LL after 72 h administration was found in the skeletal muscle when studied in different tissues. In a separate experiment male rats were given a single intra peritoneal (i.p.) dose of 20 mg LL and biliary excretion of conjugated LL was determined. It was found that more than 25 % of the dose was present as polar conjugates in bile, this was principally found in the first 4 h (Parke, Rahman and Walker 1974).

Toxicity of Linalool

In various acute toxicity rodent models, the LD_{50} of LL was found to be in the range of 2200 mg/kg to 48,800 mg/kg. Dermal LD_{50} values in rabbits exceeding 5000 mg/kg have been previously reported. LD_{50} values of LL in mice and rats ranges from 200 mg/kg to 2864 mg/kg when administered i.p. In mice, subcutaneous (s.c.) and intramuscular (i.m.) LD_{50} values for LL are 1470 mg/kg and 8000 mg/kg, respectively (Bickers *et al* 2003). Aromatherapy requires special caution because of the potential toxicities of the essential oils. At concentrations of 1 to 100 μM, LL was not cytotoxic to neuronal cells (Kim *et al* 2015).

Effect on anxiety

Cascades of neurotransmitters are released during the process of anxiety. The sympathetic nervous system is activated by the stress producing anxiety releasing catecholamines from adrenal medulla i.e. epinephrine and norepinephrine. Corticosteroids are elevated to modulate the biological response to stress. The fight-or-flight response and subsequent increase in heart rate and glycolysis result in fatigue and a weakened immune response (Selye 1976). Preoperative anxiety is another aspect in administration of anesthetics, the neurotransmitters involved in such a situation are also

because of elevated catecholamines and cortisol (Weissman 1990). These increased levels may cause harm to patients who are already in critical state which in the long run causes adverse outcome or poor wound healing (Kain *et al* 2000). Many drugs are used in anxiety and benzodiazepines are the most commonly used anti-anxiety drugs (Carlini 2003). But, there are reports that they cause a wide range of side-effects such as hypotension, myorelaxation and a high potential for addiction and abuse (Woods, Katz and Winger G 1992). LL has far reaching effects on different receptors and voltage gates. At the neuromascular junction LL modulates the nicotinic receptor whereas in the cerebral cortex it modulates the N-methyl-D-aspartate (NMDA) receptor (Re *et al* 2000; Elisabetsky, Brum and Souza 1999). In rodent models, LL was found to block the calcium channels (Gilani *et al* 2000). In a rodent model to evaluate the anxiolytic properties of inhaled LL it was found that 3% LL is an effective anxiolytic as compared to 1% LL. The result for 3% LL is comparable to diazepam which showed almost similar results in the test. These results were also corroborated by results for aggressive behavior and social interaction test which are compatible for the profile of all anxiolytic drugs (Linck *et al* 2009). The lack of effects in the social interaction test could be related to the antagonistic action of LL on NMDA receptors (Silva Brum, Elisabetsky and Souza 2001). The leaves of *Cissus sicyoides* (*C. sicyoides*) (Family: Vitaceae) were reported to have considerable LL contend. In an experiment to evaluate the anxiolytic effects of *C. sicyoides* by performing the elevated plus maze test, the average time spend by the mice for the group administered with diazepam (2.5 mg/kg, i.p.) on the open arm of the elevated plus maze was found to be 200 s. The same for the extract from the leaves of *C. sicyoides* (600 mg/kg, i.p.) was found to be 150 s which was comparable to diazepam (De-Almeida *et al* 2009).

Effect on convulsion

The etiology of convulsion can be linked to both inhibitory and excitatory neurotransmitter systems (Obrenovitch, Urenjak and Zilkha 1996). Overstimulation of glutamate receptor might be a reason behind the activation of excitatory neurotransmitters whereas reduced GABAergic activity might be the cause of inhibitory changes causing seizures (Lipton and Rosemberg 1994). As already mentioned LL has antagonistic action on NMDA receptor which is a type of glutamate receptor, so it might have potential effect as an anti-convulsant also (Meldrum 1992). Quinolinic acid is a NMDA agonist, synthesized in neuronal and glial cells. It has the ability to cause convulsion when given i.v. Intracerebral administration of LL was found to be effective in protecting against quinolinic acid induced convulsion. In Pentylenetetrazol (PTZ) kindling, repeated subconvulsive doses of PTZ causes development of behavioral

convulsive activity (Cain 1989). Experimental results indicate that LL partially inhibits and significantly delays the behavioral expression of PTZ-kindling (Parke, Rahman and Walker 1974). PTZ convulsions are also related to inhibition of GABAergic transmission, LL's effects on this system cannot be ruled out (Giorgi *et al* 1991). In an experiment, *C. sicyoides* (1000 mg/kg, IP) was found to be significantly effective ($P<0.01$) in neutralizing convulsion caused by PTZ (Jager *et al* 1992).

Effect on inflammation and pain

Pain is a sensorial modality which in many cases represents only as a symptom for the diagnosis of several diseases (Almeida, Navarro and Barbosa-Filho 2001). Nitric oxide (NO) is evidentially proven to be a mediator in inflammation and pain (Lyons 1995). NO increases the synthesis of cytokines, prostanoids and reactive oxygen species which are mediators for inflammation (Marcinkiewicz, Grabowska and Chain 1995; Sautebin *et al* 1995). Inducible nitric oxide synthase (iNOS) triggers the cyclo-oxygenase 2 (COX 2) which is the chief architect of inflammation (Dudhgaonkar *et al* 2004). In an experiment to investigate the effect of LL on the formation and release of NO in macrophages cell line (J774.A1), LL in a concentration-dependent manner, inhibited nitrite accumulation in the culture medium. This effect was due to the inhibitory interaction of LL on the iNOS enzyme (Peana *et al* 2006). Studies have also shown that LL modulates glutamatergic neurotransmission through NMDA receptor interactions which has been previously indicated in this article (Tanabe *et al* 1993; Silva Brum *et al* 2001). Both types of glutamate receptors i.e. ionotropic and metabotropic receptors, play an important role in modulating nociceptive processing at both peripheral and spinal levels (Fundytus 2001; Ozawa, Kamiya and Tsuzuki 1998). In a study to evaluate the anti-nociceptive effect of LL on rodent models, it was found that the anti-nociceptive action of LL was due to its interaction with glutameteric system more specifically through interaction with the ionotropic receptors. This assertion is supported by the demonstration that LL (200mg/kg) administered i.p., a dose that produced significant effect on glutamate-induced paw licking, significantly attenuated the biting response induced by intrathecal injection of glutamate and NMDA and, to a lesser extent, that induced by α-amino-3-hydoxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors (Batista *et al* 2008). In another study to evaluate the anti-nociceptive potential of LL (200mg/kg, s.c.) on rodent model, the effect of this compound was linked not only with glutamate but also to different transmission systems such as opioids, acetylcholine, dopamine, K^+channels when the experiment was conducted by inducing pain with prostaglandin E_2 (PGE_2) (200 ng/paw, Intra- thecal) (Peana *et al* 2004). The antihyperalgesic effect of LL might result from the indirect

stimulation of cholinergic M_2, opioidergic and dopamine D_2 receptors that are coupled to Gi/Go proteins that are able to induce the opening of K^+ channels and consequent cellular hyperpolarization (Childers 1991). *Lavandula angustifolia* Mill. (*L. angustifolia)* (Family: Lamiaceae) is an LL containing aromatic herb (Renaud , Charles and Simon 2001). In an experiment to evaluate the anti-inflammatory potential of the essential oil from *L. angustifolia* it was found that 100 and 200 mg/kg of essential had considerable anti-nociceptive effect in both formalin test as well as in acetic acid test and it seems that at least a large part of the analgesic effect of the plant is due to its essential oil content (Hajhashemi, Ghannadi and Sharif 2003).

Effect on sedation

Psychopharmacological evaluations suggested that LL administered either i.p. or intracerebral (i.c.v.) has marked sedative and anticonvulsant effects in various mouse models (Elisabetsky, Brum and Souza 1999). Hardy and co-workers showed that inhalation of the odor of lavender, a plant containing LL could replace hypnotic drugs in humans (Hardy, Kirk-Smith and Stretch 1995). Lis-Balchin and co-workers produced some evidence that relaxation of smooth muscle of ileum (*in- vitro)* can be correlated with the relaxant effect of LL in humans (Lis-Balchin and Hart S 1997). The effects of LL as a sedative can be linked to its relaxing effect on CNS which may be because LL acts as a competitive antagonist of L-[^{3}H]-glutamate binding, and it also shows a dose-dependent non-competitive inhibition of dizocilpine (also known as MK801) binding, indicating antagonism of NMDA glutamate receptors (Elisabetsky, Brum and Souza 1999; Silva Brum, Elisabetsky and Souza 2001). LL also decreases the potassium-stimulated glutamate release and uptake in mice cortical synaptosomes (Singh *et al* 2002). In an experiment to evaluate the sedative action of LL, it was found that LL (1% and 3%) inhaled for 60 min is sedative, inducing hypothermia, reducing locomotion and increasing pentobarbital-induced sleeping time. Plasma concentration of LL for the same experiment was found to be 2.7 ng/ml after 60 min of inhalation (Linck *et al* 2010). Shaw and co-workers reported that LL induces relaxation without producing motor impairments or marked sedation, this is of obvious advantage as most of the marketed sedatives produce more or less some kind of motor impairment (Shaw *et al* 2007). In a study to evaluate the sedative effect of LL on human, it was found that LL decreases beta wave in human subjects (Sugawaraa *et al* 1998). Jasmine tea, one of the most popular beverages in China has LL as a major component (Yang and Koo 1997; Ito *et al* 2002). In a study to evaluate the sedative activity of jasmine tea on human volunteers it was found that it has major sedative action on the volunteers and it may be

due to an increase in parasympathetic nerve activities after administration of LL containing jasmine tea (Kuroda *et al* 2005).

Effect on Alzheimer's disease (AD)

Research on AD suggest the role of plaques and tangles. Plaques are deposits of a protein fragment called beta amyloid that builds up in the spaces between nerve cells. Tangles are twisted fibers of another protein called tau that builds up inside the cells. They somehow cause destruction and death of nerve cells which subsequently causes memory failure, personality changes, problems in carrying out daily activities and other symptoms of AD (Alzheimer's association 2005). But the research on drugs for curing AD is presently concentrating on various pathways involving tumor necrosis factor alpha (TNF-α), interlukin-1beta (IL-1β), NO, PGE_2 and their subsequent effect on AD. The drugs used in AD are acetylcholinesterase inhibitors, such as galantamine and the NMDA antagonist memantine which only provide symptomatic relief rather than complete amelioration of AD (Kang *et al* 2014; Bassil and Grossberg 2009). Since these compounds only provide symptomatic relief newer lead compounds are being studied to treat AD. Natural products are also looked upon as prospective drugs to completely cure AD. Amongst all the compounds studied, monoterpenes were reported with the maximum efficacy (Dinda, Chowdhury and Mohanta 2009; Tabassum *et al* 2015). As previously discussed the effect of LL on NO, and its inhibition on nitrite accumulation *in-vitro*. NO also has a role in AD. NO is an important signaling molecule in the regulation of cerebral blood flow and modulation of neuronal activity with both protective and deleterious functions (Murad 2006). Inappropriate NO production was found to cause various deleterious effects on the human physiology resulting from oxidative stress (Ogino and Wang 2007). Oxidative stress is the major cause of damage associated with elevated NO (Murphy 1999; Obrosova *et al* 2005). In patients with neurodegenerative diseases such as Alzheimer's and Parkinson's the production of NO and the expression of iNOS were reported to be in an increased state (Youn *et al* 2007; Katsuse, Iseki and Kosaka 2003). Another pathway in prognosis of AD is associated with the role of lipopolysaccharide (LPS) another mediator in inflammation. Resident immune cells in the CNS i.e. microglia gets activated by LPS or β-amyloid and release various inflammatory mediators such as TNF-α, IL-1β and PGE_2 in association with NO (Griffiths, Neal and Gasque 2007; Wang *et al* 2015; Zhu *et al* 2015). These inflammatory mediators lead to neuronal damage and pathogenesis of neurodegenerative diseases (Yan *et al* 2014; Heneka, Kummer and Latz 2014). LL has a number of neuroprotective functions, Research suggest that LL protects against glucose/serum deprivation in PC12 cells, a cell line derived from pheochromocytoma of

the rat adrenal medulla, against acrylamide (ACR) induced neurotoxicity (Alinejad, Ghorbani and Sadeghnia 2013). LL increases the glutathione content while decreasing the ACR-induced lipid peroxidation in rat brain tissue (Mehri, Meshki and Hosseinzadeh 2014). In the Morris Water Maze (MWM) test to evaluate the effect of LL on neuropathological and behavioral impairment, it was found that spatial learning abilities were restored in old triple transgenic Alzheimer's (3xTg-AD) mice treated with LL for 3 months. It was also found that the LL treatment successfully reversed spatial memory impairment (Sabogal Guáqueta, Osorio and Cardona Gómez 2016). It was observed that the deposition of amyloid which is a typical phenomenon in AD was significantly reduced in the hippocampus, entorhinal cortex and amygdala of the LL treated 3xTg-AD mice (Oddo *et al* 2003). These studies represent strong evidence that regular administration of LL can prevent age-related cognitive impairments and β-amyloid accumulation. LL also has antioxidant properties and shows protective effects against hydrogen peroxide induced oxidative stress in brain tissue (Celik and Ozkaya 2002). In an experiment to evaluate the neuroprotective effect of LL against Sodium Nitroprusside (SNP) induced cytotoxicity in caspase dependent apoptosis in human neuroblastoma cells (SH-SY5Y), it was found that LL protected SH-SY5Y cells against SNP-induced cytotoxicity by decreasing the production of NO. SNP has been reported to mimic NMDA induced neurotoxicity and to induce oxidative stress (Nakamura *et al* 1997; Lushchak and Lushchak 2008). The above mentioned experiment similarly found the neuroprotective effects of LL were associated with an increase in antioxidants, as measured by DPPH assays (Kim *et al* 2015). In another experiment to evaluate the role of LL in LPS induced inflammation in BV2 Microglia cells by activating nuclear factor (erythroid-derived 2)-like 2 also known as Nrf2, it was reported that results showed that LL inhibited LPS-induced inflammatory mediators production through activation of Nrf2/hemeoxygenase (HO-1) signaling pathway (Li *et al* 2015). In another study to evaluate cognitive-enhancing and antioxidant activities of inhaled coriander volatile oil which chiefly contains LL, in rat model of AD, it was reported that multiple exposures to coriander volatile oil could effectively restore antioxidant brain status and may confer neuroprotection due to alleviation of oxidative damage (Cioanca *et al* 2013).

Conclusion

Herbal-based traditional medicine has become popular in developed countries in recent years, and its use is likely to increase in the coming years (Thatoi and Patra 2011). The literature survey on *H. aromatica* suggest that it has tremendous medicinal potential as antifungal, larvicidal, insecticidal, antibacterial etc. Linalool is the chief constituent of the essential oil fraction of *H. aromatica* as already been indicated in the article. From

the detail review, it is seen that linalool is a potent agent in anxiety, convulsion, pain, sedation and in Alzheimer's disease. Linalool is capable of acting on various brain neurotransmitters (GABA, glutamic acid, serotonin, acetylcholine, dopamine,) and ionic channels but the mechanisms of activity are still not properly understood. *H. aromatica* also consist of substantial amount of other essential oils such as terpene-4-ol, δ-cadinene, α-cadinol, M-cymene, T-muurolol, viridiflorol, α-selinene. The effect of these essential oils on CNS is not studied in detail till now. There are challenges in incorporation of this knowledge into developing a formulation from the different essential oil fractions of *H. aromatica* as bioavailability of most of these essential oils are very poor. Proper and detail studies on the synergistic effects of all the above mentioned oil fractions on CNS is needed. Therefore this review justifies proper scientific study on the essential oil fraction of *H. aromatica*, so that it can be looked upon as future drug candidate in CNS disorders.

References:

Alinejad B, Ghorbani A, and Sadeghnia HR (2013). Effects of combinations of curcumin, linalool, rutin, safranal and thymoquinone on glucose/serum deprivation induced cell death. Avicenna J Phytomed, 3(4):321-328.

Almeida RN, Navarro DS, and Barbosa-Filho JM (2001). Plants with central analgesic activity. Phytomedicine, 8(4):310–322.

Alzheimer's association (2005). Basics of Alzheimer's disease. http://alz.org/alzheimers_disease_publications_alz_basics.asp. Accessed on 29.04.16 at 1030 hrs.

Anonymous (1988). The Wealth of India, Raw Materials, Vol I-XI. Publications and information directorate, CSIR, New Delhi.

Barua CC, Talukdar A, Phukan B, Hazarika S, Barua AG, and Baishya G (2014). Phytochemical screening and *in-vitro* antioxidant activity of ethanolic extract of *Homalomena aromatica* (Araceae) root. Der Pharma Lett, 6(1):128-138.

Bassil N and Grossberg GT (2009). Novel regimens and delivery systems in the pharmacological treatment of Alzheimer's disease. CNS Drugs, 23(4):293-307.

Batista PA, Werner MF, Oliveira EC, Burgos L, Pereira P, Brum LF and Santos AR (2008). Evidence for the involvement of ionotropic glutamatergic receptors on the antinociceptive effect of (-)-linalool in mice. Neurosci Lett, 440(3):299–303.

Bickers D, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, Sipes IG, Smith RL, and Tagami HA (2003). A toxicologic and dermatologic assessment of linalool and related esters when used as fragrance ingredients. Food Chem Toxicol, 41(7):919–942.

Buchbauer G, Jirovetz L, Jager W, Dietrich H, and Plank C (1991). Aromatherapy: Evidence for sedative effects of the essential oil of lavender after inhalation. Z Naturforsch C, 46:1067–1072.

Cain DP (1989). Long-term potentiation and kindling: how similar are the mechanisms. Trends Neurosci, 12(1):37-43.

Carlini EA (2003). Plants and the central nervous system. Pharmacol Biochem Behav, 75(3):501–512.

Celik S, and Ozkaya A (2002). Effects of intraperitoneally administered lipoic acid, vitamin E, and linalool on the level of total lipid and fatty acids in guinea pig brain with oxidative stress induced by H_2O_2. J Biochem Mol Biol, 35(6):547-552.

Chadha A, and Madyastha KM (1984). Metabolism of geraniol and linalool in the rat and effects on liver and lung microsomal enzymes. Xenobiotica, 14:365–374.

Chandana CB, Anindita T, Acheenta GB, Debesh CP, and Iswar CB (2014). Ulcer protective activity of ethanolic extract of *Homalomena aromatica* (Spreng.) Schott. (Araceae) root. Adv Tech Bio Med, 117, doi:10.4172/atbm.1000117.

Childers SR (1991). Opioid receptor-coupled second messenger systems. Life Sci, 48(21):1991– 2003.

Chungsamarnyart N, Jiwajinda S, and Jansawan W (1991). Larvicidal effect of plant crude-extracts on the tropical cattle tick (*Boophilus microplus*). Agric Nat Resour, 25:80-89.

Chungsamarnyart N, Ratanakreetakul C, and Jansawan W (1994). Acaricidal activity of the combination of plant crude extracts to tropical cattle ticks. Agric Nat Resour, 28(4):649-660.

Cioanca O, Hritcu L, Mihasan M, and Hancianu M (2013). Cognitive-enhancing and antioxidant activities of inhaled coriander volatile oil in amyloid β (1–42) rat model of Alzheimer's disease. Physiol Behav, 120:193–202.

De-Almeida ER, Rafael KR, Couto GB, and Ishigami AB (2009). Anxiolytic and anticonvulsant effects on mice of flavonoids, linalool, and α-tocopherol present in the extract of leaves of *Cissus sicyoides* L. (Vitaceae). J Biomed Biotechnol, doi: 10.1155/2009/274740.

Dinda B, Chowdhury DR, and Mohanta BC (2009). Naturally occurring iridoids, secoiridoids and their bioactivity: An updated review, part 3. Chem Pharm Bull, 57(8):765-796.

Dudhgaonkar SP, Kumar D, Naik A, Devi AR, Bawankule DU and Tandan SK (2004). Interaction of inducible nitric oxide synthase and cyclooxygenase-2 inhibitors in formalin-induced nociception in mice. Eur J Pharmacol, 492(2-3):117– 122.

Dutta B, Lahkar M, Augustine BB and Lihite RJ (2013). Hepatoprotective activity of *Tamarind indica* and *Homalomena aromatica* in rats. Int J Pharm Pharm Sci, 5(2):436-438.

Elisabestky E, Marschner J and Souza DO 1995. Effects of linalool on glutamatergic system in the rat cerebral cortex. Neurochem Res, 20:461–465.

Elisabetsky E, Brum LF and Souza DO (1999). Anticonvulsant properties of linalool in glutamate-related seizure models. Phytomedicine, 6(2):107-113.

Elisabetsky E, Coelho De Souza GP, Dos Santos MAC, Siqueira IR, Amador TA and Nunes DS (1995). Sedative properties of Linalool. Fitoterapia, 115(5):407-414.

Elisabetsky EE and Setzer R (1985). Caboclo concepts of disease, diagnosis and therapy: Implications for ethnopharmacology and health systems in Amazonia. In E.P. Parker, ed. The Amazon Caboclo: historical and contemporary perspectives. Williamsburg: Studies on Third World Societies Publication Series, pp. 243-278.

Fundytus ME (2001). Glutamate receptors and nociception: implications for the drug treatment of pain, CNS Drugs, 15(1):29–58.

García MD, Quílez AM, Sáenz MT, Martínez-Domínguez ME and De-la-puerta R (2000). Anti-inflammatory activity of *Agave intermixta* Trel. and *Cissus sicyoides* L., species used in the Caribbean traditional medicine. J Ethnopharmacol, 71(3):395–400.

Gilani AH, Aziz N, Khan MA, Shaheen F, Jabeen Q, Siddiqui BS and Herzig JW (2000). Ethnopharmacological evaluation of the anti-convulsant, sedative and anti-spasmodic activities of *Lavandula stoechas* L. J Ethnopharmacol, 71(1-2):161-167.

Giorgi O, Orlandi M, Geic M and Corda MG (1991). MK-801 prevents the decrease in 35S-TBPS binding in the rat cerebral cortex induced by pentylenetetrazol kindling. Brain Res Bull, 27(6):835-837.

Griffiths M, Neal JW and Gasque P (2007). Innate immunity and protective neuroinflammation: new emphasis on the role of neuroimmune regulatory proteins. Int Rev Neurobiol, 82:29–55.

Hajhashemi V, Ghannadi A and Sharif B (2003). Anti-inflammatory and analgesic properties of the leaf extracts and essential oil of *Lavandula angustifolia* Mill. J Ethnopharmacol, 89(1):67–71.

Hardy M, Kirk-Smith MD and Stretch DD (1995). Replacement of drug treatment for insomnia by ambient odour. Lancet, 346(8976):701.

Hazarika S, Dhiman S, Rabha B, Bhola RK and Singh L (2012). Repellent activity of some essential oils against *Simulium* species in India. J Insect Sci, 12, doi: 10.1673/031.012.0501.

Heneka MT, Kummer MP and Latz E (2014). Innate immune activation in neurodegenerative disease. Nat Rev Immunol, 14:463–477.

Ito Y, Sugimoto A, Kakuda T and Kubota K (2002). Identification of potent odorants in Chinese jasmine green tea scented with flowers of *Jasminum sambac*. J Agric Food Chem, 50(17):4878–4884.

Jager W, Buchbauer G, Jirovetz L and Fritzer M (1992). Percutaneous absorption of lavender oil from a massage oil. J Soc Cosmet Chem, 43:49–54.

Jirovetz L, Buchbauer G, Jager W, Raverdino V and Nikiforov A (1990). Determination of lavender oil fragrance compounds in blood samples. Fresenius J Anal Chem, 338:922–923.

Joint Expert Committee on Food Additives (JECFA) (1999). Safety evaluation of certain food additives. WHO Food Additives Series: 42. Prepared by the Fifty-first

meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization, Geneva.

Kain ZN, Sevarino F, Pincus S, Alexander GM, Wang SM, Ayoub C, and Kosarussavadi B (2000). Attenuation of the preoperative stress response with midazolam: effects on postoperative outcomes. Anesthesiology, 93(1):141-147.

Kainer KA and Duriea ML (1992). Tapping women's knowledge: Plant resource use in extractive reserves, Acre, Brazil. Econ Bot, 46(4):408-425.

Kang JH, Ryoo NY, Shin DW, Trojanowski JQ and Shaw LM (2014). Role of cerebrospinal fluid biomarkers in clinical trials for Alzheimer's disease modifying therapies. Korean J Physiol Pharmacol, 18(6):447-456.

Katsuse O, Iseki E and Kosaka K (2003). Immunohistochemical study of the expression of cytokines and nitric oxide synthases in brains of patients with dementia with lewy bodies. Neuropathology, 23(1):9-15.

Kim KY, Lee HS, Min SS and Seol GH (2015). Neuroprotective effect of (-)-linalool against sodium nitroprusside-induced cytotoxicity. Med Chem, 5:178-182.

Komalamisra N, Trongtokit Y, Rongsriyam Y and Apiwathnasorn C (2005). Screening for larvicidal activity in some Thai plants against four mosquito vector species. Southeast Asian J Trop Med Public Health, 36(6):1412-1422.

Kuroda K, Inoue N, Ito Y, Kubota K, Sugimoto A, Kakuda T and Fushiki T (2005). Sedative effects of the jasmine tea odor and (R)-(-)-linalool, one of its major odor components, on autonomic nerve activity and mood states. Eur J Appl Physiol, 95(2-3):107–114.

Laishram KS, Nath DR, Bailung B and Baruah I (2006). *In-viro* antibacterial activity of essential oil from rhizome of *Homalomena aromatica* against pathogenic bacteria. J Cell Tissue Res, 6(2):849-851.

Li Y, Lv O, Zhou F, Li Q, Wu Z and Zheng Y (2015). Linalool Inhibits LPS-induced inflammation in BV2 microglia cells by activating Nrf2. Neurochem Res, 40(7): 1520-1525

Linck VM, Da Silva AL, Figueiró M, Piato AL, Herrmann AP, Dupont Birck F, Caramão EB, Nunes DS, Moreno PR and Elisabetsky E (2009). Inhaled linalool induced sedation in mice. Phytomedicine, 16(4):303–307.

Linck VM, DaSilva AL, Figueiro M, Caram EB, Moreno PRH and Elisabetsky E (2010). Effects of inhaled linalool in anxiety, social interaction and aggressive behavior in mice. Phytomedicine, 17(8-9):679–683.

Lipton SA and Rosemberg PA (1994). Excitatory amino acids as a final common pathway for neurologic disorders. N Engl J Med, 330(90):613-622.

Lis-Balchin M and Hart S (1997). Correlation of the chemical profiles of essential oil mixes with their relaxant and stimulant properties in man and smooth muscle preparations *in-vitro*. In: Franz C, Mathe CA, Buchbauer G, eds. In Proceedings of the 27th International Symposium on Essential Oils. Vienna: Alured Publishing, Carol Stream, pp 24–28.

Lushchak OV and Lushchak VI (2008). Sodium nitroprusside induces mild oxidative stress in *Saccharomyces cerevisiae*. Redox Rep, 13(4):144-152.

Lyons CR (1995). The role of nitric oxide in inflammation. Adv Immunol, 60:323– 371.

Majumdar K and Datta B.K (2007). A study on ethnomedicinal usage of plants among the folklore herbalists and Tripuri medical practitioners: Part-II. Nat Prod Radiance, 6(1):66-73.

Marcinkiewicz J, Grabowska A and Chain B (1995). Nitric oxide up-regulates the release of inflammatory mediators by mouse macrophages. Eur J Pharmacol, 25(4):947–951.

Mehri S, Meshki MA and Hosseinzadeh H (2014). Linalool as a neuroprotective agent against acrylamide-induced neurotoxicity in wistar rats. Drug Chem Toxicol, 38(2):162-166.

Meldrum BS (1992). Excitatory amino acids in epilepsy and potential novel therapies. Epilepsy Res, 12(2):189-196.

Murad F (2006). Nitric oxide and cyclic GMP in cell signaling and drug development. N Engl J Med, 355:2003-2011.

Murphy MP (1999). Nitric oxide and cell death. Biochim Biophys Acta, 1411(2-3):401-414.

Nakamura Y, Yasuda M, Fujimori H, Kiyono M and Pan-Hou H (1997). Cytotoxic effect of sodium nitroprusside on PC12 cells. Chemosphere, 34(2):317-324.

Obrenovitch TP, Urenjak J and Zilkha E (1996). Evidence disputing the link between seizure activity and high extracellular glutamate. J Neurochem, 66(6):2446-2454.

Obrosova IG, Mabley JG, Zsengellér Z, Charniauskaya T, Abatan OI, Groves JT and Szabó C (2005). Role for nitrosative stress in diabetic neuropathy: evidence from studies with a peroxynitrite decomposition catalyst. *FASEB J*, 19(3):401-403.

Oddo S, Caccamo A, Shepher JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y and La Ferla FM (2003). Triple-transgenic model of Alzheimer's disease with plaques and tangles: Intracellular abeta and synaptic dysfunction. Neuron, 39(3):409-421.

Ogino K, and Wang DH (2007). Biomarkers of oxidative/nitrosative stress: an approach to disease prevention. Acta Med Okayama, 61(4):181-189.

Ozawa S, Kamiya H and Tsuzuki K (1998). Glutamate receptors in mammalian central nervous system. Prog Neurobiol, 54(5):581–618.

Parke DV, Rahman KHMQ and Walker R (1974). Effect of linalool on hepatic drug-metabolizing enzymes in the rat. Biochem Soc Trans, 2(4):615–618.

Peana AT, De Montis MG, Sechi S, Sircana G, D'Aquila PS and Pippia P (2004). Effects of (-)-linalool in the acute hyperalgesia induced by carrageenan, L-glutamate and prostaglandin E_2. Eur J Pharmacol, 497(3):279– 284.

Peana AT, Marzocco S, Popolo A and Pinto A (2006). (-)-Linalool inhibits *in-vitro* NO formation: Probable involvement in the antinociceptive activity of this monoterpene compound. Life Sci, 78(7):719 – 723.

Policegoudra RS, Goswami S, Aradhya SM, Chatterjee S, Datta S, Sivaswamy R, Chattopadhyay P and Singh L (2012). Bioactive constituents of *Homalomena aromatica* essential oil and its antifungal activity against dermatophytes and yeasts. J Mycol Med, 22(1):83-87.

Re L, Barocci S, Sonnino S, Mencarelli A, Vivani C, Paolucci G, Scarpantonio A, Rinaldi L and Mosca E (2000). Linalool modifies the nicotinic receptor-ion channel kinetics at the mouse neuromascular junction. Pharmacol Res, 42(2):177-182.

Renaud ENC, Charles DJ and Simon JE (2001). Essential oil quantity and composition from 10 cultivars of organically grown lavender and lavandin. Journal of Essential Oil Research, 13(4):269–273.

Sabogal Guáqueta AM, Osorio E and Cardona Gómez GP (2016). Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer's mice. Neuropharmacology, 102:111-120.

Sautebin L, Ialenti A, Ianaro A and Di Rosa M (1995). Modulation by nitric oxide of prostaglandin biosynthesis in the rat. Br J Pharmacol, 114(2):323–328.

Selye H (1976). Further thoughts on “stress without distress”. Med Times, 104(11):124-144.

Shaw D, Annett JM, Doherty B and Leslie JC (2007). Anxiolytic effects of lavender oil inhalation on open-field behaviour in rats. *Phytomedicine*, 14(9):613–620.

Shi F, Zhao Y, Firempong CK and Xu X (2016) Preparation, characterization and pharmacokinetic studies of linalool-loaded nanostructured lipid carriers. Pharm Biol, 1-9, doi:10.3109/13880209.2016.1155630.

Shukla AC, Lalsangluaii F, Singh B, Kumar A, Lalramnghinglova H and Dikshit A (2015). *Homalomena aromatica*: an ethnomedicinal plant, can be a potential source of antimicrobial drug development. Eur J Environ Ecol, 2(2):96-104.

Silva Brum LF, Elisabetsky E and Souza D (2001). Effects of linalool on [(3)H] MK801 and [(3)H] muscimol binding in mouse cortical membranes. Phytother Res, 15(5):422–425.

Silva Brum LF, Emanuelli T, Souza DO and Elisabetsky E (2001). Effects of linalool on glutamate release and uptake in mouse cortical synaptosomes. Neurochem Res, 26(3):191–194.

Singh G, Kapoor IPS, Singh OP, Rao GP, Prasad YR, Leclercq PA and Klinkby N (2000). Studies on essential oils, part 28: Chemical composition, antifungal and

insecticidal activities of rhizome volatile oil of *Homalomena aromatica* Schott. Flavour Fragr J, 15(4):278–280.

Singh G, Singh OP, Rao GP and Sharma SR (2002). The vapour action of essential oils and monoterpenoids against pathogenic fungi. Suger Tech, 4(1):69-71.

Sugawaraa Y, Haraa C, Tamuraa K, Fujiia T, Nakamuraa K, Masujimab T and Aokic T (1998). Sedative effect on humans of inhalation of essential oil of linalool: sensory evaluation and physiological measurements using optically active linalools. Anal Chim Acta, 365(1-3):293-299.

Sung TV, Steffan B, Steglich W, Klebe G and Adam G (1992). Sesquiterpenoids from the roots of *Homalomena aromatica*. Phytochemistry, 31(10):3515-3520.

Tabassum R, Vaibhav K, Shrivastava P, Khan A, Ahmed ME, Ashafaq M, Khan MB, Islam F, Safhi MM and Islam F (2015). Perillyl alcohol improves functional and histological outcomes against ischemia-reperfusion injury by attenuation of oxidative stress and repression of COX-2, NOS-2 and NF-κB in middle cerebral artery occlusion rats. Eur J Pharmacol, 747:190-199.

Tanabe Y, Nomura A, Masu M, Shigemoto R, Mizuno N and Nakanishi S (1993). Signal transduction, pharmacological properties, and expression patterns of two rat metabotropic glutamate receptors, mGluR3 and mGluR4. J Neurosci, 13(4):1372-1378.

Thatoi H and Patra JK (2011). Biotechnology and Pharmacological Evaluation of Medicinal Plants: An Overview. J Herbs Spices Med Plants, 17:214-248.

Toledo MCF, Reyes FGR, Iaderoza M, Fancis FJ and Draetta IS (1983). Anthocyanins from Anil Trepador (*Cissus sicyoides*, Linn.). *J Food Sci*, 48(4):1368–1369.

Wang S, Jing H, Yang H, Liu Z, Guo H, Chai L and Hu L (2015). Tanshinone I selectively suppresses pro-inflammatory genes expression in activated microglia and prevents nigrostriatal dopaminergic neurodegeneration in a mouse model of Parkinson's disease. J Ethnopharmacol, 164:247–255.

Weissman C (1990). The metabolic response to stress: an overview and update. Anesthesiology, 73(2):308-327.

Williams RT (1959). Detoxification Mechanisms: The Metabolism and Detoxication of Drugs, Toxic substances and other Organic compounds. London: Chapman and Hall Limited, pp. 67–69.

Woods JH, Katz JL and Winger G (1992). Benzodiazepines: use, abuse, and consequences. Pharmacol Rev, 44(2):151–347.

Yan J, Fu Q, Cheng L, Zhai M, Wu W, Huang L and Du G (2014). Inflammatory response in Parkinson's disease (review). Mol Med Rep, 10(5):2223–2233.

Yang TT and Koo MW (1997). Hypocholesterolemic effects of Chinese tea. Pharmacol Res, 35(6):505–512.

Youn H, Ji I, Ji HP, Markesbery WR and Ji TH (2007). Under-expression of Kalirin-7 increases iNOS activity in cultured cells and correlates to elevated iNOS activity in Alzheimer's disease hippocampus. J Alzheimers Dis, 12(3):271-281.

Zhu M, Wang X, Schultzberg M, and Hjorth E (2015). Differential regulation of resolution in inflammation induced by amyloid-β42 and lipopolysaccharides in human microglia. J Alzheimers Dis, 43(4):1237–1250.

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