EFFECTS OF SELECTED AROMA COMPOUNDS ON PHYSIOLOGICAL ACTIVITIES AND EMOTIONS

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เอการัตน์ ศิวะพงษ์ธงชัย : ผลของสารหอมบางชนิดที่มีผลต่อสรีรวิทยาและอารมณ์ความรู้สึก. (EFFECTS OF SELECTED AROMA COMPOUNDS ON PHYSIOLOGICAL ACTIVITIES AND EMOTIONS) อ.ที่ปรึกษาหลัก : ผศ. ดร.เนาวรัตน์ กาญจนาคาร, อ.ที่ปรึกษาร่วม : รศ. ดร.วรสิทธิ์ ศิริพรพาณิชย์,รศ. ดร.ชนิดา พลานุเวช

จากงานวิจัยในปัจจุบันได้แสดงถึงผลและคุณสมบัติทางการรักษาของสารหอมหลายชนิด แต่การศึกษาผลการดมของสารหอมแต่ละชนิดในแง่ของระบบประสาทส่วนกลาง สภาวะทางอารมณ์ และระบบประสาทอัตโนมัตินั้น ยังคงมีอยู่อย่างจำกัด ดังนั้น การศึกษานี้จึงมีวัตถุประสงค์เพื่อตรวจสอบผลทางสรีรวิทยาและอารมณ์ของการดมสารหอมที่ถูกเลือกมาได้แก่ *d*-borneol (BO), *d*-camphor (CH), methyl eugenol (ME), methyl chavicol (MC) ซึ่งใช้เครื่องมือทางวิทยาศาสตร์ในการวัดผลระบบประสาทอัตโนมัติ บันทึกแบบสอบถามเรื่องสภาวะทางอารมณ์ และบันทึกคลื่นไฟฟ้าสมอง งานวิจัยนี้เป็นงานวิจัยเชิงทดลองโดยใช้ pretest-posttest design คณะกรรมการพิจารณาจริยธรรมแห่งจุฬาลงกรณ์มหาวิทยาลัยอนุมัติการศึกษานี้โดยได้รับใบอนุญาตเลขที่ COA ฉบับที่ 074/2020 อาสาสมัครที่เต็มใจเข้าร่วมในการศึกษานี้ได้ส่งหนังสือยินยอมเป็นลายลักษณ์อักษรก่อนเข้าร่วมการวิจัย ได้ทำการคัดเลือกผู้เข้าร่วมที่มีสุขภาพดีจำนวนทั้งหมด 96 คน (ชายและหญิง) ที่มีอายุระหว่าง 20 ถึง 35 ปี และแบ่งผู้เข้าร่วมออกเป็น 4 กลุ่ม (ผู้เข้าร่วม 24 คนในแต่ละกลุ่ม) โดยมีการบันทึกพารามิเตอร์ระบบประสาทอัตโนมัติ ได้แก่ ความดันโลหิตsystolic และdiastolic อัตราการเต้นของหัวใจ อัตราการหายใจ และอุณหภูมิของผิวหนัง แบบสอบถามเกี่ยวกับสภาวะทางอารมณ์ได้วัดความรู้สึกส่วนตัวของผู้เข้าร่วม EEG ใช้สำหรับบันทึกคลื่นไฟฟ้าสมอง วิเคราะห์ข้อมูลโดยใช้ paired sample t-test โดยใช้แพ็คเกจสถิติ SPSS เวอร์ชัน 22 ค่า p-value <0.05 ถือว่า มีนัยสำคัญทางสถิติ การทดสอบด้วย Shapiro-Wilk ใช้สำหรับการทดสอบการแจกแจงปกติของข้อมูล ผลการวิจัยพบว่า ลักษณะทั่วไปของผู้เข้าร่วมทุกคนภายในแต่ละกลุ่มมีความคล้ายคลึงกัน ในกลุ่ม BO การดม BO เพิ่มความดันโลหิต systolic ความดันโลหิต diastolic และอัตราการเต้นของหัวใจอย่างมีนัยสำคัญทางสถิติ การดม BO ทำให้ความรู้สึกดี สดชื่น กระปรี้กระเปร่า เคลิบเคลิ้มรัญจวนใจเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ แต่ทำให้ความรู้สึกไม่ดี หงุดหงิด เครียด อึดอัด และรังเกียจ ขยะแขยงลดลงอย่างมีนัยสำคัญทางสถิติ BO เพิ่มคลื่นเบต้าในพื้นที่สมองส่วน posterior ด้านซ้ายและขวาอย่างมีนัยสำคัญทางสถิติ ในกลุ่ม CH การดม CH ลดความดันโลหิต systolic ความดันโลหิต diastolic อัตราการหายใจ อัตราการเต้นของหัวใจอย่างมีนัยสำคัญทางสถิติ ในขณะที่ CHเพิ่มอุณหภูมิของผิวหนัง การดม CH ทำให้ความรู้สึกผ่อนคลายและจิตใจสงบนิ่งเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ แต่ทำให้ความรู้สึกกระปรี้กระเปร่าลดลงอย่างมีนัยสำคัญทางสถิติ การดม CH เพิ่มคลื่นอัลฟ่าที่บริเวณสมองทั้งหมด ได้แก่ anterior ทั้งด้านซ้ายและขวา, สมองส่วนกลาง, posterior ทั้งด้านซ้ายและขวาอย่างมีนัยสำคัญทางสถิติ ในกลุ่ม ME การดม ME ลดความดันโลหิต systolic และความดันโลหิต diastolic อัตราการเต้นของหัวใจและอัตราการหายใจอย่างมีนัยสำคัญทางสถิติ การดม ME ทำให้รู้สึกเฉื่อยชาง่วงซึมเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ แต่ทำให้ความรู้สึกกระปรี้กระเปร่าและสดชื่นลดลงอย่างมีนัยสำคัญทางสถิติ การดม ME เพิ่มทั้งคลื่นเดลต้าในส่วน anterior ด้านซ้ายและขวาอย่างมีนัยสำคัญทางสถิติ และคลื่นธีต้าในส่วน anterior ด้านซ้ายและขวาและสมองส่วนกลางอย่างมีนัยสำคัญทางสถิติ ในกลุ่ม MC การดม MC ลดความดันโลหิต systolic ความดันโลหิต diastolic อัตราการเต้นของหัวใจ และอัตราการหายใจอย่างมีนัยสำคัญทางสถิติ การดม MC ทำให้ความรู้สึกผ่อนคลายเพิ่มขึ้นอย่างมีนัยสำคัญ แต่ทำให้ความรู้สึกไม่ดีและอึดอัดลดลงอย่างมีนัยสำคัญทางสถิติ การดม MC เพิ่มคลื่นอัลฟ่าในพื้นที่สมองส่วนใหญ่ ได้แก่ ส่วน anterior ด้านซ้ายและขวา สมองส่วนกลาง และส่วน posterior ด้านขวาอย่างมีนัยสำคัญทางสถิติ โดยสรุปผลจากการศึกษานี้พบว่า *d*-borneol เป็นสารหอมเพียงชนิดเดียวที่มีผลกระตุ้น ขณะที่สารหอมชนิดอื่นๆ ได้แก่ *d*-camphor, methyl eugenol และ methyl chavicol มีผลทำให้ผ่อนคลายผ่านการดมในผู้เข้าร่วมที่มีสุขภาพดี

สาขาวิชา	วิทยาศาสตร์สาธารณสุข	ลายมือชื่อนิสิต .....
ปีการศึกษา	2564	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....
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Akarat Sivaphongthongchai : EFFECTS OF SELECTED AROMA COMPOUNDS ON PHYSIOLOGICAL ACTIVITIES AND EMOTIONS. Advisor: Asst. Prof. NAOWARAT KANCHANAKHAN, Ph.D. Co-advisor: Assoc. Prof. Vorasith Siripornpanich, M.D.,Ph.D.,Assoc. Prof. CHANIDA PALANUVEJ, Ph.D.

Current literature has revealed the effects and therapeutic properties of a wide variety of aromatic compounds but studies on the inhalation effects of single aromatic compounds in terms of central nervous system, emotional states and autonomic nervous system are still very limited. So, this study aimed to examine the physiological and emotional effects of selected volatile compounds inhalation namely *d*-borneol (BO), *d*-camphor (CH), methyl eugenol (ME), methyl chavicol (MC) using scientific techniques on autonomic nervous system (ANS), self-evaluated questionnaire on emotional states and brain wave activities. Sweet almond oil was used as a carrier oil and a diluent control. This research was an experimental study using pretest-posttest design. The Ethical Review Committee from Chulalongkorn University approved this study with permissions No. COA No. 074/2020. Volunteers who were willing to participate in this study submitted a written consent form before participating in the study. A total number of 96 healthy participants (males and females) aged between 20 and 35 years were recruited and divided into 4 groups (24 participants in each group). ANS parameters including systolic, diastolic blood pressures, heart rate, respiratory rate and skin temperature were recorded. The questionnaires on emotional states measured subjective feelings of the participants. EEG was used to record brain wave activities. Data were analyzed using paired sample t-test by using SPSS statistical package version 22. A p-value <0.05 was considered significant. The Shapiro-Wilk test was used for the normality test. The results showed that the general characteristics of all the participants within each group were similar. In BO group, BO inhalation increased systolic blood pressure, diastolic blood pressure and heart rate significantly. BO inhalation increased good, fresh, active, romantic feelings significantly but decreased bad, annoyed, stressed, frustrated and disgusted feelings significantly. BO increased the beta wave over the left and right posterior brain areas significantly. In CH group, CH inhalation decreased systolic blood pressure, diastolic blood pressure, respiratory rate, heart rate significantly while increasing skin temperature. CH inhalation increased relaxed, calm feelings significantly but decreased active feelings significantly. CH inhalation increased the alpha wave power at all the brain regions namely left anterior, right anterior, center, left posterior and right posterior significantly. In ME group, ME inhalation decreased systolic blood pressure and diastolic blood pressure, heart rate and respiratory rate significantly. ME inhalation increased drowsy feelings significantly but decreased active and fresh feelings significantly. ME inhalation increased both the delta wave in left anterior, right anterior significantly and the theta wave in left anterior, right anterior and center significantly. In MC group, MC inhalation decreased systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate significantly. MC inhalation increased relaxed feelings significantly but decreased bad, frustrated feelings significantly. MC inhalation increased the alpha wave in most areas namely left anterior, right anterior, center, and right posterior significantly. In conclusion, d-borneol was the only selected volatile compound with stimulating effects while the other selected volatile compounds namely d-camphor, methyl eugenol and methyl chavicol seemed to possess sedative effects through inhalation in healthy participants.

Field of Study:	Public Health Sciences	Student's Signature .....
Academic Year:	2021	Advisor's Signature .....
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Akarat Sivaphongthongchai

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

LIST OF ABBREVIATIONS

%	Percent
℃	Degrees Celsius
μV	Microvolts
ANS	Autonomic Nervous System
cm	Centimeter
CNS	Central Nervous System
EEG	Electroencephalography
GC	Gas chromatography
GEOS	Geneva emotion and odour scale
Hz	Hertz
kg/m^2	kilogram per square meter
L/min	Liter per minute
LD50	Fifty percent lethal dose
m	Meter
mg	Milligram
mg/kg	Milligram per kilogram
ml	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
ST-SIT	Sto-Tomas Smell Identification Test
bpm	beat per minute
SO	Sweet almond oil
BO	*d*-borneol
CH	*d*-camphor
ME	methyl eugenol
MC	methyl chavicol

CHAPTER 1
INTRODUCTION

1.1 Background and significance of the study

People have been using aromatic plants for longer than recorded history. The earliest evidence of people using plants as medicine dates back to approximately 20,000 years ago. In Paleolithic times, ancient people depicted aromatic plants as medicines on the cave in Lascaux, France (Berger, 2006). Aromatic plants are capable of synthesizing essential oils which are the mixture of volatile aromatic substances. These essential oils have been renowned for their fragrance and pharmaceutical properties due to the actions of one or more of their constituents. Additionally, each constituent has its individual characteristic odor as well as therapeutic pattern affecting the body (Baser & Buchbauer, 2010).

Volatile compounds are popular in cosmetics, flavoring food and pharmaceutical industries due to the use of their fragrances and some pharmaceutical properties (Demyttenaere, 2012). Aromatic vegetables are the natural sources of volatile compounds as well as common ingredients in Asian cuisine. For instance, plants in mint family (Lamiaceae) such as sweet basil (*Ocimum basilicum*) and holy basil (*Ocimum tenuiflorum*) contain a high number of volatile compounds in their essential oils including methyl chavicol and methyl eugenol, respectively (Chalchat & Özcan, 2008; Dey & Choudhuri, 1985). Other aromatic vegetables that contain methyl chavicol and methyl eugenol which are commonly used in cooking are betel leaf (*Piper betle*) and wild betel leaf (*Piper sarmentosum*) (S. Das, Parida, Sriram Sandeep, Nayak, & Mohanty, 2016; Salehi et al., 2019). Various biological activities of methyl eugenol have been previously reported including antibacterial (Yamani, Pang, Mantri, & Deighton, 2016), anesthetic (Sell & Carlini, 1976), hypothermic, myorelaxant and anticonvulsant effects (Dallmeier & Carlini, 1981). The single use of methyl chavicol also exhibited some biological activities such as inducing muscle contraction by increasing myoplasmic calcium and blocking neuromuscular transmission (Albuquerque, Sorenson, & Leal-Cardoso, 1995), antimicrobial (Friedman, Henika, & Mandrell, 2002; Lachowicz et al.,

1998), intestinal smooth muscle relaxing (Coelho-de-Souza, Barata, Magalhães, Lima, & Leal-Cardoso, 1997), vascular smooth muscle relaxing (Soares et al., 2007) and anti-inflammatory (Ponte et al., 2012) activities.

Apart from aromatic plants, the other common volatile compounds consist in various traditional remedies are camphor and borneol. In Thailand, camphor and borneol are the important ingredients in Ya-Dom and Ya-Hom. The use of nasal inhaler (Ya-Dom) is a cultural phenomenon which has long been popular among Thai people as it offers a simple and inexpensive treatment to relieve nasal congestion, dizziness and lightheadedness (Philip, 2013). On the other hand, Ya-Hom, which literally means "fragrance medicine", has been used internally for the treatment of circulatory disorder symptoms (Sripanidkulchai, Fangkratok, Saralamp, & Soonthornchoreonnon, 2007). Camphor and borneol are obtained naturally from the tropical plants, *Cinnamomum camphora* and *Dryobalanops aromatica*, respectively. They are important economic compounds which can be extracted through steam or hydro-distillation. Moreover, these two volatile compounds are famous therapeutic drugs among Asian traditional medicine (Evans, Evans, & Trease, 2009). *d*-Borneol and *d*-camphor are the natural form of these two compounds (Guo et al., 2016; Ho, Hung, Shih, Yiin, & Chen, 2018). It has been shown that both of them possessed numerous biological activities such as analgesic (Jiang et al., 2015), anti-hyperglycemic, anti-hyperlipidemic (Madhuri & Naik, 2017), anti-oxidant, anti-inflammatory, neuroprotective (R. Liu et al., 2011), antimicrobial (Soković & van Griensven, 2006), antiviral (De Logu, Loy, Pellerano, Bonsignore, & Schivo, 2000), antitussive (Kumar et al., 2012), antinoceptive (Xu, Blair, & Clapham, 2005), insecticidal (Fu et al., 2015), antimutagenic and anticancer activities (Hamidpour, Hamidpour, Hamidpour, & Shahlari, 2013).

Furthermore, the inhalation of essential oils or volatile compounds are one of the treatment processes in aromatherapy which has long been recognized as complementary and alternative medicine (The National Association for Holistic Aromatherapy, 2019). Scientifically, the fragrance from aromatic plants containing volatile compounds are chemical component with a molecular weight of less than 300 Da that humans perceive through the olfactory system (Buckle, 2015). The sense of smell or olfactory system is one of the most significant sensory systems vital to human survival. The

olfactory system is triggered by odor stimulus including volatile compounds. When humans inhale volatile compounds, the odor molecules of volatile compounds enter the nose and trigger the olfactory nerves which are the only cranial nerves activated by external stimulus. After that, the olfactory nerves transmit the stimulation to the cerebral cortex. In other words, when the odor molecules of volatile compounds reach the cilia of nasal mucosa, they trigger the limbic system and hypothalamus through the olfactory nerves causing the effects on the nervous and endocrine systems. Therefore, the molecules of volatile compounds can activate neurotransmitters in central nervous system (CNS) including serotonin and dopamine leading to emotional states namely relaxation, stimulation, sedation and excitement (Sánchez-Vidaña et al., 2017). Moreover, many researches also reported the effects of odor on autonomic nervous system (ANS) resulting in the alteration of physiological activities including skin temperature, heart rate, respiratory rate and blood pressure (Bensafi et al., 2002; C.-J. Chen et al., 2015).

There have been a large body of current research studies carried out to examine the effects and therapeutic properties of a wide variety of essential oils. Sayorwan (2011) conducted a clinical study on the effects of lavender, rosemary, jasmine and citronella oils inhalation on emotional states, autonomic nervous system and brain electrical activity. This research study is one of the first clinical research studies in Thailand which included all the 3 levels of arousal of human responses to essential oil inhalation. The researchers concluded that inhalation of lavender and citronella essential oils reduced the autonomic arousal while rosemary and jasmine essential oils increased the autonomic arousal. Additionally, the inhalation of these essential oils indicating the alteration of brainwave showing individual emotional responses as enthusiasm, freshness and relaxing effect among healthy participants.

In general, essential oils contain major chemical compounds which may cause stimulating or sedative effects. These effects are the results of each essential oil with its chemical compounds functioning together as a whole. Nevertheless, it is still unknown which major compounds in essential oils can cause such effects. All four selected volatile compounds namely d-borneol, d-camphor, methyl chavicol and methyl eugenol used as single compounds or major compounds in essential oils are widely applied in various industries including pharmaceuticals, food and beverages as well as cosmetics.

Despite the effectiveness of essential oil inhalation and its therapeutic properties, the effects of single volatile compound inhalation are still necessary to give more insight and new knowledge to existing literature. There have been a large body of current research studies carried out to examine the effects and therapeutic properties of a wide variety of essential oils. However, the current research studies on the inhalation of single volatile compounds in terms of CNS, ANS and emotional states are still very limited. With respect to the literature review, this research study is one of the first clinical research studies in Thailand to investigate the effects of the inhalation of the selected volatile compounds namely *d*-borneol, *d*-camphor, methyl chavicol and methyl eugenol on CNS or brainwave activities, ANS including respiratory rate, heart rate, blood pressure and skin temperature as well as emotional states.

1.2 Research questions

1. How do the selected volatile compounds affect brainwave activities by electroencephalography (EEG) monitoring?
2. How do the selected volatile compounds affect autonomic nervous system (ANS) parameters: heart rate, blood pressure, respiratory rate and skin temperature?
3. How do the selected volatile compounds affect emotions measured by perception questionnaire?

1.3 Research hypotheses

The inhalation of each selected volatile compounds has effects on the central nervous system (brain wave activity), autonomic nervous system (heart rate, blood pressure, respiratory rate, skin temperature) and emotional states which are different from the inhalation of sweet almond oil.

1.4 Objectives of the research study

1. To evaluate the effects of selected volatile compounds on central nervous system.
2. To evaluate the effects of selected volatile compounds on autonomic nervous system.

3. To evaluate the effects of selected volatile compounds on emotions.

1.5 Benefits of the study

1. This research trial provides new insight and profound knowledge on how these volatile compounds function and how they trigger bodily responses including central nervous system, autonomic nervous system and emotional state among the participants.

2. The research results offer clinical significance on the applications of these volatile compounds according to their unique therapeutic properties.

3. The research results and clinical implications of these volatile compounds provide novelty and new findings to fulfill the existing literature.

4. The selected volatile compounds have potential for the alternative medicine especially aromatherapy.

1.6 Conceptual Frameworks

The conceptual frameworks of this research are scoped in a chart below.

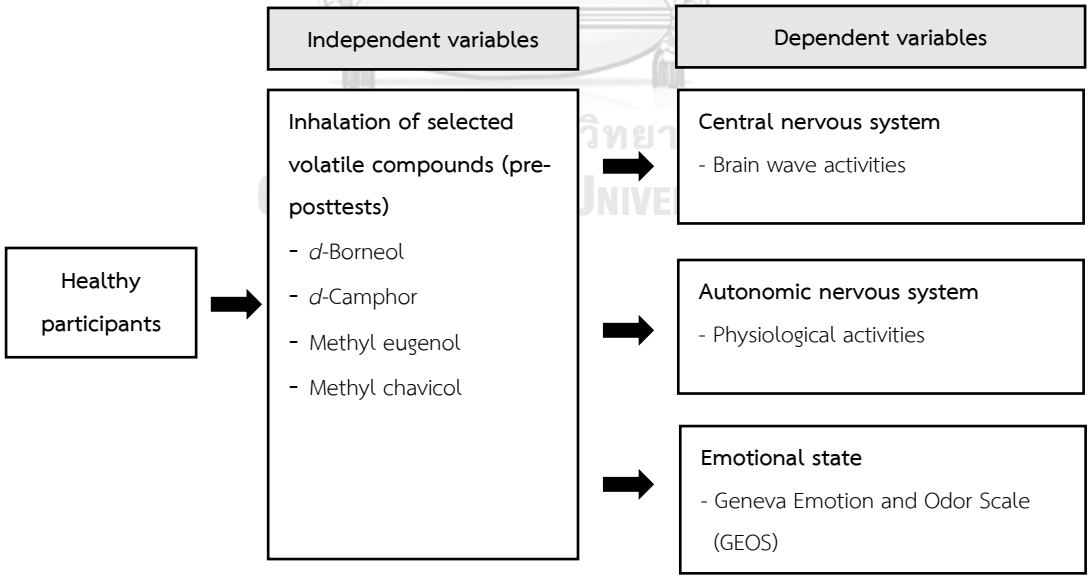
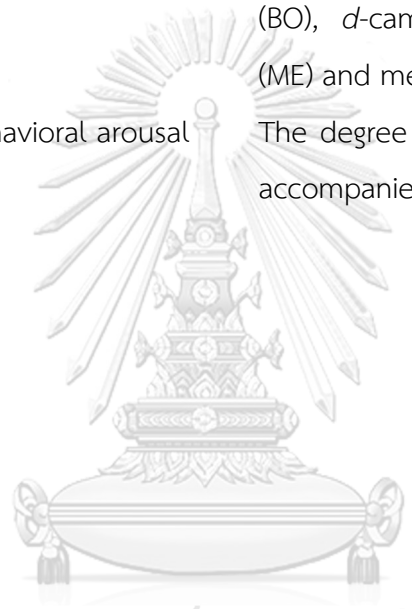


Figure 1 Conceptual Frameworks

1.7 Terms and definitions

Terms	Definitions
Arousal	The physiological and psychological state of being awoken or of sense organs stimulated to a point of perception
Artifacts	Different forms causing interferences to brainwave activities
Autonomic arousal	Changes in the activity of sympathetic and parasympathetic branches of the autonomic nervous system (ANS)
Brainwave activities	Changes in electrical signals produced by the brain which can be recorded and measured
Cortical arousal	An abrupt shift of brain wave activities in EEG recordings
Electrodes	The channels through which the electrocortical potentials are transferred to the amplification apparatus
Electroencephalography (EEG)	A graphic record of brainwave activities to identify different levels of voltage found in various cerebral locations in specific time
Emotional state	A reaction containing objective and subjective components to an emotion-specific cause in which objective components include expressive, bodily components but subjective components are composed of subjective feelings.
Excitatory Postsynaptic Potential (EPSP)	The depolarization of the postsynaptic cell caused by the spread of the action potential which transmits to the postsynaptic membrane

Terms	Definitions
Inhibitory Postsynaptic Potential (IPSP)	The signal which results in the hyperpolarization of the postsynaptic cell
Physiological activities	Mechanical, physical, and biochemical functions that determine human health
Selected volatile compounds	Four volatile compounds chosen as the interventions in this study namely d-borneol (BO), *d*-camphor (CH), methyl eugenol (ME) and methyl chavicol (MC)
Subjective behavioral arousal	The degree of activation or intensity that accompanies an emotional state



CHAPTER 2
LITERATURE REVIEWS

2.1 Nervous systems

Neurons or nerve cells are specialized cells responsible for transmitting information quickly from one part of another within an animal. They are the basic units transmitting the signals to allow humans to think, move muscles, feel the external world and create memories. Neurons contain the body, dendrites and axon which are activated by electrical signals or impulses. The neurons are classified into three categories.

1. Sensory neurons work by receiving and sending the nerve impulses from sensory organs as receptors to central nervous system, which regulates the changes inside and outside the human body.

2. Motor neurons work by sending the nerve impulses from central nervous system to the muscles as a physical reaction with the muscle contraction.

3. Interneurons are the nerve cells connected between sensory and motor organs in the central nervous system.

All the neurons of humans and other living organisms as well as their supporting cells are considered as an integrated unit called a nervous system. A neuron exists to execute interactive functions. Therefore, it has two activities which involve the conduction of a stimulus from one cell to another and the synaptic transmission or the interaction between the cells nearby. An impulse or an action potential refers to a wave of electrical depolarization which is spreading in the neuron's surface membrane. A stimulus happening to a part of the neuron triggers an impulse which goes to other parts of the cell. Technically, neurons possess long cytoplasmic processes called neurites, which terminate in the surfaces of other cells. The termination of the neurites is considered as synaptic terminals whereas the cell-to-cell contacts are known as synapses. Complex animals usually have the neurites available to create dendrites and axons which transmit signals to and away from cell body (Kiernan & Rajakumar, 2013).

Human nervous system involves three major functions: sensory input, data integration and motor output. For the voluntary level, the conscious section of the

brain allows the action. In short, the brain has three main duties which are to receive and to process sensory input, to stimulate organs and muscles as well as to initiate motivation for certain action (Mel, 2002).

Excitable nerve cells or neurons and synapses in the nervous system are produced between the neurons and link them to body centers or to other neurons. Sensory input happens when neurons, glia and synapses collect information from the whole body. Glia cells in tissues are not excitable but contribute to myelination, extracellular fluid and ionic regulation. The neurons function on excitation or inhibition. The balance between excitation and inhibition is a basic characteristic of in vivo network activity. The neuronal networks in vivo function in a balanced pattern in which excitatory and inhibitory neuron activities preserve highly correlated levels of activity (Dehghani et al., 2016). Nerve cells are different in size and location but the way they communicate with each other defines their function. These nerves transmit impulses from sensory receptors to the brain and spinal cord. When the brain processes the data, it is called data integration taking place in the brain only. After the brain completes the data integration, impulses from the brain and spinal cord are transmitted to glands and muscles, this process is known as motor output.

Human nervous system is very crucial to sustain human life since it is one of the major systems regulating and maintaining bodily functions as well as responding to stimulus. The two major sections which constitute the nervous system are central nervous system (CNS) and peripheral nervous system (PNS), in which the nerves bring impulses to and from the central nervous system. The central nervous system (CNS) encompasses the brain and spinal cord protected by the cranium and the vertebral column. The brain is the body's command center. The CNS comprises many centers which receive and perform sensory input, data integration and motor output. These centers are further divided into higher centers connecting the brain by effectors and lower centers namely brain stem and the spinal cord. The autonomic nervous system (ANS) and sensory-somatic nervous system (SNS), a nervous system under the peripheral nervous system (PNS), functions to maintain the conditions in the human body. Thus, the nervous system can be summarized as the chart in Figure 1. There are four important functions of nervous system described below.

1. Nervous system activates important physical movements including the ones which facilitate life.
2. Nervous system senses the impulses from both internal and external stimulus.
3. Nervous system functions with the endocrine system to give responses to maintain homeostasis.
4. Nervous system regulates behaviors, thoughts and emotions.

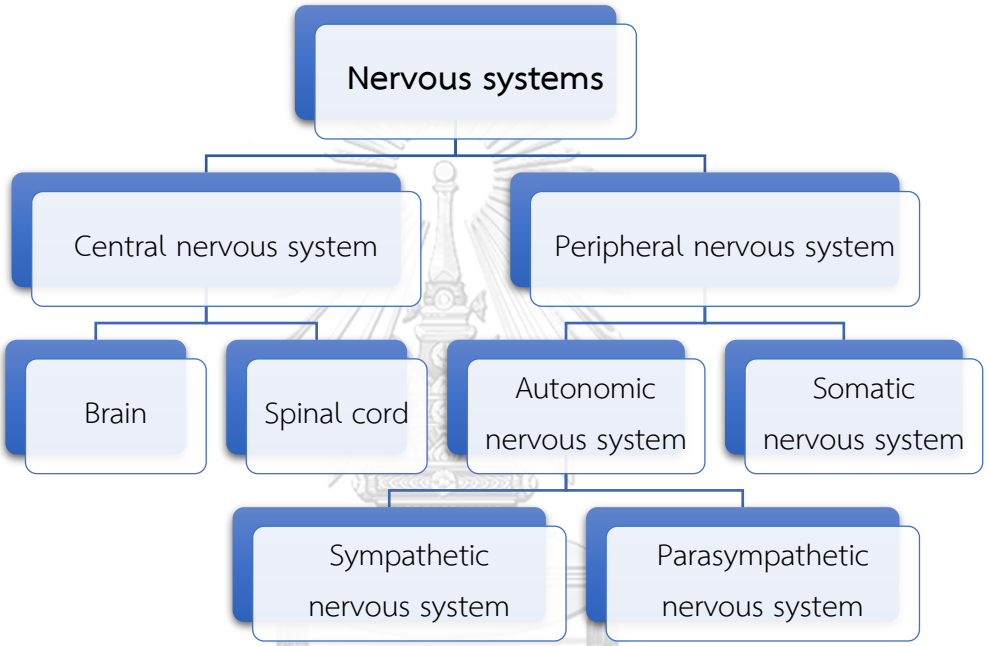


Figure 2 The chart of nervous systems
Adapted from FitzGerald, Folan-Curran, and Tibbitts (2002)

2.1.1 Central nervous system

The central nervous system (CNS), a part of nervous system, constitutes the brain and the spinal cord, which are the largest part of the nervous system. The CNS is the main system whose role is to process information and to give motor output as a response to a sensory input. When the CNS gives such a response automatically, the CNS giving automatic responses is referred to as an autonomous system (Brodal, 2014). When the brain and spinal cord work together, they become the primary regulators and integrators of nerve signals (Ohtaki & Shioda, 2015).

The cranium and the vertebral column protect CNS which is connected by bundles of axons known as nerves to all the body parts. CNS consists of neuronal cell bodies which reside in the regions called gray matter. In contrast, white matter is the regions of CNS tissue which have axons without neuronal cell bodies. The outer, thicker layer of the brain functioning as a protective shield is regarded as the dura matter. Nerves are considered as the most unique features of the peripheral nervous system (PNS). Moreover, neuronal cell bodies exist in nodular structures known as ganglia (singular: ganglion) in the peripheral nervous system, which is another part of the nervous system. So, the peripheral nervous system contains the nerves and ganglia located outside CNS.

In summary, the nervous system including nerves, brain, spinal cord and sensory organs are responsible for controlling and coordinating bodily activities which need immediate reactions. It is so significant in identifying external changes and responding to them. It also regulates higher functions such as memory, consciousness and creativity (Lauralee Sherwood, 2015).

2.1.2 Human brain

Human brain is the most complicated organ located in the cranial cavity. As a jelly-like mass of tissue, it consists of one billion nerve cells called neurons and the higher nerve centers whose duties are to coordinate the sensory and motor systems of the brain. It produces action, memory, thoughts, emotions and experience of the world. As the most anterior region of the brain, the cerebrum is separated by a deep crevice named as the longitudinal sulcus, which divides the celebrum into the right and left hemispheres. Cerebral cortex, basal ganglia and the limbic system are located in these hemispheres. A bundle of nerve fibers known as the corpus callosum connects these 2 hemispheres together. The right hemisphere is in charge of the left side of the body while the left hemisphere is in charge of the right side of the body. Human brain consists of 3 parts based on their locations: forebrain (Prosencepphalon), midbrain (Mesencephalon) and hindbrain (Rhombencephalon) (Figure 3).

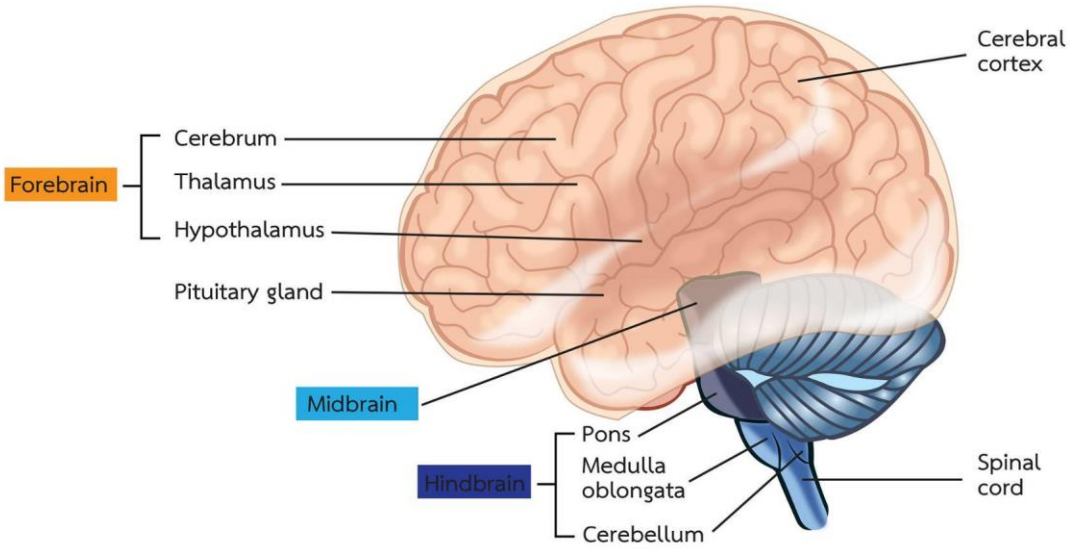


Figure 3 The main parts of the brain based on their location

Adapted from FitzGerald et al. (2002)

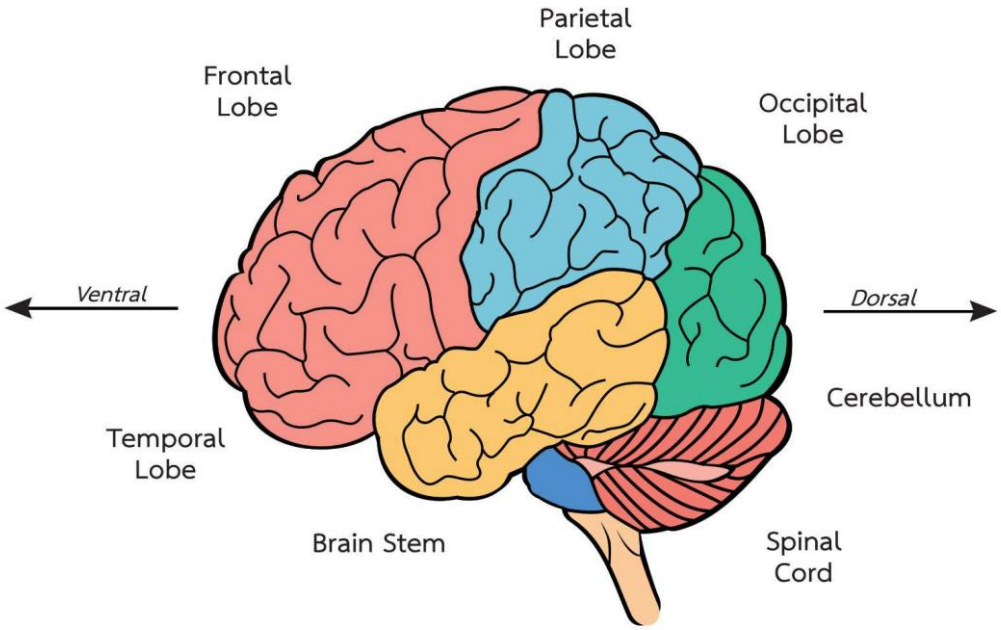


Figure 4 Medial aspect of the human brain

Adapted from FitzGerald et al. (2002)

In forebrain, each of these 2 hemispheres are classified into four different lobes as shown in Figure 3: the frontal lobe for specialized motor control, planning,

learning and speech, parietal lobe for somatic sensory functions, occipital lobe for vision control and temporal lobe consisting of speech and hearing centers. Forebrain is the center of perception, cognition, conscious awareness and voluntary action which takes the nerve impulses through extensive networks of sensory and motor neurons of the brain stem and spinal cord. The forebrain is divided into two regions: telencephalon and diencephalon. Telencephalon is referred to as cerebrum, which is the main region of the forebrain. Diencephalon is further separated into two sections: hypothalamus and thalamus. The forebrain is the largest and most developed structure of the brain. It functions to interpret the nerve impulses in terms of movement, communication, inhalation and memory. As a region of the forebrain, cerebral cortex serves as a speech and linguistic center within frontal lobe. The forebrain also regulates the inhalation by the olfactory bulb in the forebrain.

The brain stem contains the lower nerve centers divided into midbrain, pons and medulla. The midbrain works as the main reflex center linked to the visual and auditory reflex. The midbrain governs the motor neuron of basal ganglia which functions to control the bodily movements.

Hindbrain consists of medulla and pons. Medulla is the control center in charge of digestive, respiratory and cardiovascular functions. Pons has the control centers governing respiration and inhibitory functions and it communicates with the cerebellum. Cerebellum is the brain region located posterior to the medulla oblongata and pons. It cooperates with skeletal muscles to create smooth movements. The cerebellum receives inputs from different sensory systems including ears, eyes, muscles, joints about the current position of human body called proprioception. Besides, the cerebellum receives outputs from cerebral cortex about where these body parts should be. After the cerebellum finishes processing the output, it transmits motor impulses from the brainstem to the skeletal muscles. So, the cerebellum is mainly responsible for cooperation, body balance and posture. It helps humans in learning a new motor skill namely playing sports or a musical instrument. The cerebellum has a role in emotions as well

2.1.3 Spinal cord

The spinal cord is referred to a long cylinder of nerves which runs from the base of human brain via the vertebral canal and backbone. As a part of central nervous system (CNS), it is divided into various sections. Each section consists of a pair of roots from nerve fibers. The two roots in each pair are known as the dorsal towards the back and the ventral from the back. The nerve impulses from any organ in human body transmit both input and output via the spinal cord to the brain or related organs. Its functions are associated with motor and somatosensory organization (Figure 5).

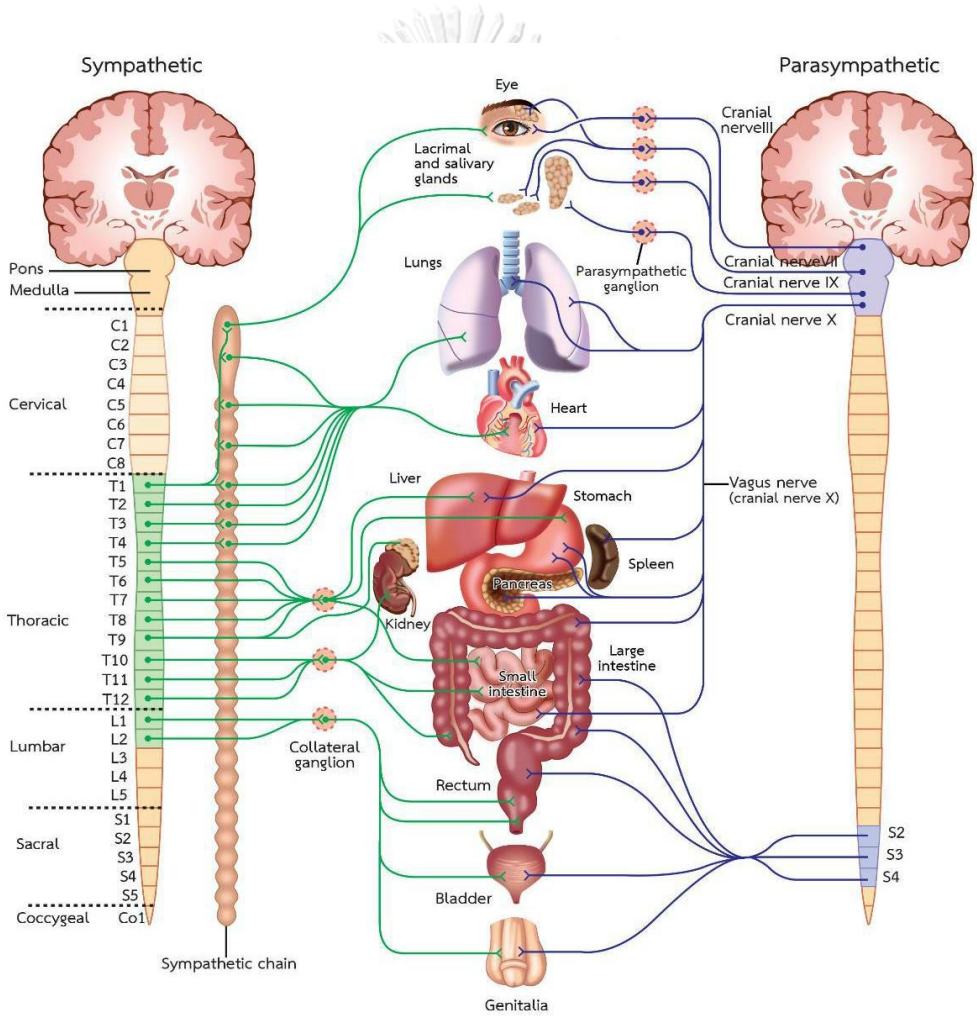


Figure 5 Comparing sympathetic and parasympathetic nervous systems

Adapted from Fix (1995)

2.1.4 Peripheral nervous system

Peripheral nervous system (PNS) functions as a receiver and a sender of the nerve impulses to the central nervous system (CNS). PNS as a branched system from CNS is classified into two systems: the somatic nervous system (SNS) and the autonomic nervous system (ANS). ANS monitors all autonomic actions including reflexes and activities during sleep or unconsciousness. Humans are not aware or conscious of most ANS activities which are carried out automatically. ANS is responsible for vital bodily functions such as heart rate, respiration rate, digestion, salivation, perspiration and so on, which are performed unconsciously to keep human body well and alive. It is the communication gateway between the central nervous system to the whole body via nerve impulses which control the functions of the human body.

Peripheral nervous system is distinguished into two types based on their functions: voluntary nervous system and involuntary nervous system.

1. Voluntary nervous system or somatic nervous system is a structure monitoring the skeleton muscles triggered by environmental stimulus.

2. Involuntary nervous system is considered as a part of the nervous system which supervises major involuntary bodily functions. The system functions automatically under the command of the brain and the spinal cord as reflex action during the interaction between the stimulus and the sensory organs.

2.1.5 Autonomic nervous system

Autonomic nervous system (ANS) is a section under the peripheral nervous system which affects the functions of internal organs. It is a comprehensive network of integrated neurons spreading throughout the human body. ANS is the major system governing bodily functions including heart rate, respiratory rate, sexual arousal and blood pressure. The ANS is further divided into 2 major subdivisions which are sympathetic nervous system and parasympathetic nervous system.

Sympathetic nervous system stimulates the human body to be prepared and active for the “fight or flight” response. Such response is referred to as sympathetic-adrenal response of human body because the pre-ganglionic sympathetic fibers in the adrenal medulla release acetylcholine, which activates adrenaline release.

Parasympathetic nervous system calms down the human body through “rest and digest” response. The parasympathetic nervous system conserves energy since it decreases the heart rate, increases gland and intestinal activity and relaxes sphincter muscles in the gastrointestinal tract. After highly stressful situations, the parasympathetic nervous system has a backlash response which balances the reaction of the sympathetic nervous system.

2.1.6 Sensory-somatic nervous system

The sensory-somatic nervous system contains cranial and spinal nerves. The sensory organs including nose, skin and eyes transmit the signals as sensory input via sensory neuron to the central nervous system. Somatic nervous system is a division of the peripheral nervous system related to the voluntary control of bodily movements via skeletal muscles and reception of external stimulus. The somatic nervous system contains afferent fibers which gain information from external sources and efferent fibers which control muscle contraction. So, the somatic system involves the pathways from the skin and skeletal muscles to the central nervous system. This system is also related to activities which require consciousness.

Cranial nerves refer to the nerves of the human brain arising directly from the brain and entering the skull or the cranium. There are 12 pairs of cranial nerves arising from the lower part of the brain. Each of these pairs goes into the skull to the periphery or outer border of the body. The main function of cranial nerves is to transmit information between the brain and other body organs especially head and neck. The cranial nerves are included as components of the peripheral nervous system (PNS). The cranial nerves supply sensory and motor nerves for the head and neck particularly general and special sensory as well as voluntary and involuntary muscle control (Wilson-Pauwels, Akesson, & Stewart, 2002). The 12 cranial nerves are shown in Figure 6.

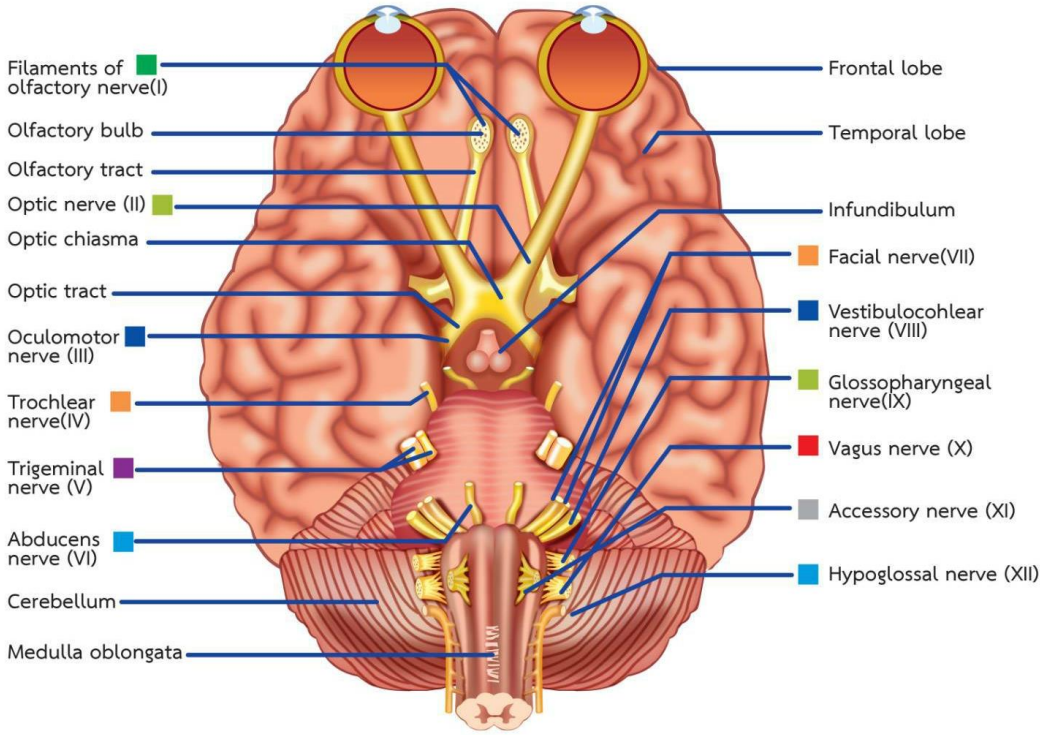


Figure 6 The human cranial nerves and their areas of innervation
Adapted from Young, Young, and Tolbert (2014)

Spinal nerves are considered as mixed nerves which bring motor, sensory and autonomic signals between the spinal cord and the whole body. The vertebral column consists of 31 pairs of spinal nerves as shown in Table 1. An area of skin that is supplied by a single spinal nerve is called dermatome which consisting of eight cervical nerves, 12 thoracic nerves, five lumbar nerves and five sacral nerves. Additionally, each of these nerves communicate sensation, such as pain, from a particular area of the skin to the brain as shown in Figure 7.

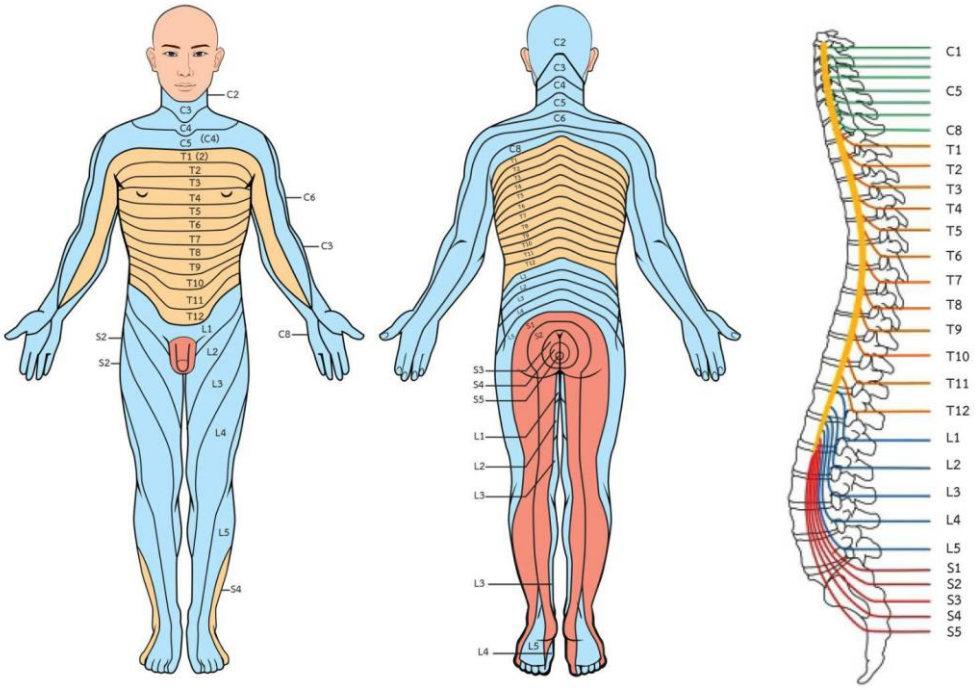


Figure 7 Location of spinal cord and dermatome map

Adapted from Kandel, Schwartz, and Jessell (1991)

Table 1 Spinal nerves and their functions

Level	Motor Function
C1-C6	Neck flexors
C1-T1	Neck extensors
C3, C4, C5	To supply diaphragm
C5, C6	To move shoulders, raise arms (deltoid), flex elbow (biceps)
C6	To rotate (supinate) the arm externally
C6, C7	To extend elbow and wrist and pronate wrist
C7, C8	To flex wrist
T1-T6	Intercostal and trunk above the waist
T7-L1	Abdominal muscles
L1-L4	To flex thighs
L2, L3, L4	To adduct thighs and extend legs
L4, L5, S1	To abduct thighs and flex legs
L5, S1, S2	To extend legs at the hip, plantar flex feet and toes

2.2 Human olfactory systems

Olfaction refers to the sense of smell which is one of human five main senses originally described by Aristotle (Sorabji, 1971). It is one of the most important sensory systems which humans rely on every day as the primary sense that detects chemicals dissolved in the air, which influences physiological effects of stress, emotional states and working capacity. The volatile chemicals that evoke a sensation of smell are called odors, odorants, fragrances or aromas which humans can perceive by using the olfactory system. These volatile chemicals can reach the olfactory sensory cells in humans via orthonasal route (nose) and retornasal route (mouth). Most of this literature review is devoted to olfaction via orthonasal route in humans.

2.2.1 Olfactory structure and function

Olfactory system is a complex process that depends on sensory organs, nerves and the brain. The main anatomical structures of the olfactory system are shown in Figure 8 and describes in Table 2.

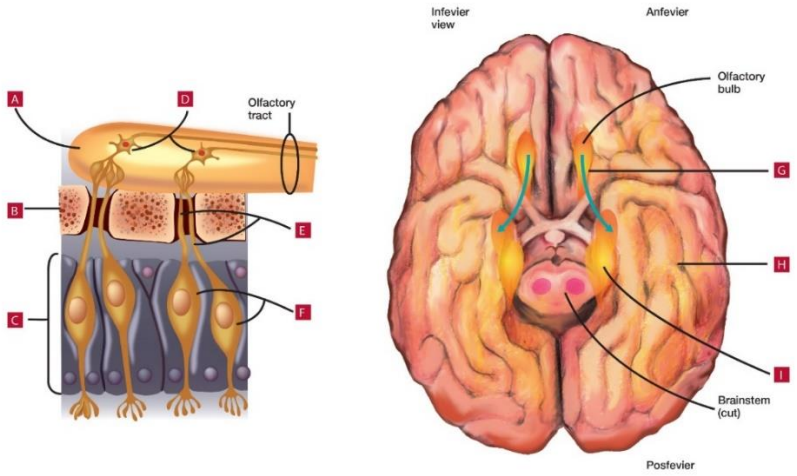


Figure 8 Olfactory connections projected on the basal aspect of the brain: (A) olfactory bulb, (B) Cribriform plate, (C) olfactory epithelium, (D) Mitral cell of the olfactory bulb, (E) filament of olfactory nerve, (F) olfactory sensory neuron, (G) olfactory bulb, (H) olfactory projection area, (I) uncus

Adapted from Young et al. (2014)

Table 2 Anatomical structures of the olfactory system

Structure	Description
Nasal cavity	A region that is lined with mucosa and divided by the nasal septum into right and left passages behind the nose.
Olfactory epithelium	The specialized type of epithelial cells located in the nasal cavity which contains olfactory nerve cells that send the impulses to the olfactory bulbs. The olfactory epithelium is divided into three major cells which are olfactory receptor cells, supporting cells and basal cells. In other words, peripheral processes of the primary sensory neurons in the olfactory epithelium function as sensory receptors while supporting cells defend olfactory receptors and provide optimum environment for the receptors.
Cribriform plate	The ethmoid bone that separates the brain and the nasal cavity. Olfactory nerve fibers extend through this porous bone to the olfactory bulbs.
Olfactory nerve	The first cranial nerve (CN I) that contains sensory nerve fibers extending from the mucous membrane, through the cribriform plate, to the olfactory bulbs.
Olfactory bulbs	A neural oval-shaped structure in the anterior part of the brain (forebrain), located in the left and right hemispheres where the first cranial nerve end and the olfactory tract begins. Each olfactory bulb is located above the cribriform place of the ethmoid bone and on the ventral aspect of the frontal lobes. The olfactory bulbs are characterized by olfactory nerves which synapse on mitral cells. Then, mitral cells with axons conveying the information travel to the olfactory cortex.

Table 2 Anatomical structures of the olfactory system (Cont.)

Structure	Description
Olfactory tract	A long tube that acts like a bridge between the olfactory bulb and the cerebral hemispheres. The olfactory tract is divided into 2 sections which are medial olfactory stria and lateral stria. The medial olfactory constructs a link between subcallosal area, paraterminal gyrus and anterior commissure while the lateral stria creates a network with parahippocampal gyrus, ambient gyrus, uncus and amygdaloid body.
Orbitofrontal cortex	The region in the brain (cerebral cortex) that processes information about odorants and receives nerve signals from the olfactory blubs.

2.2.2 Human olfactory process

In humans, the molecules of the volatile chemicals flow into the nasal cavity and interact with specific olfactory receptor neurons in olfactory epithelium. The olfactory receptor neurons have a single dendrite that extends to the outermost layer of the epithelium, where cilia emerge from the end of the dendrite and spread over the surface of the olfactory epithelium. The olfactory sensory neurons transmit the signals to the brain through the olfactory bulb and higher olfactory cortex to the prefrontal cortex, orbitofrontal cortex and limbic system especially the amygdala-hippocampal formation, which is significant for emotional expression and memory (Angelucci et al., 2014). The signals regulate the brain functions namely thoughts, emotional states and memory. Previous research explains that the inhalation of volatile oils affects the brain functions highly because the chemical compounds can pass over the blood-brain barrier and reach the receptors in the CNS directly (Kutlu, Yılmaz, & Çeçen, 2008; Touhara & Vosshall, 2009).

Olfactory system consists of olfactory nerves which transmit information of stimulus to the sensory cortex. The structures in the central nervous system (CNS) related to olfactory system are regarded as the “nose” brain or rhinencephalon. When all

the olfactory organs function together as an integrated olfactory system, the processes in which the information received from scent molecules is sent from the olfactory receptors to olfactory cortex is considered as olfactory pathways (Figure 9). Another system that is significant and related in emotion and olfactory system is limbic system.

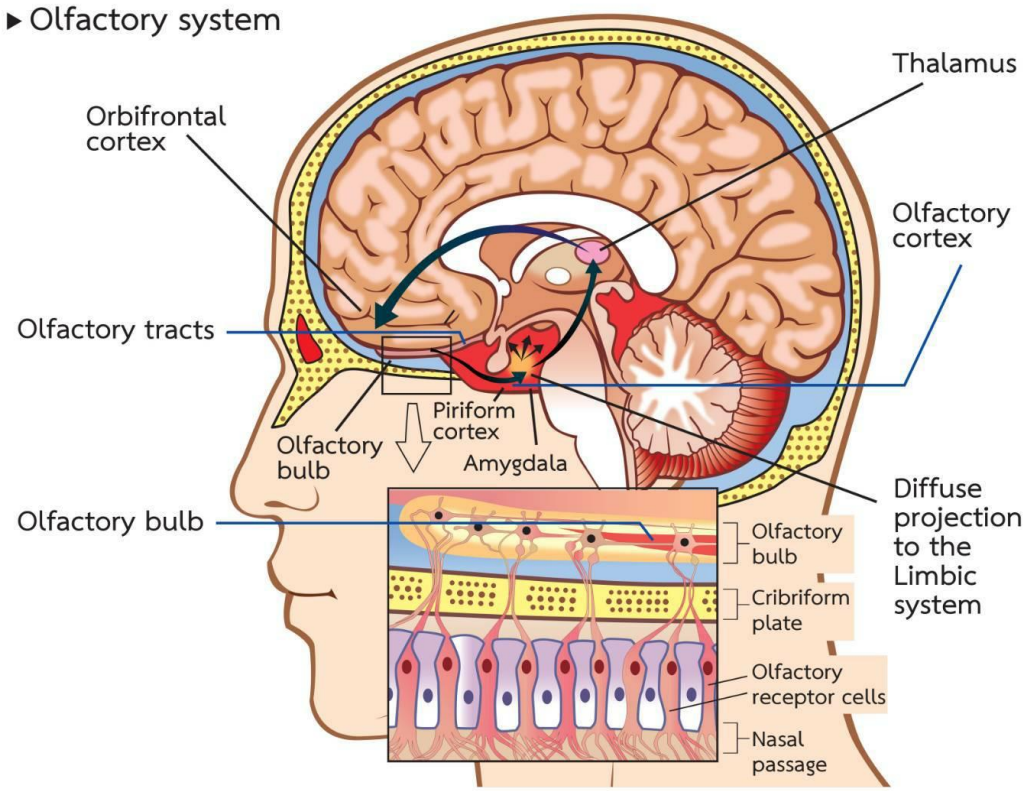


Figure 9 Olfactory system

Adapted from Nolte (1993)

2.2.3 Limbic system

The limbic system is a complex set of structures located under the cerebrum and on both sides of the thalamus including thalamus, hypothalamus, hippocampus, amygdala, and several other nearby areas (Figure 10). It is a network of interdependent nuclei and cortical structures which can be found in the telencephalon and diencephalon. These nuclei are responsible for many duties including basic survival, preservation and supervision over autonomic and endocrine function responding to emotional

stimulus. It integrates primitive emotions and higher mental functions into one system. The limbic system is also known as the emotional nervous system. It is in charge of emotional states and higher mental functions including learning and memory formation. The limbic system is also considered as the feeling and reacting brain because it functions as a gateway between the cognitive brain and the output mechanisms of the nervous system.

When odor molecules of certain volatile compounds enter the human body, these molecules are absorbed into different parts of the human body based on the bodily requirement and usage for optimum benefits. If the human body does not require the volatile compounds anymore, the human body will excrete it within 48 hours. The pathway of volatile compound inhalation begins when odor molecules go through the nose and activate the olfactory system by stimulating the olfactory receptors within it. Then, the molecules reach the olfactory bulb sending the odor input to the limbic system, an inner complex ring in the brain. The limbic system responds the odor input via 53 regions and 33 related tracts. The odor input is transmitted further to the amygdala and the hippocampus, which interpret the odor input and react through physiological effects and responses including emotional states, sedative effects, memories, depression and energizer. The effects of odor molecules in volatile compounds depend on the functions of limbic system which consists of four major sections: thalamus, hypothalamus, amygdala and hippocampus. Thalamus works by transmitting the information from sensory receptors to the brain. Hypothalamus regulates sexual and other stimuli. Amygdala monitors emotional states including fear and anxiety. Hippocampus has a significant role in learning and cognition. To activate the limbic system, sensory neurons in the nasal cavity transmit the odor molecules of essential oils (Lemogne et al., 2006; Olsen, Moses, Riggs, & Ryan, 2012; Petrovich, Canteras, & Swanson, 2001; Small, Schobel, Buxton, Witter, & Barnes, 2011).

The thalamus is one of the most cognitively flexible brain regions, which mean that it is related to a wide variety of behavioral tasks. The thalamus is referred to as a passive relay station of information from sensory organs or subcortical structures to the cortex. It has broad connections with the whole cerebral cortex, which functions to combine information processing between cortical regions. The

thalamus consists of two types of nuclei: first order and higher order thalamic nuclei (Sherman, 2007). First order thalamic nuclei including the lateral geniculate nucleus (LGN) and the ventral posterior (VP) nuclei receive inputs from sensory pathways or other subcortical brain regions. On the contrary, higher-order thalamic nuclei including the mediodorsal (MD) and the pulvinar nuclei receive inputs from the cortex (Hwang, Bertolero, Liu, & D'Esposito, 2017).

The hypothalamus is a small region in the brain located below the thalamus on both sides of the third ventricle. As the basic output point for the limbic system, hypothalamus is responsible for many crucial relations. The hypothalamus is associated with septal nuclei, the frontal lobes and the brain stem reticular formation through the medial forebrain bundle. The hypothalamus consists of centers which manage behavioral function, endocrine function, sexual function as well as autonomic regulation. Many kinds of inputs from body parts and olfaction are needed to activate the hypothalamus to complete these functions. The hypothalamus has a crucial role in emotions particularly anger and pleasure.

The amygdala is a large nuclear complex found next to the hippocampus within the temporal lobe. The term amygdala is drawn from its shape which is similar to almond or amygdale in Greek. The amygdala is known for its role in emotional expression and visceral or instinctive functions. Therefore, it is regarded as a part of the limbic system. The amygdala is a significant region found in the anterior temporal lobe in the uncus. The amygdala has many interactive relations with other regions of the brain namely hypothalamus, the thalamus, septal nuclei, cingulated gyrus, orbital frontal cortex, hippocampus, brain stem and parahippocampal gyrus. The olfactory bulb is the one part which transmits input to the amygdala but it does not receive interactive projections from the amygdala. It is an important hub for cooperating autonomic, behavioral and endocrine reactions to external stimulus particular the one with emotions. So, the stimulus to the amygdala can cause behavioral and emotional responses particularly anger. The stria terminalis, which is a long circuitous pathway, connects the Amygdala with the hypothalamus. The major duties of the amygdala cover three control areas which are emotions particularly fear and anger, sexual behavior as well as food and water intake. Moreover, the amygdala regulates learning and motivation.

Hippocampus is considered as an ancient region of cerebral cortex consisting of three layers located in the medial part of the temporal lobe surrounded by the medial wall of the lateral ventricle. The hippocampus has many responsibilities. It regulates corticosteroid creation. It provides the insight of spatial associations with the surroundings. Moreover, the hippocampus manages several declarative memory duties. Memory is divided into two types which are implicit and explicit. The examples of explicit or non-declarative memory are learning skills and associative learning including conditioned and emotional reactions. Explicit or declarative memory is the memory related to events and facts. Any memories which can be described into words are the examples of explicit memory. So, explicit memory requires many body regions to function together to form it, one of which is the hippocampus whose role is dominant in short-term memory leading to long-term memory models.

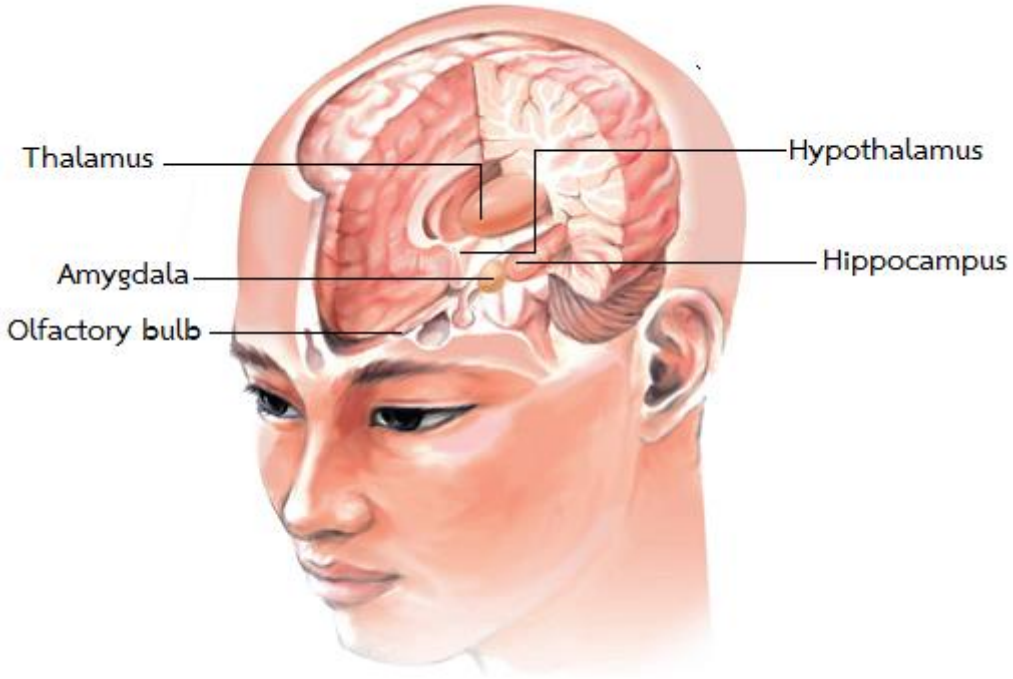


Figure 10 Structure components of the limbic system

Adapted from Kandel et al. (1991)

2.3 Emotional states

Many researchers who are interested in emotional states have proposed the relevant definitions of emotional state. For example, Schachter and Singer (1962) defined emotional states as a function of a state of physiological arousal and of cognition suitable to this state of arousal. According to the structuralist paradigm, emotional state means a reaction containing objective and subjective components to an emotion-specific cause in which objective components include expressive, bodily components but subjective components are composed of subjective feelings.

Ehrlichman and Bastone (1992) suggested another definition of emotional states. The researchers proposed that there is a significant correlation between olfaction and emotion. They believed that the experience of odors is related to hedonic tone. This proposition means that the most unique characteristic of odor is its pleasantness or unpleasantness because this characteristic is viewed as intrinsic property of odors. Therefore, whenever odors are employed in any experiment, this hedonic factor usually comes up. The researchers cited that odors have a direct impact on mood or emotional state because inhaling specific odors can cause emotional state to change. Such a direct impact on emotional state can be divided into two types which are specific and nonspecific. The specific aspect is that particular odorants have outstanding impacts on emotional state including relaxation, arousal or sensuality. The researchers emphasized that odors possess powerful motivational influence because one of the significant duties of odors is to regulate physical response to approach or avoid based on olfactory stimulus available. The sense of smell is so significant in a way that odors can provoke a wide variety of emotional states or feedbacks.

More recently, Rolls (2013) introduced a possible definition of emotional states. The researcher described emotional states as conditions evoked by rewards and punishers. The main function of emotional states is to perform to achieve rewards or avoid punishers. The researcher pointed out that remembering any reinforcing events by external reinforcing stimulus can trigger various emotional states. Stimulus can be classified as unlearned or primary reinforcers including the smell of food and secondary reinforcers through associative learning. The brain structures react to this stimulus via emotional states and behavioral responses. In particular, when humans receive stimulus

via the sensory systems including the sense of smell, this stimulus can trigger emotions and affect cognition as well (Adolphs, 2010).

The odor molecules of essential oils can affect emotions and cognition leading to changing behaviors as bodily responses identified by physiological parameters including skin temperature, heart rate, which reflects human emotional reactions. To evaluate emotional reactions, the Geneva Emotion and Odor Scale (GEOS) were designed to serve as a measurement tool to evaluate the subjective affective experience including feelings elicited by odors. The GEOS has classified the subjective feelings into five categories.

1. Pleasant feeling is associated to well-being and happiness. This feeling also signifies ecstatic feeling. The terms used to express this feeling include feel good (รู้สึกดี), which is used in this research.

2. Unpleasant feeling refers to disgust and irritation including other annoying feelings. The terms which describe this feeling are feeling bad (รู้สึกไม่ดี)uncomfortable (รู้สึกอึดอัด), disgusted (รู้สึกขยะแขยง), stressed (รู้สึกเครียด) and frustrated (รู้สึกหงุดหงิด)

3. Sensual feeling happens to humans when they have social interaction especially sociosexual behaviors. The terms used to describe it are desire and sensual. This research has assigned the term, romantic (รู้สึกเคลิบเคลิ้มรัญญวนใจ), for this feeling.

4. Relaxation is directly in line with soothing effects in which essential oils can create meditative, relaxing feelings. The terms which explain this feeling are serene (รู้สึกจิตใจสงบนิ่ง), relaxed (รู้สึกผ่อนคลาย) and drowsy (รู้สึกง่วงซึม)

5. Refreshing feeling is the result of purification, stimulation and physiological response. The terms related to this feeling are energetic (รู้สึกกระปรี้กระเปร่า) and refreshed (รู้สึกสดชื่น)

The GEOS has been proven to be very reliable based on previous research because its domain-specific set of scales is appropriate to evaluate the subjective feelings induced by odors (Porcherot et al., 2010). Therefore, this research has adjusted the conceptual model of GEOS to measure the subjective feelings of the participants after they inhaled each selected volatile compound under investigation.

2.4 Electroencephalography

Electroencephalography (EEG) is a graphic record of brainwave activities to identify different levels of voltage found in various cerebral locations in specific time. EEG refers to a monitoring technique to detect electrical activity of the brain. EEG evaluates the voltage fluctuations caused by ionic current within cerebral neurons. Cerebral neurons induce the EEG signal influenced by many factors including electrical conductive properties of the tissues between the electrical source, the recording electrode on the scalp, the conductive properties of the electrode and the orientation of the cortical generator to the recording electrode. It means that it is difficult to point out the exact location of the EEG generator by depending on scalp-recorded EEG information only (Olejniczak, 2006).

Input from a single active electrode is transferred to the amplifier and compared with ground or earth. So, the output means the potential difference between the active electrode and ground. The output could display electrocortical potentials and other environmental potentials influencing the electrode. Recording the potential difference between two electrodes on the scalp are known as bipolar recording which connects a chain of successive electrodes electronically. Potential difference can be performed by comparing the voltage at one electrode with the voltage influencing surrounding electrodes. In contrast, recording the potential difference between a scalp electrode and another point as the reference is referred to as referential recording, in which the potential difference between a certain electrode and a referential electrode is recorded. The reference could be located anywhere but contamination and artifacts should be taken into consideration. A commonly used reference is the common average reference which is to compare the voltage of an event happening under a certain electrode (input I) with the average voltage recorded by all the electrodes on the scalp (input II).

The main sources of EEG originate from cerebral cortex and 3-dimensional potential fields, which represent projected 2-dimensional fields in the function of voltage in recorded time. Visible EEG can be visualized via a combined synchronous electrical activity of around 108 neurons in a cortical area of at least 6 centimeters. The main generators of EEG fields recorded on the scalp are graded synaptic potentials

namely EPSPs and IPSPs of the pyramidal neurons. Excitatory Postsynaptic Potential (EPSP) is defined as the depolarization of the postsynaptic cell caused by the spread of the action potential which transmits to the postsynaptic membrane. In contrast, Inhibitory Postsynaptic Potential (IPSP) is referred to the signal which results in the hyperpolarization of the postsynaptic cell. Therefore, the summation of IPSPs and EPSPs in a neuronal net originate electrical currents which transmit in and around the cells and lead to a field spreading out from the origin of electrical event. The shape of potential fields is normally oval and could be limited or widespread.

The total amount of potential at postsynaptic site can be divided into depolarization or hyperpolarization. EEG can record the activity of cortical neurons near the scalp (Figure 11). However, EEG may not detect the activity of neurons generated by the inner cerebral structures including brain stem, hippocampus, and thalamus.

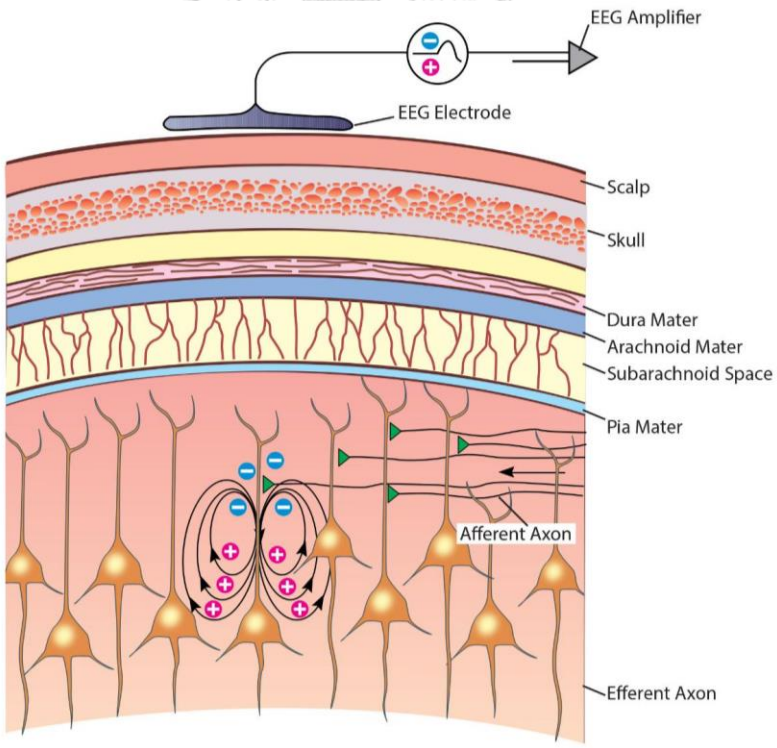


Figure 11 The generation of very small electrical fields by synaptic currents in pyramidal cells

Adapted from Bear, Connors, and Paradiso (2016)

2.4.1 General principles of EEG signal

A large number of cerebral neurons which are synchronized together and reach a peak at the scalp lead to the EEG signal. The EEG signal signifies the different levels of voltage between electrodes and reference electrode on the scalp in recorded time. The EEG signal will be processed from an analogue to a digital format to illustrate the biological signal via the computer program. The EEG signal seems to be so tiny that it has to be amplified. The tools such as gain, sensitivity and filtering are applied to adjust the EEG signal to make it detectable. The EEG signal can be explained in its frequency (Hz, cycles per second) and amplitude (uV, microvolt). Two processes which mediate the mechanisms behind EEG rhythmicity are the interaction between cortex and thalamus and the activity of thalamic pacemaker cells which cause rhythmic cortical activation.

The main factors influencing the amplitude of EEG signal changes include spatial (position) and temporal (time) parameters. The EEG amplitudes range from 10 to 100 uV and 1-2 m V (millivolt) detected from the scalp. In addition, the size of amplitude is based on the synchronization of brainwave activity. The more cerebral neurons are triggered at the same time, the higher the amplitude. Although the EEG signal offers high temporal resolution in milliseconds, it has low spatial resolution due to the limited number of electrodes and the signal changes after going through the volume conductor like skull and brain tissues. The basic rhythmic frequency of the normal awake adult brain is known as the posterior dominant rhythm (PDR) composed of sinusoidal or rhythmic alpha waves.

2.4.2 EEG protocol

There are various stages of EEG protocol to record brainwave activities which mean changes in electrical signals produced by the brain which can be recorded and measured. Researchers can choose many types of recording tool such as electrodes, caps or nets to record brainwave activities. The International 10-20 System of Electrode Placement introduced by Dr. Herbert Jasper seems to be a logical, generally accepted system of electrode placement as shown in Figure 11. Electrodes with odd numbers are on the left while those with even numbers are on the right. Its numbering was

adjusted based on the last edition to a 10-10 system. Both the 10-10 and 10-20 systems rely on precise measurements of the skulls divided into three planes: sagittal, coronal and horizontal. Sagittal plane includes the nasion or the depression at the top of the nose over the top and the head to the inion which is the prominence in the midline at the base of the occiput. Coronal plane starts from the point anterior to the tragus, which is the cartilaginous protrusion at the front of the external ear, extended to the same point on the other side. Horizontal plane can be measured from Fpz to T7 to Oz on the left and from Fpz to T8 to Oz on the right.

The International 10-20 System guarantees that the electrode names and locations are constant and in line with other laboratories. When any clinical uses or research studies require greater spatial resolution, researchers can add more electrodes apart from the standard set-up.

Electrodes are the channels through which the electrocortical potentials are transferred to the amplification apparatus. Electrode contact needs to be stable to establish low impedance or resistance to current flow. Each electrode is linked with one input of a differential amplifier which is used for a pair of electrodes. In addition, a common system reference electrode is linked with the other output of a differential amplifier whose duty is to expand the voltage between the active electrode and the reference. After recording EEG signal, it is translated via pens writing waveform in montage on paper. At present, EEG signal has been converted from analog to digital form.

As an EEG voltage signal signifies a difference between voltages at 2 electrodes, the projection of EEG can be conducted in many ways. The projection of the EEG channels is defined as montage. Montage can be divided into 4 types which are sequential montage, referential montage, average reference montage and laplacian montage. Sequential montage is a channel which indicates the difference between two adjacent electrodes. Referential montage is a channel which illustrates the difference between a specific electrode and another assigned reference electrode. Average reference montage is the outputs of all the amplifiers which are summed and averaged. Then, researchers use this averaged signal as the common reference for each channel. Laplacian montage demonstrates the difference between an electrode and a weighted average of the surrounding electrodes.

Montage means the pattern of systematic connection of the electrodes which aim to gain a logical demonstration of the electrical activity. Both the 10-10 and 10-20 systems (Figure 12) can be selected as standard electrode placement methods but there are no international standards of montage available in EEG laboratories. In practice, the longitudinal arrangement seems to be the most common for bipolar recording while another widely used arrangement is the transverse bipolar montage which is considered as appropriate for recording abnormalities happening at or near the vertex. So, the main purpose of montage arrangement is to focus on certain areas of interest through the most effective arrangement method.

One of the most significant EGG interpretations is recognizing artifacts, which refer to different forms causing interferences to brainwave activities. So, experienced electroencephalographer should possess the ability to recognize artifacts and to separate them from ongoing brainwave activities.

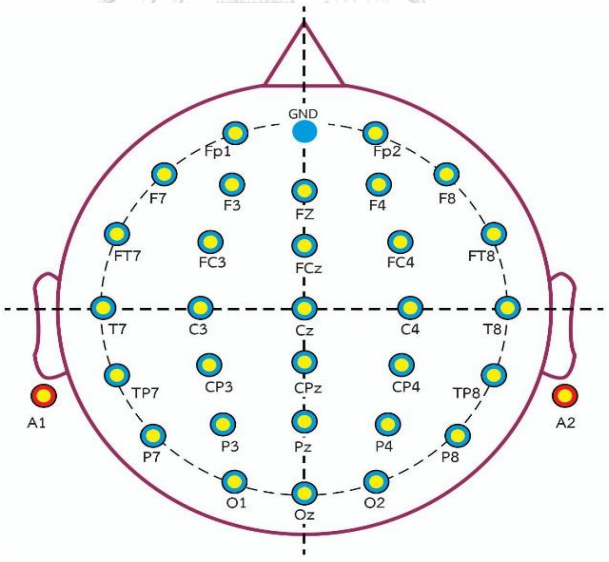


Figure 12 The international 10-20 system for electrode placement

2.4.3 Major Types of the EEG rhythms

EEG rhythms are interrelated to certain behaviors and emotional states. The rhythms of the normal brain wave are from 0.05 Hz to 200 Hz. The EEG rhythms are explained via the frequency in Hertz and amplitude and classified into various types.

Delta wave, whose frequency is the lowest between 0.5 and 3.9 Hz, is stimulated when humans are in their deep sleep (Figure 13). It is considered as a slow-wave sleep (Assenza, Pellegrino, Tombini, Di Pino, & Di Lazzaro, 2015). Delta is dominant among infants, young children and adolescents in the posterior head regions. (posterior slow waves of youth). It is considered as the slowest brain rhythms with minimal conscious brain.

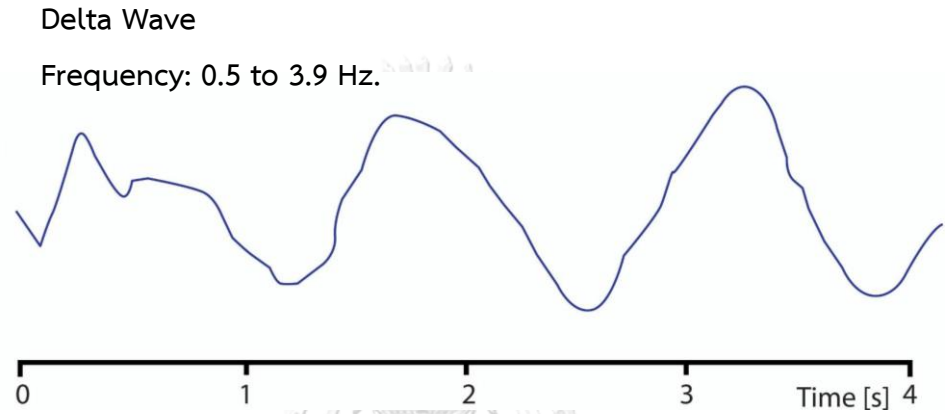


Figure 13 Delta wave from 0.5 to 3.9 Hz.

Theta wave, whose rhythm is 4-7.9 Hz, is linked with intuition or the sixth sense which helps them reach their subconscious level (Figure 14). It is stimulated when humans are dreaming or having deep meditation. Besides, it is related to creative thinking, memory and intuition. It helps humans to unlock their inner potential (Desai, Tailor, & Bhatt, 2015). Around 35% of normal young adults who are relaxed and awake display intermittent theta rhythm which is maximal in the frontocentral head regions. Theta is classified into 2 types: Theta 1 (4-6 Hz) and Theta 2 (6-8 Hz). Theta rhythm in the middle range between 6 and 7 Hz is regarded an indicator of continuous attention related to less anxiety and less phobic activity.

Theta Wave

Frequency: 0.5 to 3.9 Hz.

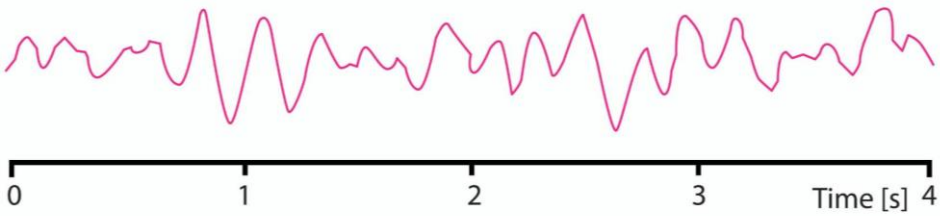


Figure 14 Theta wave from 4 to 7.9 Hz.

Alpha wave is the waking rhythm ranging from 8-12.9 Hz. as shown in Figure 15. It can be found in the posterior regions of the skull with higher voltage over the occipital part when humans are awake (Palva & Palva, 2007). The posterior dominant rhythm (PDR) found in these regions seems to be in the alpha frequency of a normal adult. Its amplitude varies considerably under 50 microvolts among adults. It can be detected when human eyes are closed or when humans feel relaxed or have mental activity (Başar, 2012). Alpha wave is subdivided into lower alpha (alpha 1, 2) and higher alpha (alpha 3). Lower alpha is an indicator of internal attention but higher alpha is an indicator of focusing on task demands. In a previous study, alpha was divided into 3 frequency bands: alpha 1 (8-8.9 Hz), alpha 2 (9-10.9 Hz) and alpha 3 (11-12.9 Hz). The researchers found that slow alpha 1 did not spread like alpha 2 and alpha 3 which showed the most power in the posterior region in the brain. Previous studies proposed that the alpha rhythm seemed to consist of two different functional components (American Society of Electroneurodiagnostic Technologists, 1996). A low alpha band with the range between 8 and 10 Hz was related to general or global attention but a high alpha band with the range between 10 and 13 Hz indicated directed attention focusing on task.

Mu wave, whose range is between 8-13 Hz, is sensorimotor rhythm. It happens during wakeful relaxation stage. Its frequencies are similar to those of alpha wave (Marcuse, Fields, & Yoo, 2016). Mu could be separated from alpha by its responsiveness

to moving a finger; it was located in the central region and it did not block eye opening. (Hammond, 2003)

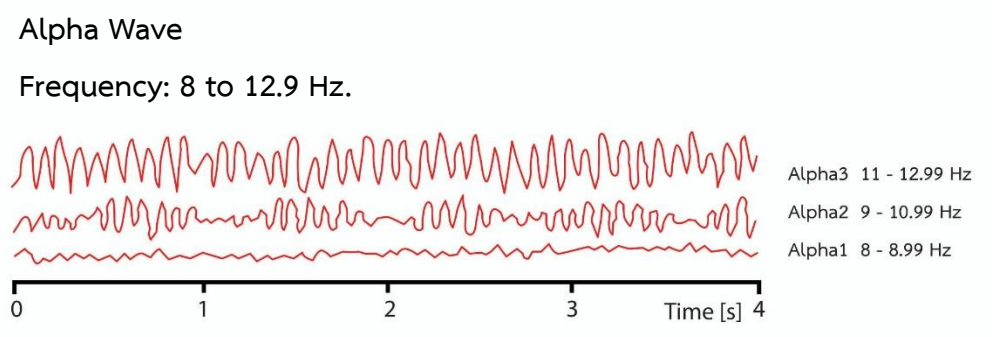


Figure 15 Alpha wave from 8 to 12.9 Hz.

Beta wave has the highest frequency around 13 and 30 Hz as shown in Figure 16. It is related to waking state of humans. Beta facilitates logical thinking, analysis and active attention (B.-G. Lee, Lee, & Chung, 2014). Maximal beta amplitude can be found in the frontocentral regions while it might be widespread. Beta wave regulates the system into attention state which permits gamma synchronization.

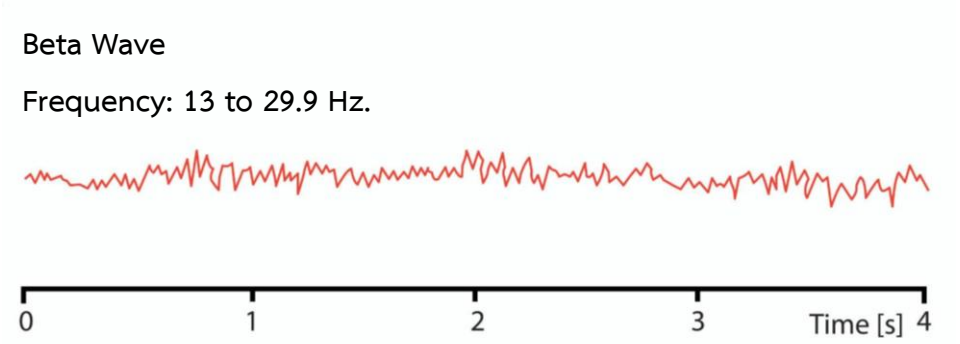


Figure 16 Beta wave from 13-29.9 Hz.

Gamma wave, the fastest brain waves which has a frequency over 30 Hz, is a pattern of neural fluctuation among humans due to its correlation of information that simultaneous processes from different brain regions (Figure 17). Thus, it is linked to a state of information processing of cortex. This wave can be found during working consciousness, spiritual emergence as well as hypnotic states (Hughes, 2008).

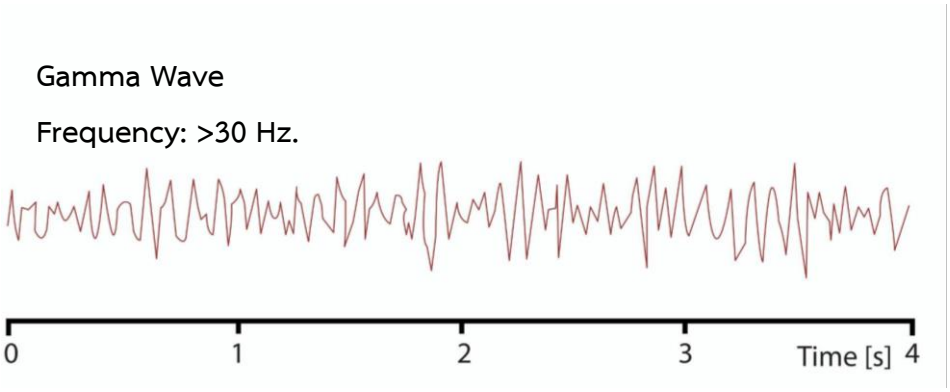


Figure 17 Gamma wave has a frequency over 30 Hz.

2.4.4 The advantages of EEG technique

Although EEG has poor spatial sensitivity, it provides many major advantages compared to other techniques. EEG hardware is much cheaper than that of other techniques. EEG has very high temporal resolution in milliseconds which can be very useful in clinical research. EEG is insensitive to the movement or artifacts of participants. The EEG sensors can be placed on more spots compared to those of other techniques such as PET, MRS, MEG, fMRI and SPECT. EEG technique is safe and silent. This permits researchers to study the participant's response to auditory stimulus. EEG is a very useful tool to monitor brainwave activities during various phrases of life. For instance, EEG sleep analysis can report crucial parts of the timing of the brain progress.

2.5 Aromatherapy

As the most ancient art of healing, aromatherapy has been practicing and improving since Egyptian era until now. In China and India, aromatherapy has been applied to treat somatic and psychological illnesses for over 3,000 years. Aroma means a scent or an odor while aromatherapy is defined as treatment with odors (Jaeger, Buchbauer, Jirovetz, & Fritzer, 1992). It is the use of essential oils to improve a person's mood and behavior. Aromatherapy encompasses the use of diluted essential oil or the blend of essential oils to massage the human skin. Aromatherapy also involves adding essential oil to the bath or burners to make it evaporate so that it can be absorbed via human nose and lungs. The sense of smell is responsible for receiving the odor molecules and transmitting them to the brain. So, aromatherapy through the sense of smell can

induce a great healing effect because of its capability to reach the brain directly (Kadohisa, 2013). These days, the effects of aromatherapy are immediate on physiological responses and recent research studies have discovered that aromatherapy is very effective in improving emotions, behaviors, cognition and sleep. Electroencephalograph (EEG) has been used as one of the effective scientific tools to prove the effects of odor inhalation on brain activities which can be used to investigate therapeutic use of volatile oils via nasal inhalation (aromatherapy). The inhalation of lavender oil exhibited the brain electrical activities by elevation of the brain waves, theta and alpha, giving the relaxation effect (Sayorwan et al., 2012). In contrast, after inhalation of rosemary oil, the brain electrical activities of alpha wave was reduced while there was the increment of beta wave detected in the anterior region of the brain (Sayorwan et al., 2013). Similar study on the effect of jasmine oil inhalation showed that beta wave increased in the left posterior and anterior center regions of the brain (Sayowan, Siripornpanich, Hongratanaworakit, Kotchabhakdi, & Ruangrungsi, 2013). Therefore, the inhalation of volatile oil containing volatile compounds has certain effects on brain activity.

The Sense of Smell Institute (SSI) coined the term “Aromachology” in 1982. Aromachology is a science related to the research on the psychological effects of essential oils particularly hedonic characteristics on emotional states and behaviors (Baser & Buchbauer, 2010). Moreover, Rene Maurice coined this term, aromchology, which referred to the topical or local or oral administration or therapeutic inhalation of essential oils to maintain health, hygiene and psychological well-being. Later, Buchbauer and Jirovetz redefined a more up-to-date definition of aromachology as “therapeutic use of fragrances or of volatile substances to cure and to mitigate or to prevent diseases, infections and indispositions only by means of inhalation.”

2.6 Properties of volatile compounds in plants

Plant metabolites have been divided into two types which are primary and secondary metabolites. Primary metabolites are the chemicals which can be found in all kinds of plants because they are the by-products of photosynthesis such carbohydrate, amino acid and lipid (Pott, Osorio, & Vallarino, 2019). Plants produce secondary metabolites necessary for long-term existence and major roles in defending predators and

attracting pollinators (Demain & Fang, 2000). Secondary metabolites are divided into three major groups: phenolics, terpenes, and alkaloids based on their biosynthetic pathways (Bourgaud, Gravot, Milesi, & Gontier, 2001).

Plants also produce mixtures of volatiles and essential oils which can be isolated from plants. Both volatiles and essential oils which characterize the essence or odorous compounds of these plants are used as flavoring agents and ingredients in perfumes and cosmetics due to their pharmaceutical properties (Figueiredo, Barroso, Pedro, & Scheffer, 2008). The mixtures of volatiles or volatile oils can be isolated by distillation, pressure or extraction with organic solvents or supercritical carbon dioxide. They are liquid at room temperature, slightly soluble in water and highly soluble in organic solvents. Moreover, the essential oils can be isolated by steam or water distillation (Figueiredo et al., 2008).

The chemical compounds in plant essential oils are divided into two different chemical classes: terpenes and phenylpropanoids. Terpene compounds can be subdivided into two main types: terpenes with a hydrocarbon structure including the monoterpenes, sesquiterpenes, and diterpenes and their oxygenated derivatives including alcohols, oxides, aldehydes, ketones, phenols, acids, esters, and lactones (Moghaddam & Mehdizadeh, 2017).

2.7 Properties of selected volatile compounds

For centuries, inhalation of volatile herbal materials has been used in complementary and alternative therapies for mental and physical balance in human. Essential oil or volatile oil refers to a concentrated hydrophobic liquid consisting of volatile compounds which can be extracted from plants or animals. Volatile compound is a complicated structure substance which mainly constitutes carbon, hydrogen and oxygen as any organic compound. Additionally, these compounds easily become vapors or gases at normal room temperature via evaporation or sublimation from the liquid or solid form of these compounds and diffuse their molecules to the surrounding air. It has been proven that various volatile compounds were given the different therapeutic effects. Thus, understanding their chemical and physical properties and obtained source should be concerned as each has its own characteristic pattern of effects on the body.

In this research, four volatile compounds including *d*-borneol, *d*-camphor, methyl eugenol and methyl chavicol were selected for the investigation (Figure 18).

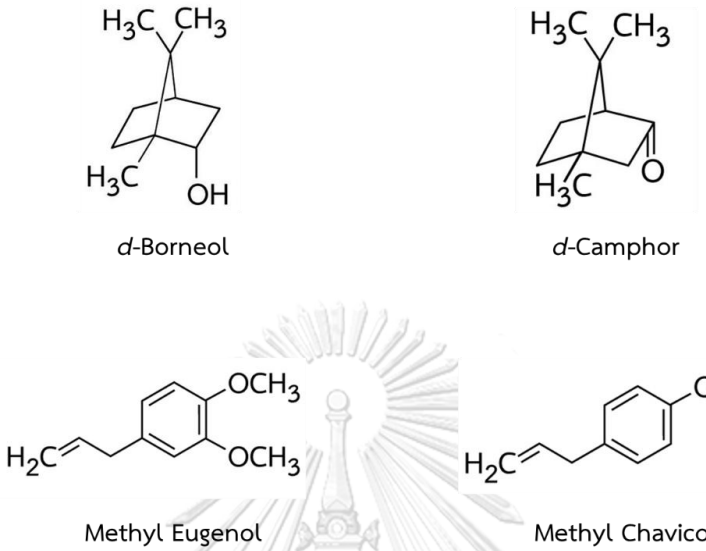


Figure 18 Chemical structures of *d*-borneol, *d*-camphor, methyl eugenol and methyl chavicol

2.7.1 *d*-Borneol

2.7.1.1 Properties of *d*-borneol

The chemical and physical characteristics of *d*-borneol or (+)-borneol were obtained from U.S. National Library of Medicine: The National Center for Biotechnology Information advances science and health (National Center for Biotechnology Information, 2019a).

Chemical formula:	$C_{10}H_{18}O$
IUPAC name:	(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol
CAS number:	464-43-7
Molar mass:	154.25 g/mol
Color and appearance:	lump-solid crystal-colorless to white
Odor:	strong, aromatic
Water solubility:	0.74 mg/ml at 25°C
Vapor pressure:	5.02×10^{-2} mmHg at 25°C

Various parts of *Dryobalanops aromatica* C.F.Gaertn were subjected for essential oil extraction and identification of the essential oil composition using GC-MS analysis as shown in Table 3. All reports indicated that monoterpenes and sesquiterpenes were the main constituents. Borneol obtained from *D. aromatica* were found in wood, exudate and leaf. Only the essential oil from the seed did not show the content of borneol.

Table 3 Chemical constituents of *Dryobalanops aromatica* C.F.Gaertn

Part of plant	Chemical constituents		Reference
Wood	α-Pinene	54.30%	Tisserand and Young (2014)
	β-Caryophyllene	18.10%	
	Borneol	8.30%	
	α-Caryophyllene	4.30%	
	α-Terpineol	3.00%	
	β-Pinene	2.50%	
	(+)-Limonene	2.50%	
Exudate	α-Pinene	21.49%	Le et al. (2016)
	β-Pinene	0.94%	
	α-Phellandrene	0.65%	
	1,4-Cineole	0.21%	
	m-Cymene	0.36%	
	D-Limonene	1.38%	
	β-Myrcene	1.85%	
	ϒ-Terpinene	3.51%	
	(+)-4-Carene	0.45%	
	(+)-2-Carene	0.42%	
	(+)-Fenchol	0.09%	
	Terpinen-1-ol	0.12%	
	(-)-Camphor	1.05%	
	Borneol	0.74%	
	Terpinen-4-ol	8.58%	

Table 3 Chemical constituents of *Dryobalanops aromatica* C.F.Gaertn (Cont.)

Part of plant	Chemical constituent		Reference
Exudate	α-Terpineol	5.89%	Le et al. (2016)
	Verbenone	0.08%	
	Bornyl acetate	0.41%	
	Copaene	0.08%	
	α-Farnesene	0.02%	
Leaf	α-Terpineol	16.00%	Kamariah, Ozek, Demirci, and Baser (2012)
	Terpinen-4-ol	15.00%	
	Globulol	8.00%	
	α-Pinene	7.00%	
	Borneol	0.59%	
Seed	α-Pinene	41.00%	
	α-Thujene	13.00%	
	β-Pinene	13.00%	
	Sabinene	6.00%	
	Limonene	6.00%	
	Bicyclogermacrene	6.00%	
	Myrcene	5.00%	

2.7.1.2 Natural source

Natural *d*-borneol (Kapur, Borneo camphor, Sumatran camphor trees) can be obtained from numerous plant families such as Lamiaceae, Valerianaceae and Asteraceae (Lei, Jianyu. Su, Lin. Li, Bing, & Wang, 2011). However, it is originally obtained from *Dryobalanops aromatica C. F. Gaertn* (Evans et al., 2009).

Botanical name: Dryobalanops aromatica C.F.Gaertn.

Synonym: *Dryobalanops sumatrensis* (J.F.Gmel.) Kosterm.
Dryobalanops camphora Colebr.
Dipterocarpus camphorus (Colebr.) Mart.
Dryobalanops junghuhnii Becc.
Dryobalanops vriesii Becc.

Family: Dipterocarpaceae

Plant description: The plant is a large tropical rainforest species known for its precious timber. As endangered tree species, the tree grows only in Malaysian Peninsular, Borneo and Sumatra. The flora of Malaysia provides the information of *D. aromatica* that "it is a medium-sized to very large tree, up to 65 m tall and 2 m in diameter, with buttresses at its base. The bark is smooth in young trees, but becomes shaggily scaly with age and smells of peppery camphor when the bark is cut. The leaves are simple, alternate, coriaceous and ovate, with an acuminate apex and cuneate base. They release a camphor-like odor when crushed. The lateral veins are numerous, fine and parallel, and joined into intramarginal veins at margin while the petiole is slender and channeled. The inflorescence takes the form of a panicle while the flowers are bisexual, with glabrous, lanceolate sepals and five waxy white petals. The fruit has five subequal wings while the nut is glabrous (*Flora of Malaysia i-Newsletter Part 2, 2013*)".

2.7.1.3 Toxicological data of *d*-borneol

Regarding the toxicity of *d*-borneol, it does not present a concern for skin sensitization in humans. Toxicity is comparable to that of camphor. The toxicity of d-borneol in animals was found that borneol increased the activity of CYP2D in rats orally treated by borneol for 7 days (J. Y. Chen, Wang, Meng, & Chen, 2015). Food and Drug Administration (FDA) as well as Flavor and Extract Manufacturers' Association States (FEMA) approved and recognized natural borneol as safe as food flavoring and adjuvant ingredients (Bhatia, Letizia, & Api, 2008).

2.7.1.4 Related reviews of *d*-borneol

Natural borneol is originally extracted from the endangered plant in Southeast Asia, *D. aromatica*. Due to its rarity and price advantage, synthetic borneol is often used instead of natural borneol. A mixture of *d*-borneol and isoborneol is commonly found in synthetic borneol obtaining from turpentine oil and camphor via the chemical transformation (Xiao-fei et al., 2008). According to the Pharmacopoeia of People's Republic of China, the quality control of natural borneol was considered and set the standard that the purity of *d*-borneol and (+)-borneol must be no less

than 96 and 85%, whereas the purity of *d*-borneol must be no less than 55% for clinical purposes (State Pharmacopoeia Committee, 2015).

d-Borneol has been reported to show numerus pharmacological effects including analgesic (Jiang et al., 2015), anti-hyperglycemic, anti-hyperlipidemic (Madhuri & Naik, 2017), anti-oxidant, anti-inflammatory and neuroprotective (R. Liu et al., 2011). In this study, most of the literature reviews were emphasized on *d*-borneol or natural borneol and its activities related to brain, emotion, nervous system and physiological activities.

Natural borneol is a bicyclic monoterpene alcohol which has been used in traditional Chinese and Japanese medicine to treat analgesia, anesthesia, anxiety and depression (Yakushigaku, 2000). In Thai traditional medicine, natural borneol is a tonic for heart and brain. It is an effective treatment for cold and other respiratory ailments by inhalation of the vapors. Natural borneol can be found in herbal plants such valerian, chamomile and lavender. The essential oils with natural borneol display significant sedative activity in human and animal researches which prove equal sedation to conventional sedative and hypnotic agents as well as better sleep depth. So, the herbal plants containing borneol are administered traditionally to treat anxiety, restlessness and insomnia (Buchbauer et al., 1991; Gyllenhaal, Merritt, Peterson, Block, & Gochenour, 2000). In the study of animal trial, *d*-borneol caused mild sedation in mice when they inhaled it but its isomer, isoborneol enhanced movement which may signify different actions at GABAa receptors in spite of their structural similarity (Buchbauer, Jirovetz, Jäger, Plank, & Dietrich, 1993).

Furthermore, animal study on GABA-induced chloride currents at $\alpha_1\beta_2\gamma_{2L}$ GABAA receptors with *d*-borneol has shown notable GABAergic effects such as sedation and anxiolytics, which were greater than that of diazepam and at least equivalent to that of anesthetic etomidate expressed in *Xenopus laevis* oocytes using two-electrode voltage-clamp electrophysiology (Granger, Campbell, & Johnston, 2005).

Due to the therapeutic potential for depression of borneol in traditional Chinese medicine, animal model using male Sprague-Dawley rats was set for the antidepressant effects. The results showed that the rats consuming the formula that contained borneol promoted the distribution of asiaticoside which has antidepressant

effect into the rat brain and significantly reduced the immobility time of rats in modified force swimming test with no significant effects. Thus, this finding indicated that borneol could promote asiaticoside distribution into the brain (Hou, Li, & Peng, 2017). There is no direct evidence to confirm that enhancing effects of borneol on BBB (blood brain barrier) permeability are related to the mechanism of vasodilatory neurotransmitters. However, it was found that histamine and serotonin level in rat brain increased in the hypothalamus after administration of borneol. Thus, the researchers suggested that borneol could be administered together with drugs aiming at hypothalamus to maximize its synergistic effect (W. R. Li, Yao, Mi, & Wang, 2004, 2006).

Hippocampus is the crucial key structure of the brain dealing with emotional, stress, anxiety and fear responses (Strange, Witter, Lein, & Moser, 2014). *d*-Borneol was injected into dorsal hippocampus showing the suppression of anxiety behaviors in the mice tested in the open field study, light/dark exploration and the elevated plus maze test (Cao et al., 2018).

Taken together, *d*-borneol or natural borneol are safe to use as medicine, food products, cosmetics and perfumes based on its long traditional medicine history as well as scientific evidences. Moreover, all previous reports also indicated that *d*-borneol demonstrated the positive effects in GABAergic system by modulating anxiety and sedation.

2.7.2 *d*-Camphor

2.7.2.1 Properties of *d*-camphor

d-Camphor or (+)-camphor is the main component in natural camphor which was used in this current research. The chemical and physical characteristics of this volatile compound were obtained from U.S. National Library of Medicine: The National Center for Biotechnology Information advances science and health (National Center for Biotechnology Information, 2019b).

Chemical formula: $C_{10}H_{16}O$

IUPAC name: (1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one

CAS number: 464-49-3

Molar mass: 152.23 g/mol

Color and appearance: colorless to white translucent crystals, granules

Odor: aromatic fragrant and penetrating odor

Water solubility: 1.6×10^3mg/L at 25°C

Vapor pressure: 0.65 mmHg at 25°C

Previous studies indicated that camphor, an aromatic compound can be obtained from many parts of *Cinnamomun camphora* (L.) J.Presl as shown in Table 4. There are six different chemical variants in this plant including camphor, borneol, linanool, 1,8-cineole, nerolidol and safrole.

Table 4 Chemical constituents of *Cinnamomum camphora* (L.) J.Presl

Part of plant	Chemical constituents		Reference
Bark	Artemesia triene	1.00%	Guo et al. (2016)
	β -Pinene	0.30%	
	4-Carene	0.20%	
	1,8-Cineole	4.30%	
	γ-Terpinen	0.30%	
	Isoterpinolene	0.40%	
	Undecane	0.20%	
	1-Methyl-5-(1-methylvinyl)cyclohexene	1.60%	
	1,3,8-p-Menthatriene	1.10%	
	7,7-Dimethyl-2-methylenenorbornane	0.50%	
	D-Camphor	51.30%	
	Terpinen-4-ol	2.00%	
	α-Terpineol	3.80%	
	Eugenol	2.10%	
	Dihydro-*cis*-α-copaene-8-ol	1.40%	
	α-Bourbonene	0.20%	
	Bergamotene	0.30%	
	Aromadendrene	0.90%	
	γ-Patchoulene	0.30%	
	α-Cubebene	1.30%	

Table 4 Chemical constituents of *Cinnamomum camphora* (L.) J.Presl (Cont.)

Part of plant	Chemical constituents		Reference
Bark	α-Caryophyllene	0.50%	
	β-Selinene	0.40%	
	1,2,3,4,6,8 alpha-Hexahydro-1-isopropyl-4,7-dimethylnaphthalene	0.20%	
	β-Cadinene	2.00%	
	α-Calacorene	0.20%	
	1,3,3-Trimethyl-2-hydroxymethyl-3,3-dimethyl-4- (3-methylbut-2-enyl)-cyclohexene	2.80%	
	3-Methyl-2-butenoic acid, oct-3-en-2-yl ester	3.10%	
Leaf	*m*-Cymene	0.40%	Guo et al. (2016)
	1,8-Cineole	11.30%	
	α-*trans*-Ocimene	0.10%	
	2,2-Dimethylheptane	0.10%	
	2,2,5-Trimethylhexane-3,4-dione	0.10%	
	4,7-Dimethyl-4,4a,5,6-tetrahydrocyclopenta[c]pyran-1,3-dione	0.30%	
	2,5,9-Trimethyldecane	0.10%	
	Linalool	22.90%	
	7,7-Dimethyl-2-methylenenorbornane	0.10%	
	D-Camphor	40.50%	
	endo-Borneol	0.20%	
	p-Menth-1-en-4-ol	1.10%	
	p-Menth-1-en-8-ol	2.30%	
	Elixene	0.30%	
	Dihydro-*cis*-α-copaene-8-ol	0.60%	
	α-Bourbonene	0.10%	
	1,5-Dimethyl-8-isopropenyl-1,5-cyclodeca-diene	0.20%	

Table 4 Chemical constituents of *Cinnamomum camphora* (L.) J.Presl (Cont.)

Part of plant	Chemical constituents		Reference
Leaf	Caryophyllene	2.20%	Guo et al. (2016)
	γ-Elemene	1.00%	
	Germacrene D	0.90%	
	α-Caryophyllene	0.20%	
	3,5-Dimethyl-4-octanone	0.10%	
	Cadina-1(10),4-diene	0.10%	
	3,7,11-Trimethyl-3-hydroxy-6,10-dodecadien-1-yl acetate	4.50%	
	Oxalic acid,di(1-menthyl) ester	0.40%	
	1,3,3-Trimethyl-2-hydroxymethyl-3,3-dimethyl-4- (3-methylbut-2-enyl)-cyclohexene	0.10%	
Fruit	Camphene	0.20%	
	2-Thujene	0.20%	
	α-Phellandrene	2.60%	
	p-Mentha-2,4(8)-diene	0.30%	
	3-Carene	0.50%	
	o-Cymene	2.70%	
	1,8-Cineole	5.30%	
	α-*trans*-Ocimene	0.20%	
	Linalool	12.80%	
	7,7-Dimethyl-2-methylenenorbornane	0.30%	
	D-Camphor	28.10%	
	p-Menth-1-en-4-ol	0.70%	
	p-Menth-1-en-8-ol	1.70%	
	B-Terpinyl acetate	1.30%	
	Safrole	29.00%	
	Dihydro-*cis*-α-copaene-8-ol	0.40%	
	γ-Patchoulene	0.20%	

Table 4 Chemical constituents of *Cinnamomum camphora* (L.) J.Presl (Cont.)

Part of plant	Chemical constituents		Reference
Leaf	α-Pinene	2.05%	H. P. Chen et al. (2014)
	Camphene	1.00%	
	2-Thujene	1.97%	
	Sabinene	1.80%	
	α-Phellandrene	0.40%	
	p-Mentha-2,4(8)-diene	0.44%	
	m-Cymene	0.44%	
	Cineole	11.26%	
	α-trans-Ocimene	0.05%	
	2,2-Dimethylheptane	0.07%	
	2,2,5-Trimethylhexane-3,4-dione	0.03%	
	4,7-Dimethyl-4,4a,5,6-tetrahydrocyclopenta [c]pyran-1,3-dione	0.31%	
	2,5,9-Trimethyldecane	0.08%	
	Linalool	22.92%	
	7,7-Dimethyl-2-methylene-norbornane	0.05%	
	D-Camphor	40.54%	
	endo-Borneol	0.23%	
	(R)-(–)-p-Menth-1-en-4-ol	1.02%	
	p-Menth-1-en-8-ol	2.30%	
	Elixene	0.33%	
	Dihydro-cis-α-copaene-8-ol	0.61%	
	α-Bourbonene	0.03%	
	(S,1Z,5E)-1,5-Dimethyl-8-isopropenyl-1,5-cyclodecadiene	0.22%	
	Caryophyllene	2.16%	
	γ-Elemene	0.98%	
	Germacrene D	0.94%	
	α-Caryophyllene	0.24%	
	3,5-Dimethyl-4-octanone	0.05%	

Table 4 Chemical constituents of *Cinnamomum camphora* (L.) J.Presl (Cont.)

Part of plant	Chemical constituents		Reference
Leaf	Cadina-1(10),4-diene	0.07%	H. P. Chen et al. (2014)
	3,7,11-Trimethyl-3-hydroxy-6,10-dodecadien-1-yl acetate	4.50%	
	Oxalic acid, di(1-methyl) ester	0.43%	
	1,3,3-Trimethyl-2-hydroxymethyl-3,3-dimethyl-4-(3-methylbut-2-enyl)-cyclohexene	0.10%	

2.7.2.2 Natural source

Cinnamomum camphora (L.) J.Presl has its common name as Camphor tree. Camphor laurel is the original source of camphor, which can be found in warm climates areas such as China, Japan, Taiwan, Vietnam, Australia, southern USA, southern Europe, southern and eastern Africa and Madagascar. It is an evergreen plant with an average lifespan of 50 to 150 years old. Camphor can be obtained through steam distillation from its leaves, stems and roots.

Botanical name: *Cinnamomum camphora* (L.) J.Presl

Synonym: Camphor tree, Camphor laurel

Camphora camphora (L.) H.Karst.

Camphora hahnemannii Lukman.

Camphora hippocratei Lukman.

Camphora officinarum Nees

Laurus camphora L.

Family: Lauraceae

Plant description: The flora of China provides the information of *C. camphora* that “Evergreen large trees, up to 30 m tall, to 3 m d.b.h.; corona broadly ovate; whole plant strongly camphor-scented. Bark yellow-brown, irregularly and longitudinally fissured. Branchlets brownish, terete, glabrous. Terminal buds broadly ovoid; bud scales broadly ovate or suborbicular, sparsely sericeous outside. Leaves alternate; petiole slender, 2-3 cm, concave-convex, glabrous; leaf blade yellow-green or gray-green and glaucous abaxially, green or yellow-green and shiny adaxially, ovate-

elliptic, 6-12 × 2.5-5.5 cm, sub leathery, glabrous on both surfaces or sparsely puberulent abaxially only when young, triplinerved or sometimes inconspicuously 5-nerved, midrib conspicuous on both surfaces, lateral veins 1-5(-7) pairs, basal veins with a few additional veins outside, axils of lateral veins and veins conspicuously dome-shaped and always villous abaxially, conspicuously bullate adaxially, base broadly cuneate or subrounded, margin cartilaginous, entire or sometimes undulate, apex acute. Panicle axillary, 3.5-7 cm; peduncle 2.5-4.5 cm, peduncle and rachis glabrous or gray- to yellow-brown puberulent especially on node. Pedicels 1-2 mm, glabrous. Flowers green-white or yellowish, ca. 3 mm. Perianth glabrous or puberulent outside, densely pubescent inside; perianth tube obconical, ca. 1 mm; perianth lobes elliptic, ca. 2 mm. Fertile stamens 9, ca. 2 mm; filaments pubescent. Ovary ovoid, ca. 1 mm, glabrous; style ca. 1 mm. Fruit purple-black, ovoid or sub globose, 6-8 mm in diam.; perianth cup in fruit cupuliform, ca. 5 mm, longitudinally sulcate, base ca. 1 mm wide, apex truncate and up to 4 mm wide (X. Li et al., 2008)".

2.7.2.3 Toxicological data of *d*-camphor

A previous study reported that the daily maximum human therapeutic dose was approximately 1.43 mg/kg, which corresponds to a therapeutic ratio for the endpoint toxicity, reflecting a wide margin of safety (Leuschner, 1997). The toxicity of *d*-camphor in rats and rabbits caused signs of toxicity. The rats consumed less food after the administered dose of 464 mg/Kg b.w. on day 1 connected with a decrease of motility and weight gain. After the rabbits treated with 681 mg/Kg b.w. on day 1, they lost body weight and consumed less food (Leuschner, 1997). The Observatoire des Consommations Alimentaires (OCA) collected data on food consumption in French population reported that the dietary exposure to d-camphor was estimated to be 25mg/kg/day (European Food Safety Authority, 2008). Food and Drug Administration (FDA) considered camphor as safe for inhalation as vapor in small amounts as a part of aromatherapy. The recommended concentration for inhalation is less than 1 tablespoon camphor solution per quart of water or not exceed 11% (American Academy of Pediatrics, 1994)

2.7.2.4 Related reviews of *d*-camphor

Natural camphor is traditionally distillated from the wood of *C. camphora* which contains *d*-camphor or (+)-camphor as the main compound (Guo et al., 2016). Not only it is a valuable traditional medicine, camphor is one of the most well-known aroma chemicals with the value of million dollars annually (Ajay, 2019). Various reports of plans containing natural camphor as the main compound or the single use of *d*-camphor exhibited the biological effects on antimicrobial (Soković & van Griensven, 2006), antiviral (De Logu et al., 2000), antitussive (Kumar et al., 2012), antinoceptive (Xu et al., 2005), insecticidal (Fu et al., 2015), antimutagenic and anticancer activities (Hamidpour et al., 2013). The literature reviews of this current research will be emphasized on natural camphor and *d*-camphor as well as their activities related to brain, emotion, nervous system and physiological activities.

Camphor has been widely used as an aromatic compound in cosmetic, flavoring food or pharmaceutical additives as well as burning material for spiritual purpose. These utilizations of camphor are not only based on its medicinal properties but also its fragrance. Thus, the sense of smell has a powerful impact on human. The relationship between olfaction and basic six emotions (anger, fear, disgust, happiness, sadness, surprise) through autonomic nervous system (ANS) responses induced by camphor inhalation at the concentration of 1:100 in mineral oil for 35 min was investigated on a total of 15 healthy participants. The pooled results from the correlation between the hedonic evaluation (pleasantness or unpleasantness) and basic emotions revealed that camphor was differentiated from both types as an intermediate, which associated with happy or surprise characteristics (pleasant odorant) and sad characteristic (unpleasant odorant) (Vernet-Maury, Alaoui-Ismaïli, Dittmar, Delhomme, & Chanel, 1999).

Traditional Chinese medicine uses natural camphor as a heart tonic to stimulate the peripheral circulation. Recently, the clinical study using independent, double-blinded, randomized, placebo-controlled models was investigated for the efficacy in orthostatic hypotension of *d*-camphor, crataegus berries extract and its combination with crataegus berries extract. Sublingual/oral administration of *d*-camphor contributed to the pressoric effects by inducing the initial rapid effect while the Crataegus berries extract was responsible for the long-lasting effect. Their combination exhibited a

dose-dependent manner in increasing supine blood pressure as well as preventing the fall in blood pressure in patients with orthostatic dysregulation (Georg & Loew, 2003). This finding initiated a clinical study on *d*-camphor and Crataegus extract combination under the name "Korodin" on hypotension treatment. A randomized, double blind, placebo-controlled study on blood pressure and cognitive performance was investigated in hypotensive women. After administration of the drug, blood pressure elevating effect, especially systolic blood pressure was observed in chronic hypotension participants as well as the enchantment in cognitive performance. However, the mechanism of this combination on hypotension and cognitive performance was still unknown (Schandry & Duschek, 2008). The systemic evaluation of d-camphor and Crataegus extract combination were investigated using the meta-analysis based on four randomized control trails. This pooled statistical analysis with the total of 221 patients has confirmed that this combination compound increased systolic and diastolic blood pressure significantly compared to placebo (Csupor et al., 2019).

Herbal inhalant containing camphor, a natural product derived from the wood of *C. camphora* tree has a long usage in history which is very popular in many Asian countries for the relief of nasal symptoms. The clinical study on 25 participants inhaled camphor vapor for five minutes reported the improvement of airflow sensation in nasal cavity with no adverse effects (Burrow, Eccles, & Jones, 1983).

Inhalation of camphor vapor has investigated on antitussive effect in conscious chemical-induced cough guinea-pigs. After inhalation of camphor vapor for five minutes at the concentrations of 500 µg/l revealing a significantly 33% reduction of cough frequency without adverse effects (Laude, Morice, & Grattan, 1994).

Presently, camphor is available in local pharmacy as it is an active ingredient in many ointments and inhalants which is popular for the treatment of nasal congestion and musculoskeletal pain. The application of natural camphor onto the skin gives a warm sensation via the activation of the transient receptor potential vanilloid type one and three (TRPV3, TRPV1) in mammalian cell lines which contribute to an antinociceptive role of camphor (Xu et al., 2005).

In conclusion, *d*-camphor or natural camphor is safe to inhale due to the use as the inhalant to treat nasal congestion at the aforementioned proposed

dosage. Interestingly, oral administration of *d*-camphor exhibited the elevation of blood pressure, thus inhalation of this volatile compound might increase some vital signs including blood pressure, temperature and pulse.

2.7.3 Methyl eugenol

2.7.3.1 Properties of methyl eugenol

The chemical and physical characteristics of methyl eugenol were obtained from U.S. National Library of Medicine: The National Center for Biotechnology Information advances science and health (National Center for Biotechnology Information, 2019c).

Chemical formula: $C_{11}H_{14}O_2$

IUPAC name: 1,2-dimethoxy-4-prop-2-enylbenzene

CAS number: 93-15-2

Molar mass: 178.231 g/mol

Color and appearance: clear colorless to pale yellow liquid

Odor: Mind-spicy earthy, slightly herbal odor

Water solubility: 500mg/L at 25°C

Vapor pressure: 0.012 mmHg at 25°C

Chemotype of the essential oil extracted from various parts of *Ocimum tenuiflorum* L. has been reported, showing the uneven distribution of methyl eugenol in the specific plant part shown in Table 5.

Table 5 Chemical constituents of *Ocimum tenuiflorum* L.

Part of plant	Chemical constituents		Reference
Whole plant	(Z)-3-hexenol	0.20%	Kothari,
	ethyl 2-methyl butyrate	0.02%	Bhattacharya,
	α-Pinene	0.10%	Ramesh,
	β-Pinene	0.06%	Garg, and
	myrcene	0.08%	Khanuja
	limonene	0.07%	(2005)
	(E)-β–ocimene	0.07%	
	γ-terpinene	0.08%	
	trans-linalool oxide	0.05%	

Table 5 Chemical constituents of *Ocimum tenuiflorum* L. (Cont.)

Part of plant	Chemical constituents		Reference
Whole plant	linalool	0.04%	Kothari et al. (2005)
	eugenol	0.88%	
	methyl eugenol	72.50%	
	β–elemene	0.50%	
	(E)-cinnamyl acetate	3.40%	
	β–caryophyllene	5.50%	
	α-guaiene	0.04%	
	α-humulene	0.38%	
	β–selinene	0.06%	
	α-muurolene	0.16%	
	δ-cadinene	0.08%	
	nerolidol	0.07%	
	caryophyllene oxide	1.53%	
	α-guaiol	0.14%	
	T-cadinol	0.26%	
	β–eudesmol	0.13%	
	α-bisabolol	0.03%	
	(E,Z)-farnesol	0.10%	
Leaf	(Z)-3-hexenol	0.05%	
	ethyl 2-methyl butyrate	0.04%	
	α-Pinene	0.11%	
	β-Pinene	0.06%	
	myrcene	0.06%	
	limonene	0.03%	
	(E)-β–ocimene	0.04%	
	γ-terpinene	0.05%	
	trans-linalool oxide	0.06%	
	linalool	0.05%	

Table 5 Chemical constituents of *Ocimum tenuiflorum* L. (Cont.)

Part of plant	Chemical constituents		Reference
Leaf	eugenol	0.79%	Kothari et al. (2005)
	methyl eugenol	72.25%	
	β–elemene	2.84%	
	(E)-cinnamyl acetate	3.44%	
	β–caryophyllene	6.37%	
	α-guaiene	0.04%	
	α-humulene	0.58%	
	β–selinene	0.09%	
	α-muurolene	0.42%	
	δ-cadinene	0.17%	
	nerolidol	0.14%	
	caryophyllene oxide	0.75%	
	α-guaiol	0.22%	
	T-cadinol	0.30%	
	β–eudesmol	0.23%	
	α-bisabolol	0.06%	
	(E,Z)-farnesol	0.53%	
	3-carene	0.18%	Tangpao, Chung, and Sommano (2018)
	Borneol	7.80%	
	α-copaene	2.07%	
	β-bourbonene	0.77%	
	β-cubebene	2.00%	
	β-elemene	6.57%	
	Methyl eugenol	68.40%	
	β-caryophyllene	14.60%	
	α-humulene	1.34%	
	Germacrene d	0.06%	
	α-cubebene	10.50%	

Table 5 Chemical constituents of *Ocimum tenuiflorum* L. (Cont.)

Part of plant	Chemical constituents		Reference
Leaf	Bicyclo [3.1.1] hept-3-enespiro-2,40 -(10, 30 -dioxane), 7,7-dimethyl	0.19%	Tangpao et al. (2018)
	β-gurjunene	0.64%	
	δ-cadinene	0.81%	
	(Z)-4-decen-1-ol	0.38%	
	Eremophilene	0.25%	
	Ethyl trichloroacetate	0.18%	
	Benzofuran, 7-(2,4- dinitrophenoxy)-3-ethoxy2,3-dihydro-2,2-dimethyl	0.01%	
	α-muurolene	0.24%	
Stem	(Z)-3-hexenol	0.65%	Kothari et al. (2005)
	ethyl 2-methyl butyrate	0.04%	
	α-Pinene	0.12%	
	β-Pinene	0.05%	
	myrcene	0.14%	
	limonene	0.02%	
	(E)-β–ocimene	0.03%	
	γ-terpinene	0.02%	
	trans-linalool oxide	0.03%	
	linalool	0.06%	
	eugenol	0.67%	
	methyl eugenol	83.70%	
	β–elemene	0.01%	
	(E)-cinnamyl acetate	0.85%	
	β–caryophyllene	2.74%	
	α-guaiene	0.04%	
	α-humulene	0.23%	
	β–selinene	0.03%	

Table 5 Chemical constituents of *Ocimum tenuiflorum* L. (Cont.)

Part of plant	Chemical constituents		Reference
Stem	α-muurolene	0.13%	Kothari et al. (2005)
	δ-cadinene	0.09%	
	nerolidol	0.04%	
	caryophyllene oxide	1.70%	
	α-guaiol	0.05%	
	T-cadinol	0.36%	
	β–eudesmol	0.41%	
	α-bisabolol	0.04%	
	(E,Z)-farnesol	0.91%	
Inflorescence	(Z)-3-hexenol	0.39%	
	ethyl 2-methyl butyrate	-	
	α-Pinene	0.12%	
	β-Pinene	0.07%	
	myrcene	0.10%	
	limonene	0.11%	
	(E)-β–ocimene	0.12%	
	γ-terpinene	0.09%	
	trans-linalool oxide	0.07%	
	linalool	0.04%	
	eugenol	0.16%	
	methyl eugenol	65.20%	
	β–elemene	0.30%	
	(E)-cinnamyl acetate	7.68%	
	β–caryophyllene	11.97%	
	α-guaiene	0.12%	
	α-humulene	0.80%	
	β–selinene	0.05%	
	α-muurolene	0.15%	

Table 5 Chemical constituents of *Ocimum tenuiflorum* L. (Cont.)

Part of plant	Chemical constituents		Reference
Inflorescence	δ-cadinene	0.08%	Kothari et al. (2005)
	nerolidol	0.06%	
	caryophyllene oxide	3.02%	
	α-guaiol	0.12%	
	T-cadinol	0.22%	
	β–eudesmol	0.11%	
	α-bisabolol	0.05%	
	(E,Z)-farnesol	0.69%	

2.7.3.2 Natural source

The previous report on the occurrence of methyl eugenol revealed that this compound can be found in a large number plant families, including Asteraceae, Apiaceae, Lamiaceae, Lauraceae, Aristolochiaceae, Rutaceae, Myrtaceae, Poaceae, Cupressaceae, Euphobiaceae and Zingibernaceae (Tan & Nishida, 2012). The presence of methyl eugenol first reported form *Cymbopogon nardus, Colocasia antiquorum* and *Carica papaya* based on their ability to attract fruit flies (Howlett, 1915). Later in 1986, the study on chemical constituent in *Cymbopogon* species was confirmed that *Cymbopogon nardus* contained methyl eugenol (Heiba & Rizk, 1986). However, another report revealed that *Ocimum tenuiflorum* L. (Lamiaceae) with its common name as holy basil or red basil, a common culinary vegetable and medicine in Southeast Asian countries contained a very high amount of methyl eugenol ranging from 78-81% of the extracted oil (Dey & Choudhuri, 1985). Therefore, this plant can be represented as one of the plants containing a high amount of methyl eugenol which can be abundantly found in tropical area.

Botanical name: *Ocimum tenuiflorum* L.

Synonym: *Ocimum sanctum* L.

Ocimum monachorum L.

Ocimum inodorum Burm.f.

Ocimum hirsutum Benth.

Ocimum caryophyllinum F.Muell.

Ocimum anisodorum F.Muell.

Family: Lamiaceae

Plant description: *Ocimum tenuiflorum* L. is commonly known as Holy basil because it is an important plant in Hinduism. *Ocimum sanctum* L. is its synonym that reflects this religious connection as the plant was frequently grown in the Hindu temples to cleanse the body. In Thailand, this plant is called Ka-Paow and commonly found in all parts of the country as herbal and culinary ingredients. The flora of China provides the information of *O. tenuiflorum* that "Subshrubs to 1 m tall, much branched. Stems erect, base woody, spreading pilose. Petiole 1-2.5 cm; leaf blade oblong, 2.5-5.5 × 1-3 cm, puberulent, glandular, pilose on veins, base cuneate to rounded, margin shallowly undulate-serrate, apex obtuse. Verticillasters 6-flowered, in pedunculate, terminal thyrses or panicles 6-8 cm; bracts sessile, cordate, ca. 1.5 × 1.5 mm, apex acute; peduncle 1-1.5 cm. Pedicel ca. 2.5 mm. Calyx campanulate, ca. 2.5 mm, villous, tube ca. 1.5 mm; middle tooth of upper lip broadly oblate, abruptly acute; lateral teeth broadly triangular, shorter than lower lip teeth, spinescent; lower lip teeth lanceolate, apex spinescent; fruiting calyx to 6 × 4 mm, conspicuously veined. Corolla white to reddish, ca. 3 mm, slightly exserted, sparsely puberulent; tube ca. 2 mm, dilated at throat; upper lip less than 1 × 2.5 mm, lobes ovate; lower lip oblong, ca. 1 × 0.6 mm, flat. Stamens slightly exserted, free; posterior filaments puberulent at base. Nutlets brown, ovoid, ca. 1 × 0.7 mm, glandular-foveolate. Fl. Feb-Jun, fr. Mar-Aug. Dry sandy areas. Hainan, Sichuan, Taiwan [Cambodia, India, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, Vietnam; Africa, SW Asia, Australia] Leaves used as a condiment in salads and other foods, and as a substitute for tea. (Hedge & Li, 1998)"

2.7.3.3 Toxicological data of methyl eugenol

Since methyl eugenol could be found in foods, spices, and herbs, the Flavor Extract Manufacturers Association (FEMA) estimated that methyl eugenol consumption from food was around 5–6 μg/kg/day (Smith et al., 2002). The toxicity of methyl eugenol was conducted in animals by National Toxicology Program (2000). Male and female F344 rats received gavage administration of 300 and 1,000 mg methyl eugenol/kg body weight for 14 weeks. The results showed that there was significant

mortality in the 1,000 mg/kg groups while the organs affected in the lower-dose groups included liver, glandular stomach, and nose (National Toxicology Program, 2000). Food and Drug Administration (FDA) approved the use of methyl eugenol as an additive ingredient in natural product and food (U.S. Food and Drug Administration, 2019b). Moreover, this volatile compound is used in fragrance perfumes as well as cosmetic products (Burdock, 1995).

2.7.3.4 Related reviews of methyl eugenol

Methyl eugenol is an analogue of phenolic compound, eugenol which is also the volatile compound constituted in essential oil of numerous aromatic plants. The odor of this volatile compound is a well-known active chemical attractant for the fruit fly as the plant kairomone (Metcalf, Mitchell, Fukuto, & Metcalf, 1975). Additionally, its odor is also beneficial to use as a fragrance in cosmetics as well as food flavoring agent (Council of Europe-Committee of Experts on Flavouring Substances, 2001). Various biological activities of methyl eugenol have been previously reported including antibacterial (Yamani et al., 2016), anesthetic (Sell & Carlini, 1976), hypothermic, myorelaxant and anticonvulsant effects (Dallmeier & Carlini, 1981).

Most of the literature reviews in this study were emphasized on methyl eugenol and its activities related to brain, emotion, nervous system and physiological activities. Normotensive rats were separated into pentobarbital-anesthetized and conscious groups. After intravenous injection of methyl eugenol, both groups exhibited a dose-dependent manner in reducing mean aortic pressure. At a high concentration level of methyl eugenol (10 mg/kg), both anesthetized and conscious rats exhibited hypotension effects associating with a bradycardia response which seemed to be related to an active vascular relaxation rather than withdrawal of sympathetic tone (Lahlou, Figueiredo, Magalhães, Leal-Cardoso, & Gloria, 2004).

Animal model using male Wistar rats was investigated to evaluate central nervous system (CNS) depressive behavior and anxiety. The rats consuming methyl eugenol showed a decrease of the immobility time in the forced swimming test while open-field, social interaction, plus-maze and holeboard tests showed no differences comparing to the control group. Therefore, administration of methyl eugenol compound exhibited anti-depressive effect in rats. Moreover, modifying the CNS mechanisms

involved with this behavior models might be the induction of anti-depressive effect of methyl eugenol (Norte, Cosentino, & Lazarini, 2005).

Hippocampus is the part of the brain which connects to emotion and memory. Cellular model was used to investigate the effects of methyl eugenol on subunit recombinant α_1-β_2-γ_2 or α_5-β_2-γ_2 which is the most common form of GABAARs in the hippocampus to mediate tonic inhibition in hippocampal neurons. The results showed that methyl eugenol inhibited the activity of hippocampal neurons as well as activated the GABAARs receptors (Ding et al., 2014).

The central amygdala plays an important role in the expression of emotional behaviors such as anxiety which has been suggested that it is related to the regulation of food intake (C. Liu, Lee, & Elmquist, 2014). Animal model using mice indicated that the mice consuming methyl eugenol showed the increment of feeding. Moreover, the enchantment of GABAergic transmission and repressed neuronal excitability of the central amygdala were detected by electrophysiological study (Zhu et al., 2018).

The anxiolytic effect in chronic anxiety mice receiving methyl eugenol also showed the reduction of anxiety-like behaviors. Moreover, the increment of tonic and phasic form of GABAergic inhibition in central amygdala neurons also implicated that methyl eugenol could be capable of reducing anxiety (Y.-M. Liu et al., 2019).

Numerous mechanisms underlying the effect of methyl eugenol on brain activity and its pharmacologic effects on CNS were established. It seemed that the compound exhibited anti-depressant and hypotension effects. Thus, the inhalation of this volatile compound might show some effects on brain wave and physiological activities.

2.7.4 Methyl chavicol

2.7.4.1 Properties of methyl chavicol

The chemical and physical characteristics of methyl chavicol were obtained from U.S. National Library of Medicine: The National Center for Biotechnology Information advances science and health (National Center for Biotechnology Information, 2019c).

Chemical formula: $C_{10}H_{12}O$

IUPAC name: 1-methoxy-4-prop-2-enylbenzene

CAS number: 140-67-0

Molar mass:	148.205 g/mol
Color and appearance:	colorless to light yellow liquid
Odor:	reminiscent of anise with a corresponding sweet taste
Water solubility:	178mg/L at 25°C
Vapor pressure:	0.165 mmHg at 25°C

Previous reports identified chemical component in the essential oil of *Ocimum basilicum* L. from various countries shown in Table 6. It was found that methyl chavicol is the main compound of *O. basilicum* L.

Table 6 Chemical constituents of *Ocimum basilicum* L.

Part of plant	Chemical constituents		Reference
Aerial part	β-myrcene	0.24%	Bunrathep, Palanuvej, and Ruangrungsi (2018)
	Limonene	0.09%	
	(E)- β-ocimene	2.27%	
	1,8-cineole	0.93%	
	Fenchone	0.07%	
	Linalool	0.10%	
	Camphor	0.33%	
	Trans-α-bergamotenel	2.14%	
	α-bulnesene	0.22%	
	γ-cadinene	0.24%	
	cubenol	0.47%	
	methyl chavicol	92.48%	
	β-Pinene	0.10%	Joshi (2014)
	Myrcene	0.30%	
	Limonene	0.20%	
	Cineol-1,8	2.10%	
	(E)- β-ocimene	0.20%	

Table 6 Chemical constituents of *Ocimum basilicum* L. (cont.)

Part of plant	Chemical constituents		Reference
Aerial part	Terpinolene	7.70%	Joshi (2014)
	Camphor	0.60%	
	Borneol	0.50%	
	Terpin-4-ol	0.10%	
	α-Terpineol	1.00%	
	Methyl chavicol	38.30%	
	Isocarveol-dehydro	0.20%	
	Chavicol	0.60%	
	Eugenol	4.50%	
	Methyl eugenol	39.30%	
	β-Copaene	0.10%	
	cis-Muurola-3,5-diene	0.10%	
	cis-Muurola-4 (14),5-diene	0.20%	
	γ-Muurolene	0.10%	
	Methyl isoeugenol	0.20%	
	δ-Amorphene	0.30%	
	Cubenol	1.90%	
	α-bulnesene	0.22%	
	γ-cadinene	0.24%	
	cubenol	0.47%	
	methyl chavicol	92.48%	
Leaf	α-Terpinene	0.02%	S.-J. Lee, Umano, Shibamoto, and Lee (2005)
	γ-Terpinene	0.04%	
	p-Cymene	0.01%	
	1,8-Cineole	2.88%	
	Linalool *cis*-furanoid	0.34%	
	trans-Sabinene hydrate	0.21%	
	Linalool *trans*-furanoid	0.37%	

Table 6 Chemical constituents of *Ocimum basilicum* L. (cont.)

Part of plant	Chemical constituents		Reference
Leaf	Ocimene oxide	0.01%	S.-J. Lee et al. (2005)
	Camphor	0.31%	
	3,7-Dimethyl-1,6-octadien-3-ol (linalool)	39.39%	
	Linalyl acetate	0.03%	
	trans-p-menth-2-en-1-ol	0.03%	
	Bornyl acetate	0.23%	
	4-Terpineol	0.03%	
	Hotrienol	0.02%	
	Lavandulol	0.20%	
	p-menth-1,8-dien-4-ol	0.02%	
	Terpinyl formate	0.02%	
	α-Terpineol	1.12%	
	Borneol	0.26%	
	Verbenone	0.01%	
	Exo-2-hydroxycineole acetate	0.03%	
	α-Citral	0.08%	
	L-carvone	0.01%	
	Linalool oxide cis-pyranoid	0.05%	
	Linalool oxide trans-pyranoid	0.08%	
	Nerol	0.02%	
	Geraniol	0.16%	
	Geranyl acetate	0.03%	
	Exo-2-hydroxycineole	0.02%	
	β-Cubebene	0.02%	
	δ-Cadinene	0.02%	
	Valencene	0.01%	
	α-Amorphene	0.01%	
	Dehydroaromadendrene	0.01%	
	Caryophyllene oxide	0.11%	

Table 6 Chemical constituents of *Ocimum basilicum* L. (cont.)

Part of plant	Chemical constituents		Reference
Leaf	α-Humulene oxide	0.03%	S.-J. Lee et al.
	Spathulenol	0.28%	(2005)
	α-Cadinol	1.82%	
	β-Bisabolol	0.02%	
	β-Bisabolol isomer	0.02%	
	Isospathulenol	0.02%	
	β-Eudesmol	0.09%	
	Dihydroactinidiolide	0.12%	
	1-Penten-3-ol	0.01%	
	(*Z*)-2-pentenol	0.01%	
	Hexanol	0.03%	
	(*Z*)-3-hexenol	0.51%	
	3-Octanol	0.04%	
	Cyclohexanol	0.01%	
	1-Octen-3-ol	0.53%	
	Octanol	0.11%	
	Hexanal	0.02%	
	(*E*)-2-hexenal	0.12%	
	(*E,Z*)-2,4-heptadienal	0.02%	
	(*E,E*)-2,4-heptadienal	0.01%	
	(Z)-3-hexenyl acetate	0.01%	
	3-Hydroxy-2-butanone	0.01%	
	6-Methyl-5-heptenone	0.02%	
	6-Methyl-(E,E)-3,5-heptadien-2-one	0.02%	
	β-Ionone	0.05%	
	cis-Jasmone	0.02%	
	trans-Beta-ionone-5,6-epoxide	0.01%	
	Benzaldehyde	0.18%	

Table 6 Chemical constituents of *Ocimum basilicum* L. (cont.)

Part of plant	Chemical constituent		Reference
Leaf	Methyl benzoate	0.05%	S.-J. Lee et al. (2005)
	Phenyl acetaldehyde	0.03%	
	1-Methoxy-4-(2-propenyl)benzene (estragole)	20.29%	
	Methyl salicylate	0.03%	
	Cuminaldehyde	0.11%	
	Anethol	0.06%	
	Safrole	0.01%	
	Benzyl alcohol	0.18%	
	Phenethyl alcohol	0.26%	
	Methyl cinnamate	2.15%	
	Methyl eugenol	0.65%	
	Anisaldehyde	0.15%	
	Methyl cinnamate	12.78%	
	Ethyl cinnnamate	0.03%	
	Eugenol	8.96%	
	2-Isopropyl-5-methylphenol (thymol)	0.15%	
	2-Isopropyl-2-methylphenol (carvacrol)	0.03%	
	4-Allylphenol	2.57%	
	3-Hydroxy-2-butanone	0.01%	
	6-Methyl-5-heptenone	0.02%	
	6-Methyl-(E,E)-3,5-heptadien-2-one	0.02%	
	β-Ionone	0.05%	
	cis-Jasmone	0.02%	
	trans-Beta-ionone-5,6-epoxide	0.01%	
	Benzaldehyde	0.18%	
	Methyl benzoate	0.05%	
	Phenyl acetaldehyde	0.03%	
	1-Methoxy-4-(2-propenyl)benzene (estragole)	20.29%	
	Methyl salicylate	0.03%	

Table 6 Chemical constituents of *Ocimum basilicum* L. (cont.)

Part of plant	Chemical constituents		Reference
Leaf	Cuminaldehyde	0.11%	S.-J. Lee et al. (2005)
	Anethol	0.06%	
	Safrole	0.01%	
	Benzyl alcohol	0.18%	
	Phenethyl alcohol	0.26%	
	Methyl cinnamate	2.15%	
	Methyl eugenol	0.65%	
	Anisaldehyde	0.15%	
	Methyl cinnamate	12.78%	
	Ethyl cinnnamate	0.03%	
	Eugenol	8.96%	
	2-Isopropyl-5-methylphenol (thymol)	0.15%	
	2-Isopropyl-2-methylphenol (carvacrol)	0.03%	
	4-Allylphenol	2.57%	
	p-Methoxycinnamaldehyde	0.03%	
	2,6-Dimethylpyrazine	0.01%	
	γ-butyrolactone	0.09%	
	Myristicin	0.01%	
	α-Thujene	0.05%	Chalchat and Özcan (2008)
	α-Pinene	0.46%	
	Camphene	0.11%	
	Sabinene	0.07%	
	β-Pinene	0.05%	
	Myrcene	0.81%	
	α-Phellendrene	4.15%	
	p-Cymene	2.32%	
	Limonene	13.64%	
	(Z)-β-Ocimene	0.31%	

Table 6 Chemical constituents of *Ocimum basilicum* L. (cont.)

Part of plant	Chemical constituents		Reference
Leaf	γ-Terpinene	0.17%	Chalchat and
	Fenchone	5.70%	Özcan (2008)
	2-Ethylbutanoate 3-methylbutyle	0.07%	
	Mentha-2,8-dien-1-ol trans	0.08%	
	Limonene oxide	0.06%	
	Camphre	0.16%	
	Estragole	52.60%	
	Endo-fenchyle acetate	1.30%	
	Exo-fenchyle acetate	10.99%	
	Trans-anethole	0.55%	
	Carvacrole	0.30%	
	α-Copaene	0.08%	
	Methyle eugenol	0.18%	
	β-Caryophyllene	0.08%	
	Germacrene D	0.47%	
	δ-Cadinene	0.11%	
	Phenyl ethyl hexanote	0.10%	
	β-Sinensal	0.07%	
Flower	α-Thujene	0.03%	
	α-Pinene	0.62%	
	Camphene	0.18%	
	Sabinene	0.03%	
	β-Pinene	0.03%	
	Myrcene	1.28%	
	α-Phellendrene	4.37%	
	δ-3-Carene	0.04%	
	p-Cymene	0.38%	
	Limonene + β-phellandrene	19.41%	

Table 6 Chemical constituents of *Ocimum basilicum* L. (cont.)

Part of plant	Chemical constituents		Reference
Flower	(Z)-β-Ocimene	1.59%	Chalchat and
	(E)-β-Ocimene	0.08%	Özcan (2008)
	γ-Terpinene	0.10%	
	Fenchone	10.10%	
	Isoamyle isovalerate	0.07%	
	Linalool	0.03%	
	Camphre	0.19%	
	Estragole	58.26%	
	Endo-fenchyle acetate	0.61%	
	Exo-fenchyle acetate	1.15%	
	Trans-anethole	0.23%	
	Methyle eugenol	0.03%	
	Germacrene D	0.19%	
	Cyclobazzanene	0.03%	
Stem	α-Thujene	0.09%	
	α-Pinene	0.10%	
	Sabinene	0.09%	
	β-Pinene	0.08%	
	Myrcene	0.26%	
	α-Phellendrene	1.66%	
	p-Cymene	1.66%	
	Limonene	2.40%	
	1,8-Cineole	1.04%	
	(*Z*)-β-Ocimene	0.07%	
	γ-Terpinene	0.51%	
	Fenchone	0.36%	
	Linalool	0.32%	
	Trans-non-2-enol	0.17%	

Table 6 Chemical constituents of *Ocimum basilicum* L. (cont.)

Part of plant	Chemical constituents		Reference
Stem	Terpinen-4-ol	0.19%	Chalchat and
	Estragole	15.91%	Özcan (2008)
	Endo-fenchyle acetate	0.31%	
	Exo-fenchyle acetate	6.14%	
	Bornyle acetate + *trans*-anethole	0.20%	
	Eugenol	0.12%	
	(*E*,*E*)-Decan-2,4-dienal	0.29%	
	α-Terpinyl acetate	0.38%	
	Trans-anethole	0.10%	
	Methyle eugenol	0.06%	
	β-Caryophyllene	0.51%	
	β-Dihydro aparofuran	0.64%	
	Kessane	1.21%	
	Elemicine	0.30%	
	(*Z*)-Isoelemicine	0.23%	
	α-Thujene	0.09%	
	α-Pinene	0.10%	
	Sabinene	0.09%	
	β-Pinene	0.08%	
	Myrcene	0.26%	
	α-Phellendrene	1.66%	
	p-Cymene	1.66%	
	Limonene	2.40%	
	1,8-Cineole	1.04%	
	(*Z*)-β-Ocimene	0.07%	
	γ-Terpinene	0.51%	
	Fenchone	0.36%	
	Linalool	0.32%	
	Trans-non-2-enol	0.17%	

Table 6 Chemical constituents of *Ocimum basilicum* L. (cont.)

Part of plant	Chemical constituents		Reference
Stem	Terpinen-4-ol	0.19%	Chalchat and
	Estragole	15.91%	Özcan (2008)
	Endo-fenchyle acetate	0.31%	
	Exo-fenchyle acetate	6.14%	
	Bornyle acetate + *trans*-anethole	0.20%	
	Eugenol	0.12%	
	(*E*,*E*)-Decan-2,4-dienal	0.29%	
	α-Terpinyl acetate	0.38%	
	Trans-anethole	0.10%	
	Methyle eugenol	0.06%	
	β-Caryophyllene	0.51%	
	β-Dihydro aparofuran	0.64%	
	Kessane	1.21%	
	Elemicine	0.30%	
	(Z)-Isoelemicine	0.23%	
	Caryophyllene oxide	1.55%	
	1,2-Epoxyhumulene	0.10%	
	Dill apiole	50.07%	
	Apiole	9.48%	
	α-Humulene	0.08%	
	Germacrene D	0.07%	
	(Z)-Falcarinol	0.91%	

2.7.4.2 Natural source

Natural methyl chavicol or estragole is an organic compound consisting of a benzene ring substituted with a methoxy group as well as a propenyl group. This compound is famous for its fragrance which can be obtained from various plants, such as anise, funnel, bay, turpentine and basil (Fahlbusch et al., 2003). In this research, methyl chavicol was extracted from *Ocimum basilicum* L. with its common names as

sweet basil, Thai basil, Common basil. This plant is native to tropical and sub-tropical regions which is widely used as a culinary herb and a medicinal plant.

Botanical name: *Ocimum basilicum* L.

Synonym: *Ocimum basilicum* var. *album* (L.) Benth.

Ocimum basilicum var. *densiflorum* Benth.

Ocimum basilicum var. *difforme* Benth.

Family: Lamiaceae

Plant description: *Ocimum basilicum* L. or Thai sweet basil is an important culinary and herbal plant in Southeast Asia. In Thailand, this plant is called Horapa which is widely used throughout Thailand. The flora of China provides the information of this plant that "Herbs annual. Stems erect, 20-80 cm tall, apex retrorse puberulent, base glabrous, tinged red, much branched. Petiole ca. 1.5 cm, ± narrowly winged apically; leaf blade ovate to oblong, 2.5-5 × 1-2.5 cm, subglabrous, abaxially glandular, base attenuate, margin irregularly dentate or subentire, apex sub obtuse to acute; lateral veins 3- or 4-paired. Thyrses 10-20 cm, puberulent; verticillasters puberulent or densely pilose, approximate apically; bracts sessile, oblanceolate, 5-8 mm, base attenuate, margin ciliate, apex acute, colored. Pedicel ca. 3 mm in flower, to 5 mm in fruit. Calyx campanulate, ca. 4 × 3.5 mm, pubescent outside, pilose at throat inside, tube ca. 2 mm; middle tooth of upper lip widest, ca. 2 × 1 mm, subcircular, concave, apex mucronate; lateral teeth broadly ovate, ca. 1.5 mm, apex acute; lower lip teeth lanceolate, ca. 2 mm, apex spinescent, ciliate; fruiting calyx persistent, conspicuously veined. Corolla purplish or with upper lip white, limb puberulent outside; tube ca. 3 mm, throat ± dilated; upper lip wide, ca. 3 × 4.5 mm, 4-lobed, ± flat; lower lip purple, ca. 6 mm. Stamens free, slightly exserted, posterior 2 dentate, base puberulent. Nutlets dark brown, ovoid, ca. 2.5 × 1 mm, glandular foveolate. Fl. Jul-Sep, fr. Sep-Dec. (Hedge & Li, 1998)".

2.7.4.3 Toxicological data of methyl chavicol

The toxicity of methyl chavicol in humans was conducted by applying a closed-patch test on human subjects for 48 hours. Methyl chavicol did not cause irritation. Another test was conducted on 25 volunteers by applying a concentration of 3% in petrolatum. The findings showed no sensitization reactions. The toxicity of

methyl chavicol in animals was conducted in rats given 4 daily oral doses of 605 mg/kg estragole. The results reported minor liver damage, consisting of discoloration, mottling and blunting of lobe edge (National Center for Biotechnology Information, 2022). Food and Drug Administration (FDA) approved the use of methyl chavicol as flavoring agent or adjuvant in food (U.S. Food and Drug Administration, 2019a). The EU Scientific Committee of Food (SCF) indicated the daily consumption of methyl chavicol that "An average daily intake of methyl chavicol is 4.3 mg per day, corresponding to ~0.07 mg/kg bw/day for a 60 kg person. This estimation is based on a relative conservative method using theoretical maximum use levels of methyl chavicol (including addition as a pure compound) in 28 food categories and consumption data for these food categories based on 7 day dietary records of adult individuals" (Scientific Committee on Food of the European Union, 2001). The U.S. Flavor and Extract Manufacturers Association (FEMA) estimated a daily consumption of methyl chavicol based on the production volume data of herbs, essential oils, and flavor substances containing methyl chavicol in the United States that "The intake of methyl eugenol must be less than 0.01 mg/kg BW a day." (Smith et al., 2002)

2.7.4.4 Related reviews of methyl chavicol

Methyl chavicol or estragole is the natural volatile compound which can be found abundantly in common culinary herbs such as sweet basil and anise (De Vincenzi, Silano, Maialetti, & Scazzocchio, 2000). The plants containing this compound reported to possess numerous activities. Sweet basil (*Ocimum basilicum*) contained approximately 70% methyl chavicol in its essential oil as the main compound (Chalchat & Özcan, 2008). It has been reported to alleviate and prevent cardiovascular disorders, diabetes mellitus, menstrual cramps, digestive disorders, neuro-degenerated disorders and cancer (Purushothaman et al., 2018). Another plant containing methyl chavicol as the primary component in its essential oil is star anise (*Illicium verum*). This herbal culinary plant exhibited many pharmacological properties including antimicrobial, antioxidant, insecticidal, analgesic, sedative and convulsive activities (G.-W. Wang, Hu, Huang, & Qin, 2011).

The single use of methyl chavicol also exhibited some biological activities such as inducing muscle contraction by increasing myoplasmic calcium and blocking

neuromuscular transmission (Albuquerque et al., 1995), antimicrobial (Friedman et al., 2002; Lachowicz et al., 1998), intestinal smooth muscle relaxing (Coelho-de-Souza et al., 1997), vascular smooth muscle relaxing (Soares et al., 2007) and anti-inflammatory (Ponte et al., 2012) activities. The literature reviews of this research emphasized on the activities of methyl chavicol related to brain, emotion, nervous system and physiological activities.

The inhalation of estragon oil containing methyl chavicol as the main compound was investigated for its effects on sympathetic activity in healthy adults. After inhalation of the essential oil 2% (wt/wt) in triethyl citrate (an odorless solvent) for the total of 10 mins, there was a significant increase in sympathetic activity showing low frequency amplitude of systolic blood pressure (SBP-LF amplitude) (Haze, Sakai, & Gozu, 2002).

Oral administration of methyl chavicol was performed to induce behavioral changes in rats. Swimming test, open-field, elevated plus-maze and holeboard tests were used to investigate animal depression. The results from those activities showed no significant differences between the control and experimental groups. These results indicated that methyl chavicol did not modify the activity of CNS related to depression. On the other hand, social interaction study was used as an animal model to study anxiety. The result showed that the rats administered methyl chavicol exhibited reduction of the time spent on active social interaction like anxiogenic drugs. In conclusion, this compound produced a reduction in locomotor activity, probably *via* the mechanisms of chemical modulation without the alteration of CNS structures related to anxiety (Cosentino, Norte, & Lazarini, 2004).

Another study was investigated and showed the action of methyl chavicol on neuronal excitability. A local anesthetic mechanism was found in methyl chavicol by using dorsal root ganglion neurons of rats. Methyl chavicol inhibited neuron excitability by blockage of voltage-dependent activation of Na+ channel conductance in dorsal root ganglion neurons (Silva-Alves et al., 2013).

CHAPTER 3
MATERIALS AND METHODS

Regarding the clinical study, this research consisted of two separate studies: a pretesting study on the concentration levels of volatile compounds and the other study on the experiments on the effects of the selected volatile compound inhalation in healthy participants. The pretesting study was conducted to determine the most appropriate concentration levels which most participants accepted so that these appropriate concentration levels were used in the experiments. The pretesting study was conducted at Chulalongkorn University while the study on the experiments was conducted at Mahidol University on Salaya campus.

3.1 Study for pretesting the concentration of volatile compounds

The researchers recruited 50 male or female participants aged between 20 and 35 years from general public at Chulalongkorn University (Nuiden, 2018). A number of 50 participants were asked to select an appropriate concentration level of the volatile compounds in a preliminary experiment conducted before the experiment. So, they were not the participants who participated in the experiment in which a total number of the participants were 96 participants from 4 groups (24 participants/group).

3.1.1 Inclusion criteria for pretesting the concentration of selected volatile compounds

1) Thai native speakers aged between 20 and 35 years old from both genders.

2) The participants had normal heart rate whose range was between 60 and 90 bpm.

3) The participants had normal blood pressure in which systolic one was not higher than 140 mmHg and diastolic one was not higher than 90 mmHg.

4) The participants had body mass index from 18.5 to 22.9 kg/m^2 based on WHO and Asian criteria values (Luisito & Llido, 2010).

5) The participants did not have any past medical history associated with epilepsy, neurological illness, and loss of consciousness longer than 30 minutes.

6) The participants did not take CNS medication and they were not currently taking recreational drugs.

7) The participants were non-smokers.

8) The participants were non-alcoholic.

9) Before the trial, the participants' sense of smell was verified by n-butyl alcohol method test. The test detected the lowest concentration of an odor stimulus which differentiated between water and n-butyl alcohol. The participants with normal sense of smell could distinguish 2 odors at the concentration lower than Step 6 (5.48 x 10-3 v/v) of n-butyl alcohol in water.

3.1.2 Exclusion criteria for pretesting the concentration of selected volatile compounds

1) The female participants were pregnant.

2) The participants who were allergic to volatile compounds were excluded from the experiment.

3.1.3 Pretesting the concentration of selected volatile compounds

Before the actual experiment, the researchers recruited a group of healthy participants aged between 20 and 35 years old to test the satisfied concentrations of the 4 selected volatile compounds namely d-borneol, d-camphor, methyl eugenol and methyl chavicol. Each participant was asked to inhale each selected volatile compound diluted in sweet almond oil at the concentration levels at 2%, 4%, 6%, 8%, 10%, 12% v/v from oxygen pump system via a plastic tube through a face mask at the constant rate 2 L/min, at the beginning. After the inhalation, he/she completed the questionnaire asking which concentration level was the most appropriate. When the data from all the questionnaires were collected, the researchers determined which concentration level most participants considered satisfactory so that the concentration level of each selected volatile compound which most participants selected were used for the experiments later.

3.2 Research design

The research design used in this research trial is a pretest-posttest design because it is an experimental study in which an individual case or each participant serves as his or her own control and the dependent variable is analyzed for each participant. The pretest-posttest design is used to evaluate the effectiveness of the interventions when they are applied to each participant. Therefore, the design is reliable to investigate the effects of volatile compound inhalation on the participants. In this study, four selected volatile compounds diluted in sweet almond oil were used as interventions in four groups and sweet almond oil was used as a carrier oil and a control. Sweet almond oil inhalation (pretest) as diluent control was compared with each selected volatile compound inhalation (posttest).

3.3 Sample size

The researchers calculated sample size based on the previous study (Sayorwan et al., 2013). The researchers modeled the calculation of the previous study of rosemary oil inhalation measuring the mean and SD values in eye closed stage of EEG changes. So, the researchers calculated the sample size based on the dependent group as shown in the following formula (George, Wayne, & Harald, 2011; Sayorwan, 2011).

$$n = \frac{2(Z_{\alpha}+Z_{\beta})^2\sigma^2}{\Delta^2}$$

n = Sample size

α = Type I error, 0.05 (two-sided) $Z\alpha = 1.96$

β = Type II error, 0.10 (two-sided) $Z\beta = 1.28$

σ = Standard deviation of mean difference

Δ = Mean difference

Sample size calculation

$$n = \frac{2(1.96+1.28)^2 1.65^2}{2.71^2} = 21$$

3.3.1 Drop out

The researchers recruited more than 10% (3 participants) of the total population number to compensate the expecting drop-outs during the experiment and to guarantee the research confidence. The number of sample size calculation was 21 participants and 3 participants as the expecting drop-outs. Therefore, there were 24 participants in each group, thus total sample size was 96 participants from 4 groups in this research.

3.3.2 Sampling technique

Purposive sampling technique has been chosen for recruiting volunteers. The volunteers who passed the inclusion criteria were purposively assigned into 4 groups each of which consisted of 12 male participants and 12 female participants to prevent gender differences since men and women may display different patterns of lateralization in emotional processing (Wager, Phan, Liberzon, & Taylor, 2003).

3.4 Research Participants

Healthy participants were recruited from general public by public announcement.

3.4.1 Inclusion criteria

1) Thai native speakers aged between 20 and 35 years old from both genders.

2) The participants did not have certain diseases including neurological diseases, hypertension, rhinolaryngologic upper respiratory infection, and cardiovascular disease.

3) The participants had normal blood pressure in which systolic one was not higher than 140 mmHg and diastolic one was not higher than 90 mmHg.

4) The participants had normal heart rate whose range was between 60 and 90 bpm.

5) The participants had body mass index from 18.5 to 22.9 kg/m^2 based on WHO and Asian criteria values (Luisito & Llido, 2010).

6) The participants did not have any past medical history associated with epilepsy, neurological illness, and loss of consciousness longer than 30 minutes.

7) The participants did not take CNS medication and they were not currently taking recreational drugs.

8) The participants were non-smokers.

9) The participants were non-alcoholic.

10) Concerning the right-handedness, the handedness of the participants was evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971). The level of their right-handedness was evaluated via 10 items such as drawing, throwing, writing, scissor-cutting, knife-cutting, tooth-brushing, broom, spoon, striking a match and opening box lid. The researchers asked each participant to fill out the questionnaire to verify the handedness by checking "+" in the columns between right and left hands which he/she preferred to use in each inventory. He/She could check "++" when he had strong preference, which meant that he could use this hand without any assistance. If he/she did not have any preference, he/she could check "+" for both hands. After the participant filled out all the items, the researchers calculated the number of "+". The researchers determined the difference of the numbers of "+" between right and left hands by dividing the total number of "+" for both hands. The participant whose handedness index was below -40 was classified as left-handed. The participant whose handedness index was over -40 was classified as right-handed. The participant whose handedness was between -40 and +40 was classified as ambidextrous. The researchers excluded the participants who were classified as left-handed. The researchers calculated the handedness based on the formula below.

$$\text{Handedness index} = \frac{\Sigma\,(R) - \Sigma\,(L)}{\Sigma\,(R) + \Sigma\,(L)}$$

Where $\Sigma(R)$ = the summation of all right-hand items

$\Sigma(L)$ = the summation of all left-hand items

11) The normal sense of smell was used as one of the inclusion criteria. Before the trial, the participants' sense of smell was verified by n-butyl alcohol method test. The test detected the lowest concentration of an odor stimulus which differentiated between water and n-butyl alcohol. The participants with normal sense of smell could distinguish 2 odors at the concentration lower than Step 6 (5.48 x 10.3 v/v) of n-butyl alcohol in water.

12) The volunteers who preferred the target level range of 2-4 from "Odor familiarity five-point Likert scale" were included into this study. The researchers asked each potential participant to inhale each selected volatile compound diluted in sweet almond oil to fill out the pleasantness from "Odor familiarity five-point Likert scale". The researchers recruited only the potential participants who indicated oil pleasantness within this target level range as participants.

3.4.2 Exclusion criteria

1) The female participants were pregnant.

2) The participants who were allergic to volatile compounds were excluded from the experiment.

3.4.3 Discontinuation criteria

1) The participants resigned from research program or could not follow the protocol procedures.

2) The participants experienced a headache or became allergic in their respiratory system during the experiment.

3) The participants whose brainwave was detected as abnormal by electroencephalogram (EEG).

3.5 Location and setting

The research trial was carried out in Mahidol University on Salaya campus. The researchers conducted the experiment in an air-conditioned, quiet room with 24±1 ℃ with a relative humidity between 50-65%. The researchers carried out the

experiments in the morning between 8.00-12.00 a.m. to reduce the impact of circadian rhythm.

3.6 Selected volatile compounds collection

Four volatile compounds were used as the interventions in this research study. All selected volatile compounds were obtained from reliable companies. *d*-Borneol was purchased from Ji'an Yufeng Co., Ltd., China and *d*-camphor was purchased from Sigma-Aldrich, USA. Methyl eugenol was purchased from Tokyo chemical companies, Japan and methyl chavicol was purchased from from Aramacs Co.,Ltd., India. Sweet almond oil was from Chemipan Corporation Co., Ltd., Thailand.

1) *d*-Borneol (CAS number: 464-43-7)
2) *d*--Camphor (CAS number: 464-49-3)
3) Methyl eugenol (CAS number: 93-15-2)
4) Methyl chavicol (CAS number: 140-67-0)
5) Sweet almond oil (CAS number: 8007-69-0)

3.6.1 Volatile compound administration

Sweet almond oil (base oil) was used to dilute the selected volatile compounds (*d*-borneol, *d*-camphor, methyl eugenol and methyl chavicol). The suitable concentration of the volatile compounds was delivered from oxygen pump system via a plastic tube through a face mask at the constant rate 2 L/min. The percent of selected volatile compounds ranged from 6% to 10% was listed below.

1) 10% of *d*-borneol diluted in sweet almond oil
2) 6% of *d*-camphor diluted in sweet almond oil
3) 10% of methyl eugenol diluted in sweet almond oil
4) 10% 0f methyl chavicol diluted in sweet almond oil

3.7 Instruments

3.7.1 Screening session

The researchers used the instruments for screening session below.

1) Health status questionnaire (Appendix A)
2) Edinburgh Handedness Inventory test (Appendix B)
3) Score sheet for odor test (butanol threshold) (Appendix C)
4) Odor familiarity (Appendix D)

3.7.2 Measurement tools on autonomic nervous system and emotions

The researchers utilized the measurement tools listed as follows:

1) A comfortable armchair
2) 70% alcohol for hygiene
3) BIOLIGHT M7000 Multi-Parameter Patient Monitor – BIOM7000
4) Case record autonomic nervous form (Appendix E)
5) Emotions recording questionnaire (Appendix F)

3.7.3 Electroencephalographic recording (EEG)

1) Nicolet EEG v32 from Natus Neurology Company, USA
2) Nu Amps amplifier
3) 15-inch USB cable coupled with EEG acquisition computer (Amplifier)
4) Serial cable with stimulation computer (Amplifier)
5) SCAN 4.3 software known as Acquire Neuroscan version 4.3 (Compumedics Neuroscan, Australia)
6) CPU and monitor for SCAN software (EEG acquisition)
7) EEG Quick Cap with 40 channels including HEOG/VEOG, reference and ground electrodes (Ag/AgCl electrodes)
8) Disposable blunt needles and syringes
9) Electro-gel
10) Ivory liquid (OMNIPEP)

3.8 Protocol

3.8.1 Screening protocol

The researcher worked with three research assistants and a doctor. The researcher asked them to help recruit the participants, made appointments with them, set up the equipment, collected the data and facilitated them. All the research team members had been well-trained on research protocol so that the research protocol was precise and consistent for each participant. The research protocol was described below.

1) The researchers announced this research study to the general public through posters, leaflets and social media.

2) The screening criteria for the participants who wished to participate in this research experiment were described below.

2.1) The potential participants filled out the questionnaire regarding their personal health status.

2.2) The researchers completed Edinburgh Handedness Inventory test to determine the handedness of the potential participants.

2.3) The researchers followed these processes to evaluate the olfactory ability of the potential participants. The researchers prepared butanol and water solutions at different concentration levels from 0 to 11 and preserve them in the bottles. The researchers asked the potential participants to detect which bottle contained the odor with initial concentration at 9. After the potential participants gave each correct answer, the researchers reduced the butanol concentration by a factor of 3. The researchers recorded the detection threshold when the potential participants gave 5 consecutive, correct answers of the butanol odor.

2.4) The researchers asked each potential participant to inhale each selected volatile compound diluted in sweet almond oil and to complete the pleasantness based on “Odor familiarity 5-point Likert scale”. The researchers recruited the potential participants who chose the oil pleasantness within the target level range of 2-4 as the research participants.

3) After potential participants passed the screening test processes, they handed in their consent form and attended the tutorial session in which they listened to the instructions and the procedures of the experiment explained by the researchers in Thai.

4) After that, each male or female participant was purposively assigned into each selected volatile compound group until each group consisted of 12 male participants and 12 female participants.

3.8.2 Before the experiment date

The researchers made the next appointment with each participant after the screening stage was complete and the participant passed all the screening criteria. The day before the experiment date, the researchers called the participants to confirm the experiment time, date and place. The researchers informed them to wash their hair by shampoo but they could use neither hairspray, body spray deodorant nor perfume on the experiment date. The participants were advised not to eat food with strong odor, basil (*Ocimum basilicum*), holy basil (*Ocimum tenuiflorum*), betel leaf (*Piper betle*) and wild betel leaf (*Piper sarmentosum*). The participants were advised not to consume caffeinated drinks. They should have enough sleep before the experiment date so that they felt fresh and ready for the experiment. The participants should not show any symptoms of fatigue or drowsiness on the experiment date. In the morning of the experiment date, the researchers phoned the participants to confirm and review the instructions before the procedures. If any female participants were on menstrual period or any participant consumed caffeine 2 hours before the trial, had cold or physical conditions that affected their sense of smell, felt drowsy before the trial, the researchers postponed and rescheduled the experiment date.

3.8.3 Measurements on autonomic nervous system (ANS)

3.8.3.1 Autonomic parameter recording

The responsible researchers included Mr. Akarat Sivaphongthongchai (main researcher) and Miss Vipa Thechasinthop (assistant researcher) who performed and measured ANS parameters. Assistant Professor Vorasith Siripornpanich, MD., the

researcher's co-advisor supervised the experiments on the ANS parameters while the researchers were conducting the experiments and recording the ANS parameters.

The researchers used Biolight M7000 Pateient Monitor to record 4 ANS parameters: skin temperature, respiratory rate, heart rate and blood pressure simultaneously in real time. They utilized life scope 8 bedside monitors to measure ANS parameters of the participants in a semi-reclining chair in quiet, air-conditioned (24±1°C), pre-ventilated room with 40-50% humidity. The researchers conducted the experiment between 8.00 a.m. and 12.00 a.m. to reduce the circadian variation. Each participant was tested individually to avoid any distraction. The room was re-ventilated with fresh air for 15 minutes before the next experiment.

Heart rate and respiratory rate of each participant were recorded every minute. The electrodes were placed in 3 positions namely left infraclavicular fossa, right infraclavicular fossa (the upper left and right sides of the chest) and left anterior axillary line below the bottom rib. The respiratory measurement was affected by the movement of chest and abdomen on the left infraclavicular fossa and the left anterior axillary line below the bottom rib. Blood pressure was recorded every 2.5 minutes. Systolic and diastolic blood pressure was recorded on the left arm. Skin temperature was recorded every minute. The sensor was placed in the middle of the back of a non-dominant hand.

3.8.3.2 Emotions recording

The researchers employed the modified Geneva Emotion and Odor Scale (GEOS) questionnaire in Thai version based on the questionnaire of the previous study conducted by Sayorwan (2011). In the previous study, the questionnaire was evaluated for Cronbach's a value. The measure with Cronbach's a value was equal to 0.752. So, the questionnaire in this study was designed to measure the emotional responses. To evaluate emotional responses, the GEOS questionnaire had classified the subjective feelings into five dimensions namely well-being, disgust, sensual, relaxation and refreshing.

A set of scales on various emotional states was employed on the conceptual model introduced by the Geneva Emotion and Odor Scale to evaluate the emotional states (Thanatuskitti, Siripornpanich, Sayorwan, Palanuvej, & Ruangrungsi, 2020). This scale measured their subjective personal feelings through a 100-mm visual

analog scale on emotional states (good, bad, active, drowsy, fresh, relaxed, stressed, frustrated, romantic, annoyed, calm, and disgusted).

3.8.4 Central Nervous System measurement

3.8.4.1 Electroencephalographic recording (EEG)

The responsible researchers included Mr. Akarat Sivaphongthongchai (main researcher) and Miss Vipa Thechasinthop (assistant researcher) who performed and measured EEG recordings. Assistant Professor Vorasith Siripornpanich, MD., the researcher's co-advisor supervised the experiments on the EEG recordings while the researchers were conducting the experiments and recording the EEG parameters.

EEG recordings were carried out according to the international 10-20 system by applying a set of 31 electrodes with one additional ground (Jasper, 1958). The researchers also used both mastoids as the recording reference, with an average of both mastoids equal to A1+A2/2. The electrooculogram (EOG) was monitored by placing electrodes in the external acanthi (HEOL and HEOR), left supraorbital (VEOU), and infraorbital (VEOL) regions. Each participant was asked to put on an electro cap of elastic spandex-type fabric with recessed silver/silver chloride (Ag/AgC1) electrodes attached to the material. The researchers set electrode impedances below five kOhms (Lorig, 2000). The researchers used the recording system known as Acquire Neuroscan version 4.3 (Compumedics Neuroscan, Australia). The researchers set the online filter to a band-pass with a low pass equal to 60 Hz and a high pass equal to 0.1. A/D rate was 500 Hz. The gain was set at 19 and the notch filter was open at 50 Hz (Ajjimaporn, Rachiwong, & Siripornpanich, 2018). During EEG analysis, the continuous EEG data were cut into 2,000 milliseconds-length EEG epochs. The post-recording filter was set as band-pass at 0.3-30 Hz, and the artifact rejection was assigned at ±80 Hz for all EEG channels (Kaewcum & Siripornpanich, 2018). The power spectrum of the respective frequency bands was analyzed based on the Fast Fourier Transform (FFT), ranging from delta (0.5-4 Hz), theta (4.5-8 Hz), alpha (8.5-13 Hz) and beta waves (13.5-30 Hz) (Siripornpanich, Sampoon, Chaithirayanon, Kotchabhakdi, & Chutabhakdikul, 2018).

3.9 Experiment procedures

1) Before the experiment, the researchers advised the participants to avoid using any hairspray, deodorant nor perfume. They were asked to avoid drinking caffeinated drinks. They did not eat food with strong odor, basil (*Ocimum basilicum*), holy basil (*Ocimum tenuiflorum*), betel leaf (*Piper betle*) and wild betel leaf (*Piper sarmentosum*). They did not display any sign of fatigue or drowsiness on the experiment date.

2) The participants handed in their consent forms and attended the tutorial session in which they listened to the research objective and the whole experiment explained by the researchers in Thai. Then, the ANS parameters of the participants were recorded.

3) The researchers asked each participant to sit in a comfortable armchair far from the ANS acquisition unit in a quiet, air-conditioned room with the temperature at 24±1 ℃ and relative humidity at 50-65%.

4) Each participant sat in a comfortable armchair far from the ANS acquisition unit in a quiet, air-conditioned room. After the 10-minute rest, the ANS parameters were recorded according to the instruction manual. Each participant filled out the emotional state questionnaire for baseline (resting period).

5) Pure sweet almond oil was then administered to each participant through inhalation for 10 minutes.

6) After that, there was a 5-minute interval when each participant filled out the questionnaire on emotions (SO period). Finally, each participant inhaled the selected volatile compound diluted in sweet almond oil for 10 minutes and filled out the questionnaire on emotions.

7) The researchers collected all the data from ANS parameters and analyzed the questionnaires.

8) On the second appointment scheduled at least 7 days after the first experiment date, the researchers measured the brainwave activities of each participant.

9) The researchers divided the second session for EEG recordings into four periods.

10) The researchers asked each participant to open his/her eyes for 5 minutes and to close his/her eyes for 5 minutes.

11) In the third trial, each participant inhaled sweet almond oil for 8 minutes while he/she was closing his/her eyes.

12) Finally, each participant inhaled the selected volatile compound diluted in sweet almond oil for 8 minutes while he/she was closing his/her eyes.

The selected time for the inhalation in this protocol was slightly modified from Sayorwan (2011) and Gulluni et al. (2018). In summary, the procedures were illustrated in a chronological order in the diagram below.

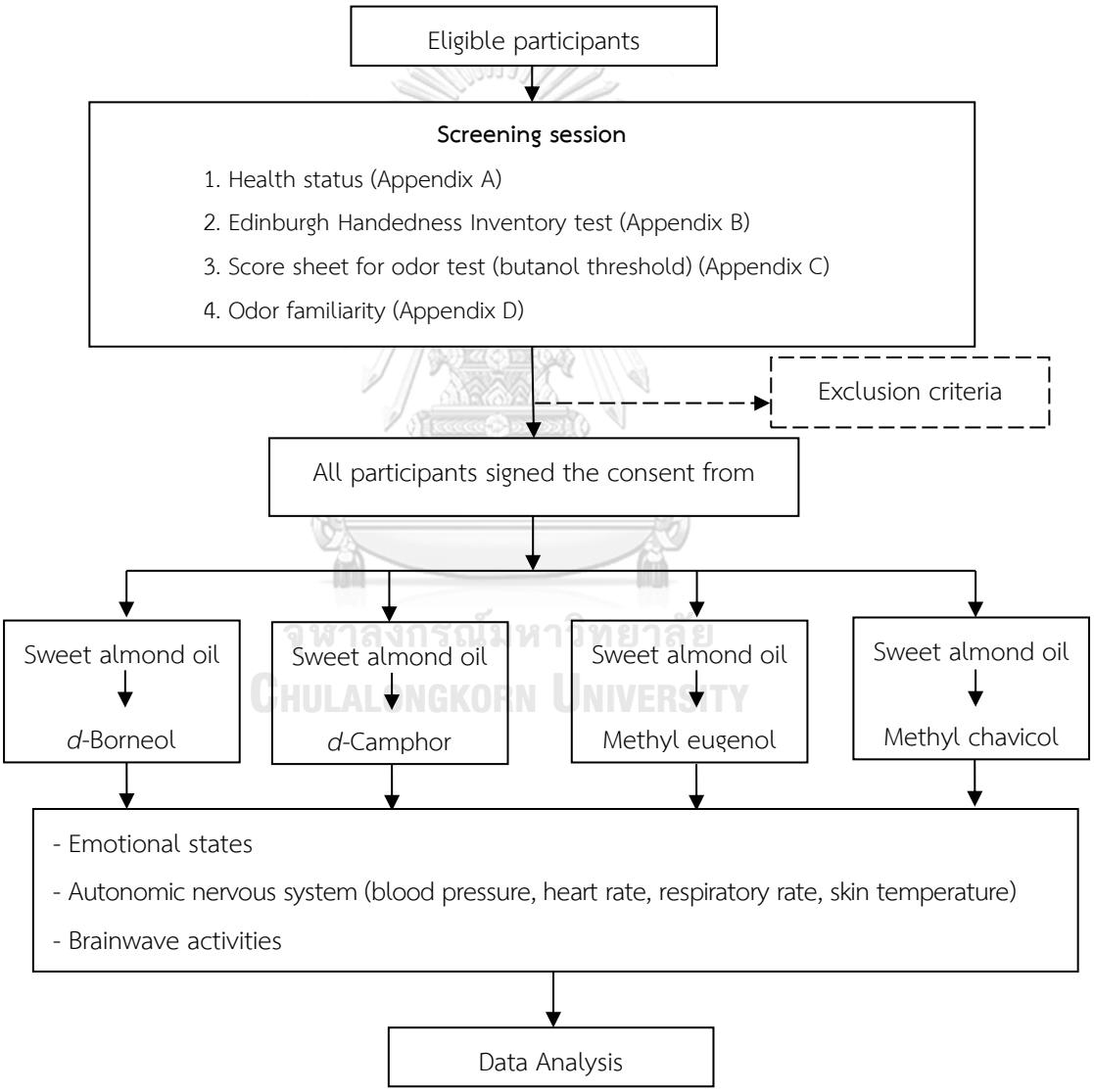


Figure 19 summary of the procedures in a chronological order

The procedures are sequenced as in a following map.

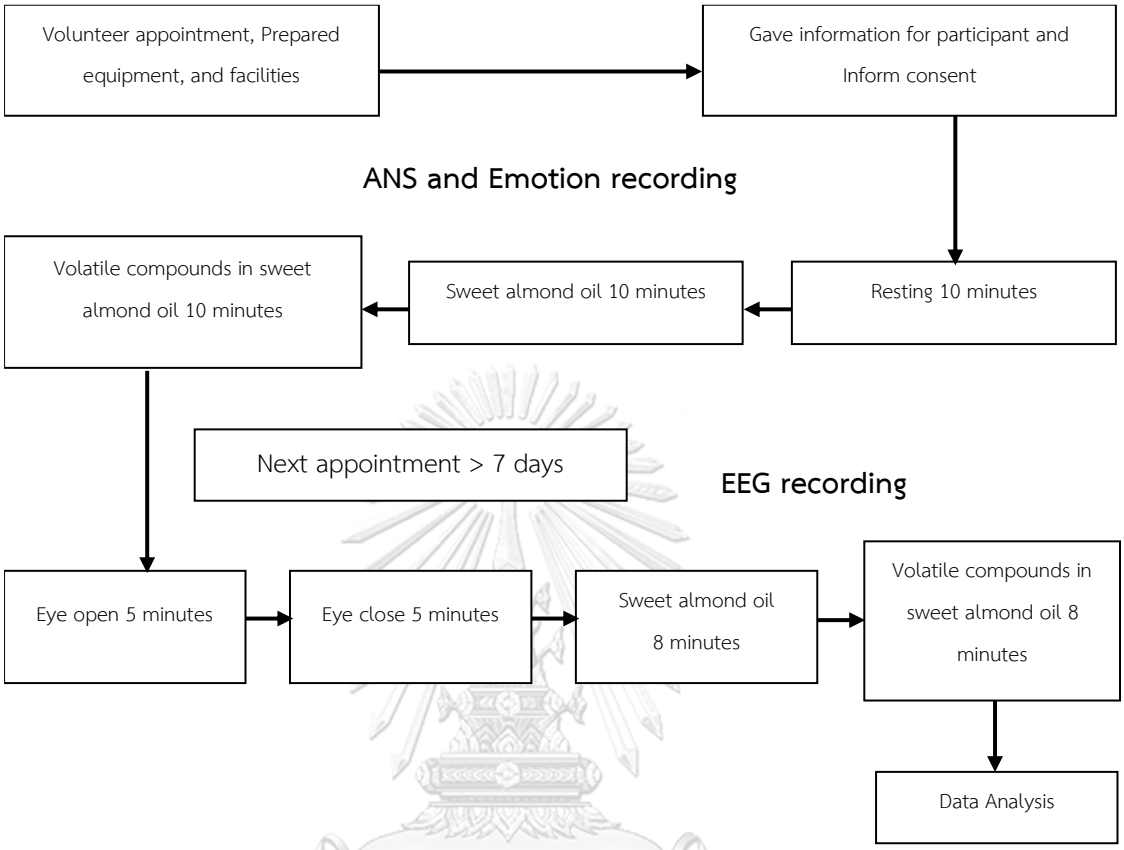


Figure 20 sequence of the research procedures

3.10 Data analysis

The pretest-posttest designs were performed in this study. SPSS statistical package version 22 was used for data analysis. Descriptive statistics, percentage, mean values and standard deviation (SD) were applied to report the general characteristics of all the participants. Paired t-test was used to analyze the results of two pairs: one pair between resting period and sweet almond oil inhalation and the other pair between sweet almond oil inhalation and each selected volatile compound inhalation in terms of the physiological and emotional changes in heart rate, respiratory rate, skin temperature, blood pressure and EEG parameters with a p-value of less than 0.05 which was statistically significant. In addition, the Shapiro-Wilk test was used for the normality test.

3.11 Ethical review

The research proposal was approved by the Ethics Review Committee for Research Involving Human Research Subjects, Health Science Group, Chulalongkorn University with Permissions No. COA No. 074/2020. The researchers explained the research protocol and the participants were asked to read and sign their consent. The participants had submitted their written informed consent before they participated in the research. They were informed that they had the rights to withdraw from the research anytime they wished. Regarding the confidentiality of the participants, the identity of all the participants was kept anonymous and their personal information were kept confidential throughout this study.

CHAPTER 4

RESULTS

The results of this study consisted of two major parts: the pre-testing study on the concentration levels of all selected volatile compounds and the clinical study on the effects of all selected volatile compounds. The pre-testing study was conducted to determine the most satisfactory concentration levels which most participants selected so that these concentration levels were used in the experiments of the clinical study. The pre-testing study was conducted at Chulalongkorn University while the clinical study was conducted at Mahidol University on Salaya campus.

4.1 The results of the pre-testing study on the concentration levels of all selected volatile compounds

4.1.1 General characteristics of the participants in the pre-testing study

Fifty healthy participants (23 males and 27 females) aged between 20 and 35 years old with normal body mass index participated in this study. The mean and SD values of the participants' age, height, weight and BMI were 22.58 (±3.06) years, 167.82 (±5.98) cm, 58.84 (±5.29) kg, 20.79 (±1.12) kg/m2 respectively.

Table 7 General characteristics of the participants in the pre-testing study

Parameters	Number	mean	SD
Age (years)	50	22.58	3.06
Height (cm)	50	167.82	5.98
Weight (kg)	50	58.84	5.29
Body Mass Index (kg/m^2)	50	20.79	1.12

4.1.2 The concentration levels of selected aromatic compounds

A total number of 50 healthy participants took part in the pre-testing study to determine the most satisfactory concentration levels of the 4 selected volatile

compounds namely d-borneol, d-camphor, methyl eugenol and methyl chavicol. Each participant was asked to inhale all the selected volatile compound diluted in sweet almond oil at the concentration levels from 2%, 4%, 6%, 8%, 10% to 12% v/v. After each participant had inhaled each selected volatile compound with the concentration levels from 2% to 12% v/v, he/she selected the concentration level of each selected compound which he/she found the most satisfactory.

The results of the pre-testing study reported the top three concentration levels most participants selected for each volatile compound in Figure 22. For d-borneol inhalation, 10% of concentration level was selected by 24 participants followed by 8% selected by 13 participants and 6% selected by 6 participants. For d-camphor inhalation, 6% of concentration level was selected by 19 participants followed by 8% selected by 15 participants and 10% selected 12 participants. For methyl eugenol inhalation, 10% of concentration level was selected 21 participants followed by 12% selected 11 participants and 8% selected by 9 participants. For methyl chavicol inhalation, 10% of concentration level was selected by 19 participants followed by 8% selected by 10 participants and 12% selected by 7 participants. The other concentration levels of each selected volatile compound were displayed in Figure 22.

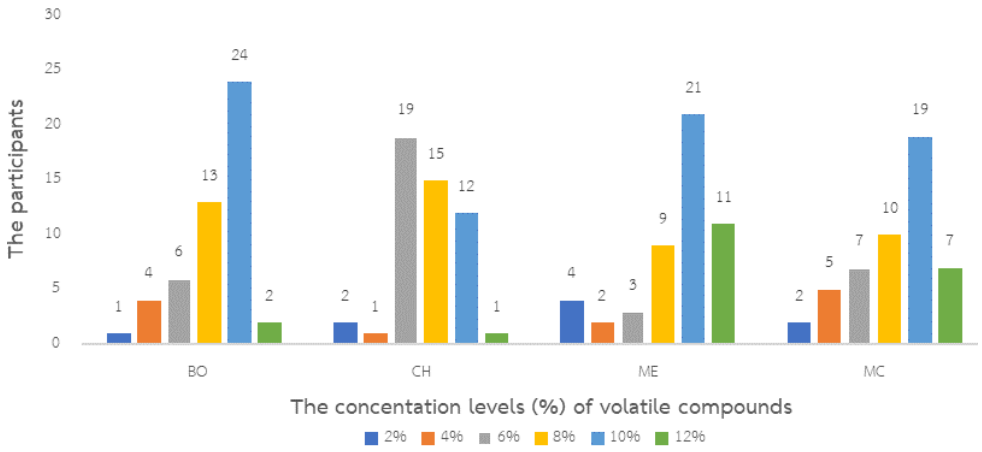


Figure 21 The bar graphs show the concentration levels (%) of volatile compounds selected by the participant

4.2 The results of the clinical study on the effects of all selected volatile compounds

The results on the clinical study were divided into 4 parts. Each part was divided into 4 sections: (1) general characteristics of participants, (2) the autonomic nervous system (ANS) parameters, (3) emotional state responses and (4) EEG recordings. General characteristics of participants included the participants' age, height, weight and BMI. ANS parameters were systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), skin temperature (ST) and respiratory rate (RR). Emotional state responses measured the participants' subjective personal feelings through a 100-mm visual analog scale on emotional states (good, bad, active, drowsy, fresh, relaxed, stressed, frustrated, romantic, annoyed, calm, and disgusted). The absolute powers of EEG recordings on brain wave activities were calculated and interpreted into frequency bands divided into five areas, including the left anterior (Fp1, F3, F7), right anterior (Fp2, F4, F8), center (Fcz, Cz, Cpz), left posterior (P3, T5, O1) and right posterior (P4, T6, O2).

There were four selected volatile compounds administered through inhalation in this study.

1. *d*-borneol 2. *d*-camphor
3. methyl eugenol 4. methyl chavicol

4.2.1 *d*-Borneol

4.2.1.1 General characteristics of participants

In the first session (ANS and emotional parameters), there were 24 participants (12 males and 12 females) aged between 20 and 35 years old with normal body mass index were asked to inhale *d*-borneol in this study. The mean and SD values of the participants' age, height, weight and BMI were 21.92 (±2.47) years old, 167.58 (±6.40) cm, 58.29 (±4.89) kg, 20.66 (±1.00) kg/m^2 respectively. In the second session (brainwave parameters) after the artifact rejection based on EEG analysis, there were 21 participants (10 males and 11 females) aged 21.90 (±2.41) years old, 167.52 (±6.72) cm, 58.33 (±5.21) kg, 20.68 (±1.07) kg/m^2. Three participants were rejected because of the artifacts in EEG analysis. So, their data were excluded from data analysis according to per protocol analysis which included complete data only.

Table 8 General characteristics of the *d*-borneol inhaling participants

Parameters	ANS and Emotional parameters (First session) (n = 24)		Brainwave parameters (Second session) (n= 21)	
	Mean	SD	Mean	SD
Age (years)	21.92	2.47	21.90	2.41
Height (cm)	167.58	6.40	167.52	6.72
Weight (kg)	58.29	4.89	58.33	5.21
Body Mass Index (kg/m^2)	20.66	1.00	20.68	1.07

4.2.1.2 ANS physiological parameters

d-Borneol inhalation caused significant changes in most ANS parameters. After sweet almond oil inhalation, skin temperature increased significantly (p-value = 0.009) while systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate decreased without statistical significance.

After *d*-borneol inhalation, systolic blood pressure, diastolic blood pressure and heart rate increased significantly (p-value = <0.001), (p-value = 0.028), (p-value = 0.026) respectively while skin temperature and respiratory rate increased without statistical significance.

Table 9 The effects on the ANS parameters after the sweet almond oil inhalation (SO) and 10% *d*-borneol inhalation (BO)

Parameters	n	Resting		SO		BO		p-value R and SO	p-value SO and BO
		Mean	SD	Mean	SD	Mean	SD		
SBP (mmHg)	24	107.67	5.78	107.00	6.01	111.96	7.48	0.084	**<0.001***
DBP (mmHg)	24	65.67	4.83	65.29	3.70	66.58	3.46	0.515	**0.028***
HR (bpm)	24	68.21	6.13	67.67	6.15	70.04	5.50	0.173	**0.026***
ST (°C)	24	31.12	0.82	31.51	1.10	31.79	1.16	**0.009***	0.057
RR (bpm)	24	15.96	2.03	15.46	1.98	16.33	2.16	0.097	0.090

* Significant difference p-value < 0.05, Systolic (SBP) and diastolic (DBP) blood pressure, Heart rate (HR), Skin temperature (ST), Respiratory rate (RR), SO=sweet almond oil, BO=*d*-boneol

4.2.1.3 Psychological parameters of emotional states

Sweet almond oil inhalation caused some significant changes in psychological parameters of emotional states. After the sweet almond oil inhalation, the mean scores of good feelings increased significantly (p-value = p<0.001) while the mean scores of drowsy and stressed feelings decreased significantly (p-value = 0.015), (p-value=0.008) respectively. Relaxed, romantic, calm, disgusted feelings increased without statistical significance whereas bad, active, fresh, frustrated, annoyed feelings decreased without statistical significance.

Positive feelings increased significantly while negative feelings decreased significantly after *d*-borneol inhalation. After *d*-borneol inhalation, the mean scores of good, active, fresh, romantic feelings increased significantly (p-value = 0.032), (p-value = p<0.001), (p-value = p<0.001), (p-value = p<0.001) respectively while the mean scores of relaxed and calm feelings increased without statistical significance. After *d*-borneol inhalation, the mean scores of bad, stressed, frustrated, annoyed, disgusted feelings decreased significantly (p-value = p<0.001), (p-value = p<0.001), (p-value = p<0.001), (p-value = 0.028), (p-value = 0.036) respectively. Relaxed and calm feelings increased without statistical significance while drowsy feelings decreased without statistical significance.

Table 10 The effects on emotional states after the sweet almond oil inhalation (SO) and *d*-borneol inhalation (BO)

Parameters	n	Resting		SO		BO		p-value	p-value
		Mean	SD	Mean	SD	Mean	SD	R and SO	SO and BO
1. good	24	5.88	0.98	6.06	0.91	6.59	1.32	**<0.001***	**0.032***
2. bad	24	1.18	0.94	1.11	0.84	0.46	0.34	0.439	**<0.001***
3. active	24	3.63	1.59	3.50	1.42	5.42	1.42	0.181	**<0.001***
4. drowsy	24	3.39	1.35	3.08	1.25	2.62	1.49	0.015*	0.088
5. fresh	24	3.60	1.40	3.55	1.45	5.72	1.63	0.415	**<0.001***
6. relaxed	24	3.96	1.51	4.20	0.95	4.50	1.34	0.149	0.185
7. stressed	24	1.81	1.70	1.26	1.09	0.61	0.60	**0.008***	**<0.001***
8. frustrated	24	1.47	1.18	1.32	1.05	0.66	0.52	0.213	**<0.001***
9. romantic	24	1.68	1.26	1.80	1.10	2.78	0.94	0.408	**<0.001***
10. annoyed	24	1.00	1.22	0.91	0.90	0.57	0.56	0.463	**0.028***
11. calm	24	4.07	0.92	4.28	0.94	4.74	1.32	0.097	0.079
12. disgusted	24	0.34	0.30	0.39	0.30	0.24	0.21	0.388	**0.036***

* Significant difference, p-value < 0.05, SO=sweet almond oil, BO=*d*-borneol

4.2.1.4 The data of EEG recordings

The absolute powers of brain activities were calculated during three experimental phases: resting, sweet almond oil inhalation and *d*-borneol inhalation. The areas of EEG recordings were divided into five brain areas: the left anterior, right anterior, center, left posterior, right posterior with band frequencies namely delta, theta, alpha and beta.

After sweet almond oil inhalation, the power of the delta wave in all brain areas decreased without statistical significance. After *d*-borneol inhalation, the power of the delta wave in right anterior increased without statistical significance while other brain areas including left anterior, center, left posterior, right posterior decreased without statistical significance

Table 11 Delta power of the brain activities during resting (R), sweet almond oil inhalation (SO) and *d*-borneol inhalation (BO)

Brain Area (n=21)	Delta Power (μV^2)						p-value resting and SO	p-value SO and BO
	Resting		SO		BO			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	15.82	4.62	14.93	3.30	14.26	4.21	0.339	0.199
Right anterior	15.71	3.54	14.62	4.29	15.16	4.45	0.226	0.583
Center	12.66	4.28	12.24	4.37	11.90	4.46	0.556	0.619
Left posterior	10.13	2.98	10.09	2.94	9.97	3.81	0.939	0.871
Right posterior	10.34	3.80	9.88	3.05	9.19	3.00	0.424	0.230

For theta power, after sweet almond oil inhalation, the power of the theta wave in right anterior and left posterior increased without statistical significance while the power of the theta wave in left anterior, center, right posterior decreased without statistical significance. After *d*-borneol inhalation, the power of the theta wave in all the brain areas decreased without statistical significance.

Table 12 Theta power of the brain activities during resting (R), sweet almond oil inhalation (SO) *d*-borneol inhalation (BO)

Brain Area (n=21)	Theta Power (μV^2)						p-value resting and SO	p-value SO and BO
	Resting		SO		BO			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	3.94	1.49	3.70	1.31	3.53	1.35	0.526	0.520
Right anterior	3.78	2.09	3.81	1.77	3.35	1.30	0.922	0.079
Center	4.90	2.02	4.51	1.82	3.94	1.41	0.469	0.286
Left posterior	2.11	0.95	2.27	0.90	2.08	0.71	0.437	0.171
Right posterior	2.57	1.67	2.12	1.03	1.97	0.92	0.078	0.462

The study on alpha power of the brain activities showed that after sweet almond oil inhalation, the power of the alpha wave in all the brain areas decreased without statistical significance. After *d*-borneol inhalation, the power of the alpha wave in all the brain areas decreased without statistical significance.

Table 13 Alpha power of the brain activities during the resting (R), sweet almond oil inhalation (SO) and *d*-borneol inhalation (BO)

Brain Area (n=21)	Alpha Power (μV^2)						p-value resting and SO	p-value SO and BO
	Resting		SO		BO			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	4.01	2.02	3.83	1.92	3.75	1.62	0.754	0.832
Right anterior	3.98	1.58	3.90	1.49	3.73	1.56	0.856	0.632
Center	4.37	1.79	3.94	1.46	3.85	1.93	0.234	0.847
Left posterior	4.14	1.85	3.89	1.38	3.60	1.44	0.731	0.387
Right posterior	3.94	1.36	3.66	1.53	3.45	1.18	0.478	0.803

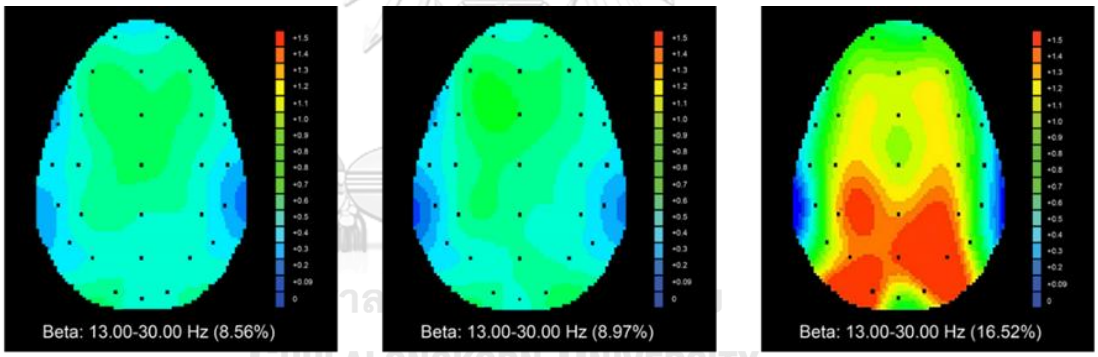
For beta power, after sweet almond oil inhalation, the power of the beta wave in all the brain areas increased without statistical significance. After *d*-borneol inhalation, the power of the beta wave over the left and right posterior brain areas increased significantly (p-value = 0.008), (p-value = 0.003) respectively. The power of

the beta wave in left anterior, right anterior and center increased without statistical significance.

Table 14 The beta power of the brain activities during the resting (R), sweet almond oil inhalation (SO) and *d*-borneol inhalation (BO)

Brain Area (n=21)	Beta Power (μV^2)						p-value resting and SO	p-value SO and BO
	Resting		SO		BO			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	0.87	0.31	0.92	0.29	0.95	0.34	0.154	0.364
Right anterior	0.89	0.32	0.94	0.35	0.96	0.40	0.222	0.707
Center	0.91	0.30	0.99	0.33	1.03	0.36	0.204	0.582
Left posterior	0.95	0.46	0.93	0.44	1.19	0.39	0.727	**0.008***
Right posterior	0.96	0.41	0.98	0.50	1.30	0.41	0.704	**0.003***

* Significant difference, p-value < 0.05, SO=Sweet almond oil, BO= *d*-borneol



(22a) Resting (22b) SO inhalation (22c) BO inhalation

Figure 22 Brain topographical map of the distribution of beta brainwave activity. The red areas indicate a significant beta power increase in the left posterior and right posterior areas during *d*-borneol inhalation.

4.2.2 *d*-camphor

4.2.2.1 General characteristics of the participants

Twenty-four participants (12 males and 12 females) aged between 20 and 35 years old with normal body mass index were asked to inhale *d*-camphor in this study. The mean and SD values of the participants' age, height, weight and BMI were 21.29 (±1.46) years, 168.63 (±6.74) cm, 59.63 (±7.00) kg, 20.89 (±1.18) kg/m^2 respectively. In the second session (brainwave parameters) after the artifact rejection based on EEG analysis, no participants were rejected because of artifacts. So, the data from 24 participants were complete.

Table 15 General characteristics of the *d*-camphor inhaling participants

Parameters	Number	mean	SD
Age (years)	24	21.29	1.46
Height (cm)	24	168.63	6.74
Weight (kg)	24	59.63	7.00
Body Mass Index (kg/m^2)	24	20.89	1.18

4.2.2.2 ANS physiological parameters

d-Camphor inhalation caused significant changes in most ANS parameters. After sweet almond oil inhalation, heart rate decreased significantly (p-value = 0.020). Systolic blood pressure, diastolic blood pressure and skin temperature increased without significance while respiratory rate decreased without statistical significance.

After *d*-camphor inhalation, most the ANS parameters including systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate decreased significantly (p-value = 0.039), (p-value = 0.027) (p-value = 0.011) (p-value = 0.025) while skin temperature increased statistically (p-value = 0.037).

Table 16 The effects on the ANS parameters after the sweet almond oil inhalation (SO) and 6% *d*-camphor inhalation (CH)

Parameters	n	Resting		SO		CH		p-value R and SO	p-value SO and CH
		Mean	SD	Mean	SD	Mean	SD		
SBP (mmHg)	24	110.00	4.85	110.79	4.91	109.29	3.75	0.103	**0.039***
DBP (mmHg)	24	68.63	4.05	69.04	3.83	67.42	3.59	0.498	**0.027***
HR (bpm)	24	82.54	8.27	79.83	10.07	77.46	9.00	**0.020***	**0.011***
ST (°C)	24	31.29	2.14	31.90	1.12	32.38	1.28	0.108	**0.037***
RR (bpm)	24	18.54	2.87	18.33	2.75	17.08	2.45	0.737	**0.025***

* Significant difference p-value < 0.05, systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), skin temperature (ST), respiratory rate (RR), SO=sweet almond oil, CH=*d*-camphor

4.2.2.3 Psychological parameters of emotional states

After the sweet almond oil inhalation, the mean scores of stressed feelings increased significantly (p-value = 0.029). the mean scores of bad, drowsy, fresh, relaxed, romantic, calm, disgust feelings increased without statistical significance whereas the mean scores of good, active, frustrated, annoyed feelings decreased without statistical significance.

After the *d*-camphor inhalation, the mean scores of relaxed, calm feelings increased significantly (p-value=0.031) (p-value = 0.008) while the mean scores of active feelings decreased significantly (p-value = 0.034). The mean scores of good, drowsy, romantic feelings increased without statistical significance but the mean scores of bad, fresh, stressed, frustrated, annoyed, disgust feelings decreased without statistical significance.

Table 17 The effects on emotional states after the sweet almond oil inhalation (SO) and *d*-camphor inhalation (CH)

Parameters	n	Resting		SO		CH		p-value R and SO	p-value SO and CH
		Mean	SD	Mean	SD	Mean	SD		
1. good	24	5.53	1.60	5.13	1.60	5.76	1.41	0.313	0.079
2. bad	24	2.80	1.37	3.09	1.04	2.79	1.49	0.163	0.265
3. active	24	4.47	1.40	4.43	1.55	3.60	1.38	0.869	**0.034***
4. drowsy	24	3.91	1.45	4.49	1.60	4.85	2.02	0.072	0.323
5. fresh	24	4.58	1.72	4.92	1.38	4.63	1.48	0.339	0.371
6. relaxed	24	4.39	1.59	4.73	1.90	5.48	1.75	0.270	**0.031***
7. stressed	24	3.86	1.23	4.43	1.33	3.72	1.72	**0.029***	0.063
8. frustrated	24	3.51	1.36	3.30	1.31	2.88	1.19	0.320	0.202
9. romantic	24	2.95	1.31	3.32	1.65	3.40	1.48	0.202	0.758
10. annoyed	24	3.09	1.15	2.91	1.20	2.60	1.20	0.306	0.222
11. calm	24	4.22	1.27	4.32	1.32	5.43	1.68	0.685	**0.008***
12. disgusted	24	2.46	1.37	2.65	1.18	2.27	0.93	0.285	0.119

* Significant difference, p-value < 0.05, SO = sweet almond oil, CH = *d*-camphor

4.2.2.4 The data of EEG recordings

The absolute powers of brain activities were calculated during three experimental phases: resting, sweet almond oil inhalation and *d*-camphor inhalation. The areas of EEG recordings were divided into five brain areas: the left anterior, right anterior, center, left posterior, right posterior with band frequencies namely delta, theta, alpha and beta.

For delta power, after sweet almond oil inhalation, the power of the delta wave in all brain areas decreased without statistical significance. After *d*-camphor inhalation, the power of the delta wave in all brain areas decreased without statistical significance.

Table 18 Delta power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and d-camphor inhalation (CH)

Brain Area (n=24)	Delta Power (μV^2)						p-value resting and SO	p-value SO and CH
	Resting		SO		CH			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	12.56	2.49	11.42	3.05	10.72	2.11	0.065	0.070
Right anterior	12.21	2.15	11.51	1.88	11.03	2.28	0.073	0.090
Center	11.54	2.43	11.14	2.63	10.64	2.96	0.318	0.128
Left posterior	7.20	2.01	6.80	2.13	6.55	2.22	0.137	0.096
Right posterior	7.52	2.11	7.28	2.19	7.15	2.17	0.249	0.384

For theta power, after sweet almond oil inhalation, the power of the theta wave in right anterior and center increased without statistical significance while left anterior, left posterior and right posterior decreased without statistical significance. After *d*-camphor inhalation, the power of the theta wave in left anterior, right anterior and center increased without statistical significance while left posterior and right posterior decreased without statistical significance.

Table 19 Theta power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and *d*-camphor inhalation (CH)

Brain Area (n=24)	Theta Power (μV^2)						p-value resting and SO	p-value SO and CH
	Resting		SO		CH			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	2.98	1.67	2.85	1.55	3.32	1.97	0.421	0.196
Right anterior	2.73	1.24	2.77	1.18	2.83	1.36	0.690	0.708
Center	3.36	1.18	3.51	1.33	3.66	1.27	0.293	0.484
Left posterior	1.96	1.14	1.97	1.03	1.94	0.90	0.900	0.729
Right posterior	2.05	1.03	2.03	0.91	1.90	0.88	0.864	0.178

The study on alpha power of the brain activities showed that after sweet almond oil inhalation, the power of the alpha wave in all the brain areas increased without statistical significance. After *d*-camphor inhalation, the power of the alpha wave in all the brain areas including left anterior, right anterior, center, left posterior, right posterior increased significantly (p-value = 0.013), (p-value = 0.004), (p-value = 0.015), (p-value = 0.008), (p-value = 0.029).

Table 20 Alpha power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and *d*-camphor inhalation (CH)

Brain Area (n=24)	Alpha Power (μV^2)						p-value resting and SO	p-value SO and CH
	Resting		SO		CH			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	3.26	1.53	4.04	1.91	6.11	3.06	0.097	**0.013***
Right anterior	3.30	1.66	3.90	2.04	6.01	3.11	0.098	**0.004***
Center	4.53	1.98	5.70	2.60	8.06	4.54	0.059	**0.015***
Left posterior	4.21	2.04	5.09	2.38	7.10	3.28	0.087	**0.008***
Right posterior	4.31	1.86	5.01	1.99	6.51	2.67	0.077	**0.029***

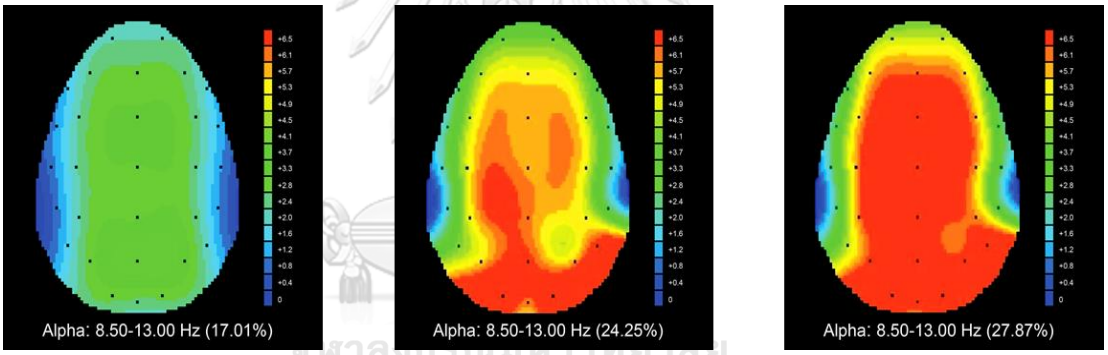
* Significant difference, p-value < 0.05, SO = sweet almond oil, CH = *d*-camphor

For beta power, after sweet almond oil inhalation, the power of the beta wave in all the brain areas decreased without statistical significance. After *d*-camphor

inhalation, the power of the beta wave in all the brain areas decreased without statistical significance.

Table 21 Beta power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and *d*-camphor inhalation (CH)

Brain Area (n=24)	Beta Power (μV^2)						p-value resting and SO	p-value SO and CH
	Resting		SO		CH			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	0.62	0.29	0.60	0.21	0.58	0.27	0.645	0.586
Right anterior	0.63	0.30	0.62	0.23	0.60	0.28	0.915	0.679
Center	0.76	0.31	0.73	0.35	0.70	0.34	0.690	0.614
Left posterior	0.77	0.37	0.74	0.34	0.71	0.40	0.664	0.616
Right posterior	0.71	0.46	0.69	0.38	0.66	0.44	0.742	0.543



(23a) Resting (23b) SO inhalation (23c) CH inhalation

Figure 23 Brain topographical map of the distribution of alpha brainwave activity The red areas indicate an increase of alpha power during sweet almond oil inhalation (23b) and a significant increase of alpha power in all regions during *d*-camphor inhalation (23c).

4.2.3 Methyl eugenol

4.2.3.1 General characteristics of the participants

In the first session (ANS and Emotional parameters), there were 24 participants (12 males and 12 females) aged between 20 and 35 years old with normal body mass index were asked to inhale methyl eugenol inhalation (ME) in this study. The mean and SD values of the participants' age, height, weight and BMI were 22.71 (±2.97) years old, 168.25 (±5.88) cm, 59.46 (±5.38) kg, 20.97 (±1.05) kg/m^2 respectively. In the second session (brainwave parameters) after the artifact rejection based on EEG analysis, there were twenty-two participants (11 males and 11 females) aged 22.82 (±3.08) years old, 168.27 (±6.13) cm, 59.59 (±5.60) kg, 21.01 (±1.06) kg/m^2 (Table 21). Two participants were rejected because of the artifact in EEG analysis and their data were excluded from data analysis according to per protocol analysis which included complete data only.

Table 22 General characteristics of methyl eugenol inhaling participants

Parameters	ANS and Emotional parameters (First session) (n= 24)		Brainwave parameters (Second session) (n= 22)	
	Mean	SD	Mean	SD
Age (years)	22.71	2.97	22.82	3.08
Height (cm)	168.25	5.88	168.27	6.13
Weight (kg)	59.46	5.38	59.59	5.60
Body Mass Index (kg/m^2)	20.97	1.05	21.01	1.06

4.2.3.2 ANS physiological parameters

Methyl eugenol inhalation caused significant changes in most ANS parameters. After sweet almond oil inhalation, heart rate decreased significantly (p-value = 0.049) while systolic blood pressure, diastolic blood pressure and respiratory rate decreased without statistical significance while skin temperature increased without statistical significance.

After methyl eugenol inhalation, systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate decreased significantly (p-value = <0.023), (p-value = 0.012), (p-value = 0.035), (p-value = 0.036) respectively while skin temperature increased without statistical significance.

Table 23 The effects on the ANS parameters after the sweet almond oil inhalation (SO) and 10% methyl eugenol inhalation (ME)

Parameters	n	Resting		SO		ME		p-value R and SO	p-value SO and ME
		Mean	SD	Mean	SD	Mean	SD		
SBP (mmHg)	24	107.17	7.10	106.21	7.82	103.29	6.97	0.317	**0.023***
DBP (mmHg)	24	66.00	8.29	64.83	5.93	63.21	5.95	0.309	**0.012***
HR (bpm)	24	73.83	9.15	71.08	7.55	68.04	7.87	**0.049***	**0.035***
ST (°C)	24	31.33	1.01	31.39	1.38	31.61	1.18	0.691	0.207
RR (bpm)	24	17.67	3.29	16.92	3.90	15.46	3.35	0.334	**0.036***

* Significant difference p-value < 0.05, systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), skin temperature (ST), respiratory rate (RR), SO = sweet almond oil, ME = methyl eugenol

4.2.3.3 Psychological parameters of emotional states

After sweet almond oil inhalation, the mean scores of bad feelings increased significantly (p-value = 0.037). The mean scores of drowsy, fresh, relaxed, stressed, frustrated, romantic, calm, disgusted feelings increased without statistical significance while good, active, annoyed feelings decreased without statistical significance.

After ME inhalation, the mean scores of active, fresh feelings decreased significantly (p-value = 0.023), (p-value = 0.010) while the mean scores of drowsy feelings increased significantly (p-value = 0.014). The mean scores of good, relaxed, frustrated, calm, annoyed feelings increased without statistical significance while the mean scores of bad, stressed, romantic, disgust feelings decreased without statistical significance.

Table 24 The effects on emotional states after the sweet almond oil inhalation (SO) and methyl eugenol inhalation (ME)

Parameters	n	Resting		SO		ME		p-value R and SO	p-value SO and ME
		Mean	SD	Mean	SD	Mean	SD		
1. good	24	5.95	1.71	5.84	1.65	6.53	1.60	0.651	0.060
2. bad	24	2.18	1.50	2.77	1.36	2.28	1.66	**0.037***	0.139
3. active	24	4.18	2.12	4.00	1.80	3.08	1.81	0.459	**0.023***
4. drowsy	24	3.47	2.22	3.59	2.09	4.45	2.28	0.730	**0.014***
5. fresh	24	3.76	1.58	3.87	1.42	3.13	1.58	0.681	**0.010***
6. relaxed	24	4.88	1.63	5.05	1.67	5.69	1.39	0.499	0.077
7. stressed	24	1.85	1.45	1.89	1.49	1.45	1.48	0.842	0.080
8. frustrated	24	1.93	1.12	2.03	1.40	1.78	1.51	0.614	0.382
9. romantic	24	3.00	1.74	3.53	1.89	3.68	1.45	0.056	0.688
10. annoyed	24	2.02	1.42	1.92	1.35	1.90	1.41	0.681	0.920
11. calm	24	4.10	1.70	4.32	1.33	5.04	1.75	0.434	0.065
12. disgusted	24	1.45	1.08	1.72	1.43	1.52	1.22	0.098	0.264

* Significant difference, p-value < 0.05, SO = sweet almond oil, ME = methyl eugenol

4.2.3.4 The data of EEG recordings

The absolute powers of brain activities were calculated during three experimental phases: resting, sweet almond oil inhalation and *d*-borneol inhalation. The areas of EEG recordings were divided into 5 brain areas: the left anterior, right anterior, center, left posterior, right posterior with band frequencies namely delta, theta, alpha and beta.

For delta power, after sweet almond oil inhalation, the power of the delta wave in all brain areas increased without statistical significance. After ME inhalation, the power of the delta wave in left anterior and right anterior increased significantly (p-value = 0.030), (p-value = 0.010) while other brain areas including center, left posterior, right posterior increased without statistical significance.

Table 25 Delta power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and methyl eugenol inhalation (ME)

Brain Area (n=22)	Delta Power (μV^2)						p-value resting and SO	p-value SO and ME
	Resting		SO		ME			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	12.97	2.78	13.03	3.77	16.15	5.59	0.947	**0.030***
Right anterior	13.38	3.20	13.45	3.40	16.27	4.46	0.930	**0.010***
Center	11.60	3.46	11.69	3.04	13.59	4.56	0.928	0.124
Left posterior	11.91	3.36	11.93	3.42	13.20	2.37	0.973	0.170
Right posterior	11.52	2.47	11.90	1.87	12.77	2.92	0.562	0.137

* Significant difference, p-value < 0.05, SO = sweet almond oil, ME = methyl eugenol

The study on theta power of the brain activities showed that after sweet almond oil inhalation, the power of the theta wave in left anterior decreased without statistical significance while right anterior, center, left posterior and right posterior increased without statistical significance. After ME inhalation, the power of the theta wave in left anterior, right anterior and center increased significantly (p = 0.014), (p = 0.013), (p = 0.004) respectively and the power of the theta wave in left posterior, right posterior increased without statistical significance.

Table 26 Theta power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and methyl eugenol inhalation (ME)

Brain Area (n=22)	Theta Power (μV^2)						p-value resting and SO	p-value SO and ME
	Resting		SO		ME			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	2.26	0.77	2.16	0.74	2.89	1.23	0.645	**0.014***
Right anterior	2.16	0.80	2.22	0.65	2.86	1.08	0.806	**0.013***
Center	2.23	1.34	2.31	0.79	3.11	0.82	0.852	**0.004***
Left posterior	1.73	0.59	1.95	0.86	2.05	1.03	0.336	0.681
Right posterior	1.52	0.62	1.70	0.98	1.96	0.85	0.413	0.313

* Significant difference, p-value < 0.05, SO = Sweet almond oil, ME = methyl eugenol

For alpha power, after sweet almond oil inhalation, the power of the alpha wave in left anterior decreased without statistical significance while right anterior, center, left posterior and right posterior increased without statistical significance. After ME inhalation, the power of the alpha wave in left anterior, right anterior and center, left posterior decreased without statistical significance while right posterior increased without statistical significance.

Table 27 Alpha power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and methyl eugenol inhalation (ME)

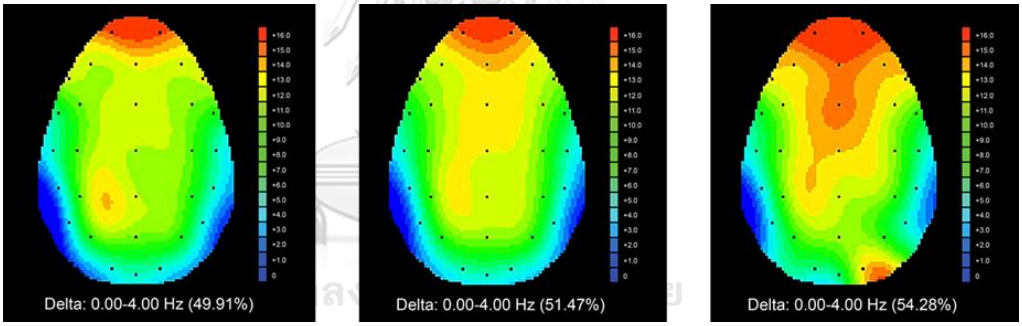
Brain Area (n=22)	Alpha Power (μV^2)						p-value resting and SO	p-value SO and ME
	Resting		SO		ME			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	4.51	2.31	4.46	2.39	4.20	2.07	0.919	0.612
Right anterior	4.40	2.61	4.84	2.75	4.38	2.25	0.377	0.398
Center	5.69	3.39	5.99	4.41	5.51	2.87	0.718	0.591
Left posterior	4.62	2.39	5.35	4.04	4.98	2.29	0.346	0.637
Right posterior	5.31	3.34	5.07	3.67	5.17	2.75	0.705	0.881

For beta power, after sweet almond oil inhalation, the power of the beta wave in left anterior, center, left posterior, right posterior decreased without

statistical significance while right anterior increased without statistical significance. After ME inhalation, the power of the beta wave in all the brain areas decreased without statistical significance.

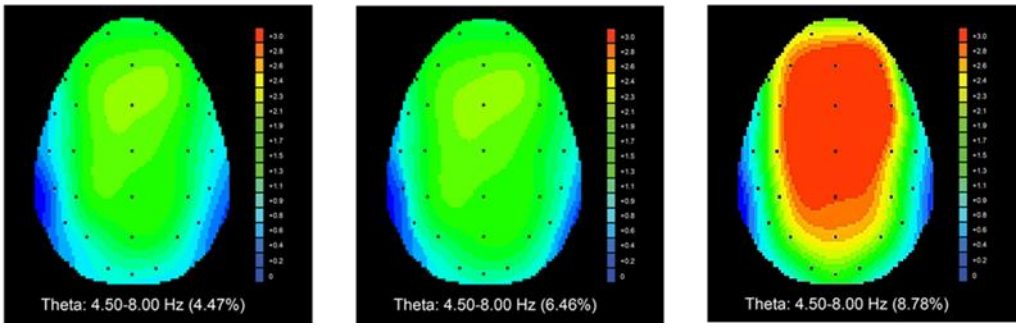
Table 28 Beta power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and methyl eugenol inhalation (ME)

Brain Area (n = 22)	Beta Power (μV^2)						p-value resting and SO	p-value SO and ME
	Resting		SO		ME			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	0.78	0.46	0.73	0.49	0.67	0.35	0.570	0.447
Right anterior	0.78	0.37	0.80	0.41	0.79	0.40	0.779	0.897
Center	0.96	0.46	0.88	0.45	0.87	0.38	0.404	0.880
Left posterior	0.84	0.43	0.77	0.52	0.71	0.44	0.333	0.421
Right posterior	0.80	0.41	0.75	0.40	0.72	0.48	0.427	0.745



(24a) Resting (24b) SO inhalation (24c) ME inhalation

Figure 24 Brain topographical map of the distribution of delta brainwave activity The red areas indicate an increase of delta power during sweet almond oil inhalation (24b) and a significant increase of delta power in left anterior, right anterior during methyl eugenol inhalation (ME) (24c).



(25a) **Resting** (25b) SO inhalation (25c) ME inhalation

Figure 25 Brain topographical map of the distribution of theta brainwave activity the red areas indicate an increase of theta power during sweet almond oil inhalation (25b) and a significant increase of theta power in left anterior, right anterior, center during methyl eugenol inhalation (ME) (25c)..

4.2.4 Methyl chavicol

4.2.4.1 General characteristics of the participants

Twenty-four participants (12 males and 12 females) aged between 20 and 35 years old with normal body mass index were asked to inhale methyl chavicol in this study. The mean and SD values of the participants' age, height, weight and BMI were 23.17 (±3.60) years, 168.33 (±6.04) cm, 59.71 (±6.28) kg, 20.98 (±1.30) kg/m^2 respectively. In the second session (brainwave parameters) after the artifact rejection based on EEG analysis, no participants were rejected because of artifacts. So, the data from 24 participants were complete.

Table 29 General characteristics of methyl chavicol inhaling participants

Parameters	Number	mean	SD
Age (years)	24	23.17	3.60
Height (cm)	24	168.33	6.04
Weight (kg)	24	59.71	6.28
Body Mass Index (kg/m^2)	24	20.98	1.30

4.2.4.2 ANS physiological parameters

Methyl chavicol inhalation caused significant changes in most ANS parameters. After sweet almond oil inhalation, systolic blood pressure decreased significantly (p-value = 0.031) while skin temperature increased significantly (p-value = 0.039) and diastolic blood pressure, heart rate and respiratory rate decreased without statistical significance.

After MC inhalation, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate decreased significantly (p-value = 0.034), (p-value = 0.004), (p-value = 0.011) (p-value = 0.008) respectively while skin temperature increased without statistical significance.

Table 30 The effects on the ANS parameters after the sweet almond oil inhalation (SO) 10% methyl chavicol (MC).

Parameters	n	Resting		SO		MC		p-value	p-value
		Mean	SD	Mean	SD	Mean	SD	R and SO	SO and MC
SBP (mmHg)	24	111.67	8.41	109.08	6.63	106.75	6.96	**0.031***	**0.034***
DBP (mmHg)	24	71.21	7.25	70.17	6.00	67.17	4.30	0.361	**0.004***
HR (bpm)	24	74.38	11.34	72.38	10.95	70.04	9.57	0.281	**0.011***
ST (°C)	24	30.66	1.84	31.54	1.49	31.71	1.74	**0.039***	0.556
RR (bpm)	24	17.63	3.99	17.50	3.79	15.42	3.45	0.864	**0.008***

* Significant difference p-value < 0.05, systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), skin temperature (ST), respiratory rate (RR), SO = sweet almond oil, MC = methyl chavicol

4.2.4.3 Psychological parameters of emotional states

After sweet almond oil inhalation, the mean scores of disgust feelings increased significantly (p-value = 0.020). The mean scores of bad, drowsy, fresh, relaxed, stressed, romantic, annoyed, calm feelings increased without statistical significance while good, active, frustrated feelings decreased without statistical significance.

After MC inhalation, the mean scores of relaxed feelings increased significantly (p-value = 0.006) while the mean scores of bad, frustrated feelings decreased significantly (p-value=0.003), (p-value = 0.017). The mean scores of good, calm feelings increased without statistical significance while the mean scores of active, drowsy, fresh, stressed, romantic, annoyed, disgust feelings decreased without statistical significance.

Table 31 The effects on emotional states after the sweet almond oil inhalation (SO) and methyl chavicol inhalation (MC)

Parameters	n	Resting		SO		MC		p-value R and SO	p-value SO and MC
		Mean	SD	Mean	SD	Mean	SD		
1. good	24	6.04	1.84	5.95	1.70	6.10	2.34	0.360	0.747
2. bad	24	2.74	1.95	2.83	2.04	1.95	1.41	0.448	**0.003***
3. active	24	4.48	1.83	4.33	1.68	4.03	1.93	0.404	0.209
4. drowsy	24	3.17	1.89	3.72	2.38	3.44	2.59	0.157	0.424
5. fresh	24	4.15	1.44	4.27	1.41	4.10	1.90	0.643	0.610
6. relaxed	24	4.30	1.92	4.38	1.59	5.27	1.56	0.775	**0.006***
7. stressed	24	2.52	1.73	2.60	1.62	2.32	1.71	0.570	0.316
8. frustrated	24	2.90	1.85	2.70	1.67	2.23	1.54	0.101	**0.017***
9. romantic	24	3.86	1.61	3.93	1.86	3.85	1.81	0.854	0.829
10. annoyed	24	2.92	1.38	3.09	1.33	2.64	1.15	0.402	0.090
11. calm	24	4.77	1.88	4.83	1.61	5.37	1.72	0.842	0.068
12. disgusted	24	1.75	1.71	2.21	1.66	1.94	1.70	**0.020***	0.292

* Significant difference, p-value < 0.05, SO = sweet almond oil, MC = methyl chavicol

4.2.4.4 The data of EEG recordings

The absolute powers of brain activities were calculated during three experimental phases: resting, sweet almond oil inhalation and methyl chavicol inhalation. The areas of EEG recordings were divided into five brain areas: the left anterior, right anterior, center, left posterior, right posterior with band frequencies namely delta, theta, alpha and beta.

For delta power, after sweet almond oil inhalation, the power of the delta wave in left anterior, right anterior, right posterior decreased without statistical significance while center and left posterior increased without statistical significance. After MC inhalation, the power of the delta wave in left anterior and right anterior increased without statistical significance while center, left posterior, right posterior decreased without statistical significance.

Table 32 Delta power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and methyl chavicol (MC)

Brain Area (n=24)	Delta Power (μV^2)						p-value resting and SO	p-value SO and MC
	Resting		SO		MC			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	14.95	4.48	13.74	4.46	14.54	4.97	0.075	0.413
Right anterior	14.60	4.12	14.31	4.45	15.89	5.59	0.577	0.088
Center	13.05	3.74	13.32	4.48	13.18	4.44	0.732	0.848
Left posterior	9.74	3.58	10.00	3.51	9.92	3.73	0.641	0.893
Right posterior	10.25	3.43	10.21	2.93	9.83	2.99	0.941	0.501

For theta power, after sweet almond oil inhalation, the power of the theta wave in all the brain areas increased without statistical significance. After MC inhalation, the power of the theta wave in all the brain areas decreased without statistical significance.

Table 33 Theta power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and methyl chavicol (MC)

Brain Area (n = 24)	Theta Power (μV^2)						p-value resting and SO	p-value SO and MC
	Resting		SO		MC			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	3.07	1.33	3.21	1.56	3.13	1.27	0.376	0.740
Right anterior	3.16	1.85	3.36	1.70	3.25	2.02	0.119	0.383
Center	4.15	2.25	4.51	2.09	4.35	2.30	0.125	0.520
Left posterior	2.02	1.05	2.07	0.91	1.97	0.93	0.696	0.383
Right posterior	2.22	1.02	2.30	0.89	2.06	0.98	0.553	0.068

The study on alpha power of the brain activities showed that after sweet almond oil inhalation, the power of the alpha wave in all the brain areas increased without statistical significance. After MC inhalation, the power of the alpha wave in left anterior, right anterior, center, right posterior increased significantly (p-value = 0.006), (p-value = 0.010) (p-value = 0.002), (p-value = 0.020) while left posterior increased without statistical significance.

Table 34 Alpha power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and methyl chavicol (MC)

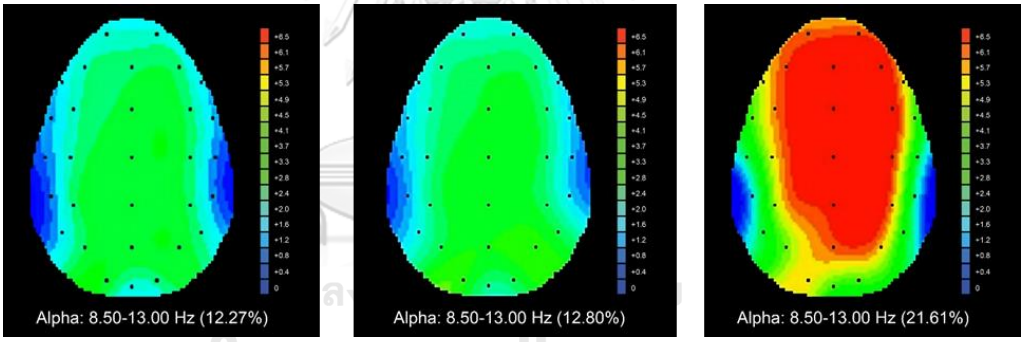
Brain Area (n=24)	Alpha Power (μV^2)						p-value resting and SO	p-value SO and MC
	Resting		SO		MC			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	3.40	1.38	3.85	1.60	5.43	2.85	0.095	**0.006***
Right anterior	3.53	1.37	4.07	1.77	5.67	2.89	0.180	**0.010***
Center	3.73	1.46	4.28	1.73	6.39	3.26	0.081	**0.002***
Left posterior	3.70	1.48	4.37	1.72	5.17	2.54	0.093	0.053
Right posterior	3.43	1.74	4.32	1.62	5.53	2.46	0.055	**0.020***

* Significant difference, p-value < 0.05, SO = sweet almond oil, MC = methyl chavicol

For beta power, after sweet almond oil inhalation, the power of the beta wave in all the brain areas decreased without statistical significance. After MC inhalation, the power of the beta wave in all the brain areas decreased without statistical significance.

Table 35 Beta power of the brain activities during resting (R), the sweet almond oil inhalation (SO) and methyl chavicol (MC)

Brain Area (n=24)	Beta Power (μV^2)						p-value resting and SO	p-value SO and MC
	Resting		SO		MC			
	Mean	SD	Mean	SD	Mean	SD		
Left anterior	0.58	0.22	0.57	0.21	0.55	0.29	0.704	0.600
Right anterior	0.59	0.24	0.58	0.23	0.57	0.28	0.845	0.794
Center	0.75	0.34	0.72	0.31	0.70	0.38	0.320	0.723
Left posterior	0.67	0.43	0.65	0.42	0.63	0.34	0.740	0.758
Right posterior	0.69	0.38	0.67	0.37	0.65	0.45	0.434	0.789



(26a) Resting (26b) SO inhalation (26c) MC inhalation

Figure 26 Brain topographical map of the distribution of alpha brainwave activity The red areas indicate a significant increase of alpha power in most areas during methyl chavicol inhalation (MC) (26c).

CHAPTER 5
DISCUSSION AND CONCLUSION

5.1 Discussion

5.1.1 A pre-test and post-test design in this study

The current research design was a pretest-posttest design because it was an experimental study in which each participant served as his or her own control and the dependent variable was analyzed for each participant. Then, the results from a study with a pretest-posttest design are performed by paired data analysis. Researchers can collect paired data when the same experimental unit such as a participant is measured on some variable on two different appointments or at the same time under different testing conditions. This design is regarded as an accurate and efficient research method since it reports feedbacks immediately to researchers on the effects of the volatile compound inhalation. The researchers will acknowledge soon enough if the selected volatile compounds as interventions are effective or not. This design authorizes the researchers to reach valid conclusions concerning the variables since the researchers will implement the procedures to control the environmental conditions and focus on observing the behavior of every participant.

When a participant is measured on two separate occasions, researchers wish to find any difference between the first and second measurements. The first measurement is known as the pretest or baseline measurement. Then, each participant receives a treatment intervention prior to the measurement of the posttest after the completion of the pretest. The second measurement is known as the posttest measurement (Bonate, 2000). The advantages of a one-group pretest-posttest design is that it allows researchers to include all interested individuals in the intervention group which results in increasing recruitment while reducing attrition. Another advantage is that a study with this design is more feasible and considerably less expensive and time consuming compared to a RCT or a non-randomized controlled study (Simon & Higginson, 2009).

The procedures used in this research can prove the effects of selected volatile compounds since these procedures have been proven by previous studies

by Sayorwan (2011) on effects of selected volatile oils commonly used in Thailand on physiological activities and emotions. The previous studies introduced the standard procedures to investigate the effects of essential oils on ANS parameters, emotional states and brain wave activities through EEG recordings.

In this study, each selected volatile compound diluted in sweet almond oil (SO) was administered to healthy participants during the three periods of the experiment. Sweet almond oil is commonly used as carrier oil for diluting essential oils and helping the essential oil to be absorbed more evenly. Pure essential oils are too concentrated to irritate the skin and nasal epithetical cells (Speedy Publishing, 2014).

5.1.2 Purposive sampling technique

In this study, purposive sampling technique was employed to select an equal number of both male participants and female participants to prevent confounders of gender differences which affect emotions and brainwave activities through EEG recordings. A previous study reported that men and women may display different patterns of lateralization in emotional processing (Wager et al., 2003). Men also exhibit greater temporal cortex asymmetry than women (Good et al., 2001). Therefore, each selected volatile compound group consisted of 24 healthy participants (12 males and 12 females) in this study.

5.1.3 The inclusion and the exclusion criteria

According to the inclusion criteria, the volunteers who were right-handed evaluated by the Edinburgh Handedness Inventory were included as the participants. This study also recruited volunteers who indicated oil pleasantness within the target level range of 2-4 from “Odor familiarity five-point Likert scale” The volunteers who indicated oil pleasantness at the extreme points of 1 or 5 were excluded from this study since their extreme like or dislike as subjective behavioral arousal towards each volatile compound may affect their brainwave activities.

One of the inclusion criteria in this study was the handedness of the participants. Only right-handed volunteers were recruited into this study since EEG asymmetry patterns between left-handed and right-handed volunteers are different (Bryden, 1982). Previous

research on neuroimaging and fMRI included only right-handed volunteers but excluded left-handed volunteers and their underrepresentation when they were recruited (Beraha et al., 2012; Spironelli & Angrilli, 2006). Moreover, 70-90% of the world population is right-handed which means that they have left brain dominance for motor function (Scerri et al., 2011). A previous study proposed that both hemispheres were required to process emotions but each hemisphere seemed to be specialized for certain types of emotions especially in the lateral frontal cortex (Wager et al., 2003). The left hemisphere was dominant for positive emotions while the right hemisphere was dominant in negative emotions (Davidson, 1992). More peaks for emotional activation were found in the left hemisphere compared to the right hemisphere but the difference was not statistically significant (Wager et al., 2003). Therefore, hemispheric asymmetry of emotion processing is still controversial.

5.1.4 The concentration levels of selected volatile compounds

Six percent dilution (w/v) of one selected volatile compound, *d*-camphor, diluted in sweet almond oil (base oil) was used while 10% dilution of the other selected volatile compounds namely *d*-borneol, methyl chavicol, methyl eugenol were used. The suitable concentration of each volatile compound was delivered from oxygen pump system via a plastic tube through a face mask at the constant rate 2 L/min. It was administered to healthy participants through inhalation during the three phases of the experiment: resting (R), the sweet almond oil inhalation (SO) and diluted volatile compound inhalation. The recommended percent of aroma such as essential oils should range from 2.5% to 10% diluted in based oils (The National Association for Holistic Aromatherapy, n.d.). The 6% use of *d*-camphor and the 10% use of other selected volatile compounds diluted in sweet almond oil were applied from the results on the participants' satisfaction from a pre-test study. The pre-test study was conducted to identify hedonics including intensity of each volatile compound. A previous study conducted on aroma effects on physiologic and cognitive function suggested that hedonics which consisting of pleasantness and intensity was one of the mechanisms contributing to aroma effects while other mechanisms included pharmacologic properties and participant expectations (Chamine & Oken, 2016). Another previous study reported that various odor types possess different characteristics of

hedonic tone. Therefore, a hedonic tone can be used as a reliable evaluation index which can determine psychological effects of an odor (J. Li, Zou, Li, Wang, & Yang, 2019).

5.1.5 Effects of sweet almond oil inhalation on psychophysiological parameters

Sweet almond oil was used as a carrier oil in this study. Sweet almond oil inhalation was also studied as diluent or vehicle control. Both sweet almond oil and each selected volatile compound diluted with sweet almond oil were delivered from oxygen pump system via a plastic tube through a face mask at the constant rate of 2L/min. The participants in *d*-borneol group, *d*-camphor group and methyl chavicol group showed skin temperature increasing but not the methyl eugenol group. Significant systolic blood pressure decreasing was found in *d*-camphor group and methyl chavicol group. Heart rate decreasing was found in only methyl eugenol group. Some participants' emotional states were affected by SO. However, the results were divergent. Some felt better (*d*-borneol group); some felt worse (methyl eugenol group); some felt more stressed (*d*-camphor group) but some felt less stressed (*d*-borneol group) and some felt more disgusted (methyl eugenol group).

The effects of sweet almond oil on ANS and emotional states were found in some participants in previous study. The decrease of heart rate was in line with previous studies by Nuiden et al. (2019), Thanatuskitti et al. (2020), Sayowan et al. (2017). The previous study also reported less stressed feelings, less good feelings but more romantic feelings (Nuiden et al., 2019). In contrast, another previous study on the effects of inhaled *Limnophila aromatica* essential oil on brain wave activities and emotional states in healthy volunteers found that sweet almond oil inhalation increased good feelings but decreased stressed feelings(Thanatuskitti et al., 2020).

However, sweet almond oil inhalation did not cause any significant changes in brain wave activities from EEG recordings in all volatile compound experiments in this study. These results were consistent with a previous study by Gulluni et al. (2018) which used sweet almond oil as a control while cannabis essential oil was used as an intervention. They discovered that sweet almond oil inhalation did not induce any significant effects on brain powers including alpha, beta, theta and delta in healthy

volunteers (Gulluni et al., 2018). Another previous study conducted on the harmonizing effects of citronella oil on mood states and brain activities also found similar results. The researchers reported that sweet almond oil was used as a carrier oil for 10% citronella oil dilution and a diluent control but there were no significant changes in brainwave activities in healthy participants compared to citronella oil inhalation (Sayowan et al., 2017). The effects of sweet almond oil on ANS parameters and emotional states were revealed. This might be due to its mild odor that was not completely comparable with room air, so it could trigger autonomic responses including skin temperature and emotional states. This study design could be beneficial for the further selection of carrier oil used in olfactory brain research.

5.1.6 Psychophysiological parameters in this study

The psychophysiological parameters in this study which included ANS parameters, emotional states and brain wave activities through EEG recordings were recorded to measure three levels of arousal which refers to the physiological and psychological state of being awoken or of sense organs stimulated to a point of perception. Hongratanaworakit (2004) proposed that the effects of aromas on the nervous system consisted of two levels of arousal which were the autonomic arousal such as heart rate, skin conductance and the cortical arousal such as brain wave activity (Hongratanaworakit, 2004). Autonomic arousal means changes in the activity of sympathetic and parasympathetic branches of the autonomic nervous system (ANS) while cortical arousal means an abrupt shift of brain wave activities in EEG recordings. Sayorwan et al. (2012) reported that various emotional states such as good, bad, active and drowsy could be considered as subjective behavioral arousal caused by odors (Sayorwan et al., 2012). Subjective behavioral arousal is defined as the degree of activation or intensity that accompanies an emotional state. Therefore, the three levels of arousal in this study comprised ANS parameters as the autonomic arousal, emotional states as subjective behavioral arousal and the brain wave activities through EEG recordings as the cortical arousal.

Clinical research is carried out on human volunteers to determine the effects of interventions. This study is considered as a clinical research study conducted to

investigate the effects of four selected volatile compounds. The autonomic arousal is measured by the ANS parameters and the subjective behavioral arousal is evaluated by the questionnaires on emotional states. The diluted volatile compound inhalation via the olfactory system triggers cortical arousal resulted in the autonomic arousal e. g. blood pressure, heart rate, respiratory rate, and skin temperature and positive or negative emotional states.

Each selected volatile compound was inhaled through the olfactory system which has direct connections to brain structures involved in memory and emotion such as the hippocampus, thalamus and frontal cortex. From the olfactory bulbs, the olfactory information was carried through the olfactory tract to the structures known as primary olfactory cortex and forwarded to other cortical and subcortical areas (Sowndhararajan & Kim, 2016). Finally, the olfactory information reached several brain regions which are responsible for olfactory perception, autonomic homeostasis and other higher brain functions (Courtiol & Wilson, 2015).

In addition, the effects of volatile compound inhalation on the central nervous system can be conducted by measuring brain wave activities through EEG recordings displayed in amplitude (time domain as a function of time) and frequency (power as a function of frequency) (Osman & Silas, 2015). Each volatile compound affects brain wave activity responses classified into power spectra namely delta, theta, alpha and beta waves. Specific brain waves are dominant based on the consciousness level of humans. Consequently, brain wave activities responses triggered by each volatile compound inhalation can reflect the consciousness level and the cortical arousal of healthy participants.

The ANS parameters used in this study included blood pressure, heart rate, skin temperature and respiratory rate as the markers of the autonomic arousal while 12 types of emotional states e. g. good, bad, active, drowsy, fresh, relaxed, stressed, frustrated, romantic, annoyed, calm and disgusted feelings were rated subjectively to measure subjective psychological behavioral arousal. The EEG recordings were collected to measure the effects on brain wave activity responses as the cortical arousal.

5.1.7 *d*-borneol

5.1.7.1 Effects of *d*-borneol Inhalation on physiological parameters and emotional states

The results from this study, by comparison with SO, reported that BO inhalation could increase systolic blood pressure, diastolic blood pressure and heart rate significantly. Blood pressure and heart rate are used to measure physiological changes affected by aroma substances. An increase in both ANS parameters might indicate stimulating effects (Hongratanaworakit, 2004). BO inhalation affected ANS parameters through significant increases of autonomic arousal.

BO inhalation caused significant enhancement for positive emotional states. After *d*-borneol inhalation, the participants felt better, fresher, more active and romantic while they felt less bad, annoyed, stressed, frustrated and disgusted moods. *d*-Borneol could induce not only a significant decrease in negative feelings but also a significant increase in positive feelings based on self-evaluated questionnaires. A previous study in 2006 conducted on the effects of aroma air supplement on active safety during car driving in a driving simulator. The findings revealed that BO inhalation triggered awakening and alerting effects on the subjective behavioral arousal based on the emotion state parameters. The feeling of exhaustion was reduced. There was also a success rate of lane departure avoidance that improved the straight-line stability of driving (Suzuki, Yasuda, Sassa, & Harada, 2006).

5.1.7.2 Effects of *d*-borneol Inhalation on brain wave activities through EEG parameters

BO inhalation caused significant changes in the absolute powers of brain wave activities particularly beta waves. Beta waves, which have the highest frequency around 13 and 30 Hz, are related to an alert state of mind, motor preparation, focused attention or attention-carrier (Neuper & Pfurtscheller, 2001). Driving drowsiness study found that the beta activity decreased while the driver fatigue level increased and the driver vigilance level decreased (B.-G. Lee et al., 2014). A directionally-specific increase in beta-band connectivity from posterior parietal cortex to motor cortex during visually-guided movement to facilitate accurate upper limb movement was reported

(Chung, Ofori, Misra, Hess, & Vaillancourt, 2017). Neurofeedback i.e. beta training is beneficial for attention and cognitive function improvement as well as creative potential enhancement (Agnoli, Zanon, Mastria, Avenanti, & Corazza, 2018).

Brain wave activities through EEG recordings demonstrated the arousal effects of jasmine essential oil inhalation on the CNS and also the emotional states (Sayowan et al., 2013). Beta waves are activated in focused mental activity, problem solving, judgment and decision making (T. Das, 2019). Beta waves are dominant when people are engaged in reading or concentrated thought, or in highly emotional or other tense mental states (Hongratanaworakit, 2004). In this study, *d*-borneol could induce a significant increase in the beta wave related to active attention during the waking rhythm of the brain (Idris et al., 2014) causing the ANS arousal through a significant increase in blood pressure and heart rate and making the participants feel better, more active, fresher and more romantic. A significant increase in systolic blood pressure, diastolic blood pressure caused by BO inhalation indicated an increase of autonomic arousal since blood pressure is one of the activities under the sympathetic branch of the autonomic nervous system (ANS) (Hongratanaworakit & Buchbauer, 2007).

The effects of BO inhalation may be classified as stimulating effects by significantly increasing both the ANS parameters as the autonomic arousal and the psychological parameters of emotional states as the subjective behavioral arousal. *d*-Borneol inhalation caused significant changes of autonomic nervous system and central nervous system among healthy adulthood. Increasing ANS parameters i. e. systolic blood pressure, diastolic blood pressure and heart rate were shown. EEG recordings exhibited the increase in absolute powers of beta activities at left and right posterior regions. The increase in beta wave could be interpreted as a cortical arousal caused by BO inhalation. The Geneva Emotion and Odor Scale was used to measure emotional effect by *d*-borneol. Not only a significant increase in positive emotional states but also a significant decrease in negative emotional states simultaneously were found.

5.1.8 *d*-camphor

5.1.8.1 Effects of d-camphor Inhalation on physiological parameters and emotional states

This pre-test and post-test study design that compared SO and CH inhalation could highlight the effects of *d*-camphor among healthy participants. In this study, *d*-camphor inhalation caused significant changes in ANS parameters as the autonomic arousal by decreasing systolic blood pressure, diastolic blood pressure, respiratory rate, heart rate significantly while increasing skin temperature. The results of this study were consistent with those of previous studies. For instance, Kim et al. (2018) investigated the effect of *Chrysanthemum indicum* Linne with *d*-camphor as a major compound on blood pressure and electroencephalogram in healthy participants. The oil administered through inhalation could induce a decrease in the systolic blood pressure and heart rate but an increase in alpha waves. The researchers concluded that *C. indicum* Linne could help reduce blood pressure and may provide mental and physical relaxation (Kim et al., 2018).

d-Camphor inhalation induced significant changes in psychological parameters of emotional states as the subjective behavioral arousal. CH inhalation increased the mean scores of relaxed, calm feelings significantly but decreased the mean scores of active feelings decreased significantly. A previous study was conducted to investigate basic emotions induced by odorants including *d*-camphor by analyzing autonomic nervous system (ANS) responses. The participants were asked to complete a hedonic scale to rate the pleasantness or unpleasantness of the odors. The results showed that camphor was ranked intermediate between happiness or surprise as characteristics of the pleasant odorants and sadness (Vernet-Maury et al., 1999). The sedative effect of *d*-camphor administered through inhalation to mice was conducted using an open field test and the result showed that *d*-camphor could decrease the amount of spontaneous motor activity indicating the sedative effect (Oshima & Ito, 2021).

5.1.8.2 Effects of *d*-camphor Inhalation on brain wave activities through EEG parameters

The data of EEG recordings were collected and interpreted to measure the effects on *d*-camphor inhalation on cortical arousal. The results showed that *d*-camphor inhalation triggered significant changes in alpha wave power whereas there were no significant changes in other 3 waves. The alpha wave power increase was found at all the brain regions namely left anterior, right anterior, center, left posterior and right posterior. Alpha waves manifest when humans are in a state of relaxed wakefulness which decreases with concentration, stimulation or visual fixation (Stern & Engel, 2005). In essence, the increases in alpha brain waves are associated with mental coordination, calmness, attention, brain consciousness and are highly associated with a reduced stressed level (Sowndhararajan & Kim, 2016). As a result, a significant increase in alpha wave which showed the cortical arousal in this study caused the participants to feel more relaxed and calmer.

d-Camphor seemed to possess sedative effects. *d*-Camphor triggered the autonomic arousal via ANS parameters, the subjective behavioral arousal via the emotional state parameters and the cortical arousal via an increase of alpha waves from EEG recordings. According to the results in this study, *d*-camphor could decrease ANS parameters, increase all areas of alpha waves, induce relaxation, calmness while reduce stress in healthy participants. The results in this study are also recommended for healthy adults who need to stay calm and relaxed by inhaling natural *d*-camphor.

5.1.9 Methyl eugenol

5.1.9.1 Effects of methyl eugenol Inhalation on physiological parameters and emotional states

In this study, methyl eugenol inhalation caused significant changes in ANS parameters as the autonomic arousal by causing systolic blood pressure and diastolic blood pressure, heart rate and respiratory rate to decrease significantly. Methyl eugenol inhalation induced significant changes in psychological parameters of emotional states as the subjective behavioral arousal. The mean scores of active and fresh feelings decreased significantly but the mean scores of drowsy feelings increased significantly.

Sampath, Mahapatra, Padhi, Sharma, and Talwar (2015) studied the effects of holy basil (*Ocimum sanctum* L.) on cognitive parameters in 40 healthy adult volunteers. Each volunteer received 300 mg daily holy basil leaf extract for 4 weeks. The researchers discovered an improvement in cognitive flexibility, short-term memory and attention (Sampath et al., 2015).

A previous study conducted by Khumpirapang, Pikulkaew, Anuchapreeda, and Okonogi (2018) found that the combined effects of 1,8-cineole and methyl eugenol could promote anesthesia response compared to separate use at the same dose in koi carp, *C. carpio* (Khumpirapang et al., 2018). Moreover, Zhu et al. (2018) reported that methyl eugenol (ME) could regulate food intake in the anorexic mice by activating $GABA_AR$s to confer an inhibitory control on neuronal excitability in CeA. The results showed that ME counteracted the anorexigenic effects significantly caused by satiety or sickness related to GABAergic inhibition in the central amygdala. ME also enhanced feeding but did not affect locomotor activity and basal anxiety in naïve mice. The researchers suggested that ME could be possibly used as a leading compound for anorexia treatment (Zhu et al., 2018).

5.1.9.2 Effects of methyl eugenol inhalation on brain wave activities through EEG parameter

The data of EEG recordings were collected and interpreted to measure the effects on methyl eugenol inhalation on the cortical arousal through changing brain wave activities. The results showed that methyl eugenol inhalation triggered significant changes in brain wave activities. The power of the delta wave in left anterior and

right anterior increased significantly and the power of the delta wave in center, left posterior, right posterior increased without statistical significance. The power of the theta wave in left anterior, right anterior and center increased significantly and the power of the theta wave in left posterior, right posterior increased without statistical significance.

The EEG brain waves can be classified into 2 types: (1) alpha, beta and gamma waves in higher frequency range, (2) delta and theta waves in lower frequency range. Alpha and beta waves are dominant when people are awake. Alpha waves are more dominant when people feel relaxed and brain waves become slower. Higher levels of alpha waves correlate with lower levels of activity. Gamma is related to learning, memory and voluntary motor movement. In contrast, delta waves are present as slow-wave sleep and during tasks which require continuous attention (Kirmizi-Alsan et al., 2006). High amplitude theta waves are related to memory function but lower amplitude ones are associated with low alertness and high drowsiness. A result of sleep deprivation can increase delta and theta wave activities (Posada-Quintero, Reljin, Bolkhovsky, Orjuela-Cañón, & Chon, 2019).

Norte et al. (2005) determined the effects of ME administration on behavioral models related to depression and anxiety in rats. The results showed that the ME administration, the major constituent of *Croton zehntneri* (Cz) essential oil, demonstrated stimulating or anti-depressive effects in rats by altering the CNS mechanisms related to the behavior without changes in structures related to anxiety (Norte et al., 2005). Anesthetic action of ME and other eugenol derivatives in rats was investigated in a previous study. The results indicated that ME anesthetized the rats more rapidly compared to pentobarbital. It was easier to operate the rats under ME anesthesia which showed less cyanosis and recovered better than those under pentobarbital. ME induced large amounts of slow wave activity of theta through EEG but did not change the total brain levels of dopamine, norepinephrine and 5-hydroxytryplamine. The researchers summarized that ME could have short-term anesthetic action in rats which was better than that of pentobarbital (Sell & Carlini, 1976).

Z.-J. Wang, Tabakoff, Levinson, and Heinbockel (2015) investigated the effects of methyl eugenol on the Na^+ channel isoform, $NA_v1.7$, using the technique of

whole-cell patch clamp recording. Methyl eugenol inhibited peripheral nerve $NA_v1.7$ channels in a concentration- and voltage dependent manner. These results indicated a possible mechanism of the antinociceptive and anesthetic actions of methyl eugenol and the herbal medicine Xixin through the inhibition of peripheral Na^+ channels. The researchers proposed using methyl eugenol as an effective local anesthetic and analgesic (Z.-J. Wang et al., 2015).

To sum up, methyl eugenol and the essential oils containing methyl eugenol as a major compound seem to possess sedative effects. According to the results in this study, methyl eugenol could decrease most ANS parameters, increase certain areas of delta, theta waves while induce drowsiness in healthy participants. Methyl eugenol triggered all the three levels of arousal particularly an increase in both delta and theta waves which are considered as slow brain waves. Therefore, methyl eugenol seemed to cause strong sedating effects compared with *d*-camphor and methyl chavicol.

5.1.10 Methyl chavicol

5.1.10.1 Effects of methyl chavicol Inhalation on physiological parameters and emotional states

In this study, MC inhalation caused significant changes in ANS parameters as the autonomic arousal. MC inhalation could decrease systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate significantly. The results in this study were consistent with previous preclinical studies. For instance, Mahmoud and Omyma performed an in-vivo experiment on the effect of basil (*Ocimum basilicum)* and cloves in lowering blood pressure in rats suffering from high blood pressure. The results indicated that basil, cloves and the mixture of both could decrease systolic and diastolic blood pressure significantly in the mean values of total lipid profile, glucose, Serum Glutamic Oxalocetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) in all treated groups compared to the control group. So, basil (*O. basilicum)* could help lower systolic and diastolic blood pressure in hypertensive rats (Mahmoud & Eldarder, 2016). In addition, antihypertensive and vasorelaxant effects of *T. lucida* extract was investigated in a previous study. The researchers tested its effects in an *in*

vivo experiment in rats by intragastric administration. The results revealed that the *T. lucida* extract could lower systolic and diastolic blood pressure on rats and it showed concentration-dependent relaxant effects. The researchers concluded that the results provided evidence and endorsed the antihypertensive properties of *T. lucida* used in traditional medicine (Estrada-Soto et al., 2021).

Moreover, MC inhalation induced significant changes in psychological parameters of emotional states as the subjective behavioral arousal. MC inhalation could decrease bad, frustrated feelings significantly but increase relaxed feelings significantly. MC inhalation seemed to possess sedative effects by decreasing bad, frustrated feelings while increasing relaxed feelings. These results were similar to those in previous preclinical studies. For example, a previous study was conducted on the analgesic and sedative effect of *O. basilicum* alcoholic extract in 20 male rats. The results showed that the fourth group which received 100 mg/kg manifested the potent sedative effect in pentobarbitone sleeping time test and open field test. The researchers concluded that *O. basilicum* extract had analgesic and sedative effect on male rats because of its active and sedative compounds (Al-Ghurabi, 2014).

Rabbani, Sajjadi, and Vaezi (2015) evaluated the anxiolytic and sedative effect of essential oil of *O. basilicum* in mice and its chemical composition. The major components were methyl chavicol (42.8%), geranial (13%), neral (12.2%) and β-caryophyllene (7.2%). This previous study showed the anxiolytic and sedative effect of *O. basilicum* because of the phenol components of *O. basilicum* (Rabbani et al., 2015). Silva-Alves et al. (2013) conducted a study to investigate the mechanism of action of estragole on neuronal excitability in rats. Intact and dissociated dorsal root ganglion neurons of rats were used to record action potential and Na+ currents. The results indicated that estragole could block neuronal excitability by direct inhibition of Na+ channel conductance activation. Therefore, the researchers discovered an additional effect of estragole which was a local anesthetic effect (Silva-Alves et al., 2013). Ratta, Rana, Rajasekaran, and Tupas (2021) investigated the antihypertensive effects of sweet basil *(O. basilicum)* leaves as adjunct therapy for stage 1 and 2 hypertension in volunteers. The results showed that systolic and diastolic blood pressure in the treatment group after 2 weeks were significantly different and lower compared to those

at baseline. The researchers concluded that their study supported the antihypertensive action of *O. basilicum* L. among humans (Ratta et al., 2021).

Essential oils including basil, clove, jasmine and peppermint seemed to stimulate central nervous system (CNS) causing alertness and inducing a feeling of well-being (Skaria, 2007). Hongratanaworakit and Buchbauer (2007) reported that essential oils consisting of chemical compounds such as limonene, pinene or methyl chavicol possibly mediated the stimulating effects on sympathetic activity (Hongratanaworakit & Buchbauer, 2007). However, these results in this study varied from the previous study by Hongratanaworakit and Buchbauer (2007) because this study administered pure volatile compound of MC inhalation with different concentration level to healthy participants and used a different measurement tool which was EEG recordings to measure brain wave activities.

5.1.10.2 Effects of methyl chavicol inhalation on brain wave activities through EEG parameter

Five various brain waves namely alpha, beta, theta, delta and gamma relay and process all the bodily functions. The frontal region of the brain serves as a center for personality, behavior, emotions, judgment, planning, problem-solving, body movement, intelligence, concentration and self-awareness. The parietal covering the central regions serves as a center for linguistic interpretation, sensory and motor strip. The occipital region is responsible for the interpretation of visual stimuli while the temporal region is responsible for hearing, sequencing and organization (L. Sherwood, 2007). In this study, MC inhalation caused significant responses in brain wave activities as the cortical arousal in this study. MC inhalation could increase the alpha wave in most areas namely left anterior, right anterior, center and right posterior significantly except left posterior without statistical significance through EEG recordings. The results from *d*-camphor group in this study showed that the alpha wave in all areas namely left anterior, right anterior, center, left posterior and right posterior was found to increase significantly after *d*-camphor inhalation.

Stern and Engel (2005) reported that alpha waves could reflect a relaxed wakefulness which decreased with concentration, stimulation and visual fixation. A previous study has warranted that alpha wave is the main brain wave of normal relaxed

adults. It is also about relaxation and freedom. The alpha wave is dominant during the active activity of the brain and in mentally relaxed state (Hongratanaworakit, 2004). In addition, Koudelková and Strmiska (2018) reported that the alpha wave helped connect the gap between human conscious thinking and subconscious mind. It helped humans to calm down and promoted a feeling of relaxation (Koudelková & Strmiska, 2018). An increase in the alpha wave could promote relaxation in conscious adults. Therefore, brain waves determine human levels of consciousness, psychological state and degree of arousal (Hongratanaworakit, 2004).

MC inhalation induced physiological effects on cortical arousal through a significant increase in alpha brain wave responses and vagus nerve through brain-gut connection leading to ANS parameters under the control of parasympathetic nervous system. The hypothalamus regulates energy storage and expenditure through ANS (Isganaitis & Lustig, 2005). The parasympathetic nervous system mediated by vagus nerve provides both excitatory and inhibitory control over gastric, intestinal and pancreatic functions to maintain homeostatic regulation (Browning & Travagli, 2014). So, the parasympathetic nervous system through vagus nerve promotes energy storage inducing appetite (Isganaitis & Lustig, 2005). The parasympathetic nervous system stimulates digestion, lowers ANS parameters namely blood pressure, heart rate and allows restoration and rebuilding of organs under the “rest and digest” response (Benzl, 2018). In essence, the parasympathetic nervous system functions to create a sense of well-being to restore harmony and equilibrium by relaxing muscles, blood vessels and internal organs (Sands, 2002). So, MC as a major compound extracted from various herbal plants, such as anise, funnel, bay, turpentine, basil, *T. lucida* are widely consumed to stimulate appetite and relax intestinal organs.

In conclusion, methyl chavicol and the essential oils containing methyl chavicol as a major compound seemed to possess sedative effects. According to the results in this study, methyl chavicol could decrease ANS parameters, increase all areas of alpha waves, decrease negative (bad, frustrated) feelings but increase positive (relaxed) feeling in healthy participants. In essence, methyl chavicol decreased the autonomic arousal through ANS parameters and affected the cortical arousal by

increasing alpha waves leading to the changing subjective behavioral arousal via more positive emotional states.

5.2 Conclusion

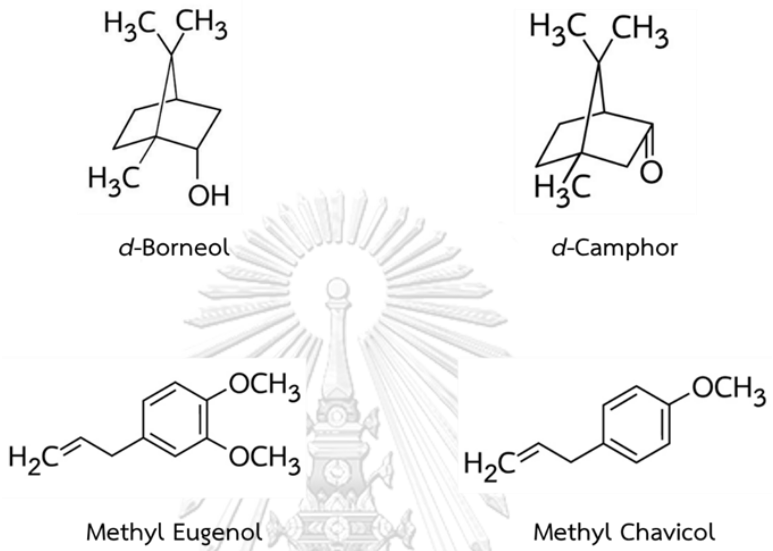


Figure 27 The chemical structures of four selected aromatic compounds: *d*-borneol, *d*-camphor, methyl eugenol and methyl chavicol

The findings in this study revealed that the inhalation of selected volatile compounds namely *d*-borneol (monoterpene alcohol), *d*-camphor (monoterpene ketone), methyl eugenol (phenylpropanoid) and methyl chavicol (phenylpropanoid) had significant effects on the autonomic arousal via ANS parameters (heart rate, blood pressure, respiratory rate and skin temperature), the cortical arousal via CNS parameters (brainwave activities) and the subjective behavioral arousal via emotional states (questionnaires on subjective feelings). First, *d*-borneol seemed to possess stimulating effects by increasing ANS parameters, increasing in positive emotional states while decreasing negative emotional states as well as increasing beta power at left and right posterior regions. Second, *d*-camphor seemed to possess sedative effects by decreasing ANS parameters, inducing relaxation, calmness while reducing stress while increasing all areas of alpha waves. Third, methyl eugenol also had sedative effects

by decreasing ANS parameters, inducing relaxation, calmness while reducing stress and increasing all areas of alpha waves. Finally, methyl chavicol seemed to have sedative effects by decreasing ANS parameters, increasing positive (relaxed) feeling while decreasing negative (bad, frustrated) feelings but increasing all areas of alpha waves.

To sum up, *d*-borneol was the only selected volatile compound with stimulating effects while the other selected volatile compounds namely *d*-camphor, methyl eugenol and methyl chavicol seemed to possess sedative effects through inhalation in healthy participants.

5.3 Further research

Future research could be conducted on the effects of volatile compound inhalation on other groups of participants to provide more health-related scientific data and knowledge. Then, the general public can apply the use of volatile compounds safely and properly. Future research should have two groups of participants: an intervention group and a control group so that the control group could be used to compare the effects of volatile compounds.

5.4 Limitations

The olfactory memory might be affected by repeated exposure of the odor since ANS parameters and EEG recordings could not be conducted simultaneously in the same experiment and ANS parameters were not measured continuously. Each selected volatile compound was administered as a single compound in this study. If other essential oils contained these four volatile compounds as compounds or single compounds mixed with other substances, the effects would be different. The effects of these four selected volatile compounds in this study were caused in healthy participants who indicated oil pleasantness within the target level range of 2-4 from “Odor familiarity five-point Likert scale”.

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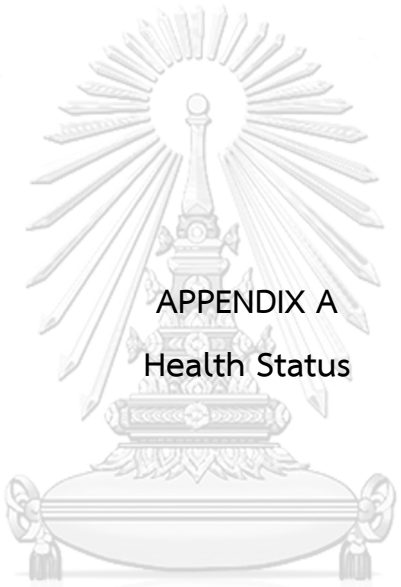
APPENDICES



APPENDIX A

Health Status

..... *Pretesting* แบบสอบถามข้อมูลสุขภาพ (ภาษาไทย)

..... *Screening*

Date.....

โปรดตอบแบบสอบถามต่อไปนี้ ตามข้อมูลที่เป็นจริง ตรงกับตัวท่านมากที่สุด

1. ข้อมูลส่วนบุคคล

เพศ.....อายุ..... น้ำหนัก.....กก. ส่วนสูง.....ซม.

ผลการวัด อุณหภูมิ..... องศา ชีพจร.....ครั้ง/นาที หายใจ.....ครั้ง/นาที

ความดันโลหิต .....มม.ปรอท ดัชนีมวลกาย..... kg/m^2

เบอร์โทรศัพท์ที่สามารถติดต่อได้สะดวก

2. ข้อมูลด้านสุขภาพ

1) ท่านมีโรคประจำตัวดังต่อไปนี้ หรือไม่

- โรคทางระบบประสาท ☐ มี ☐ ไม่มี ☐ ไม่ทราบ ☐ ไม่แน่ใจ
- โรคลมชัก ☐ มี ☐ ไม่มี ☐ ไม่ทราบ ☐ ไม่แน่ใจ
- โรคติดเชื้อต่าง ๆ ☐ มี ☐ ไม่มี ☐ ไม่ทราบ ☐ ไม่แน่ใจ
- โรคติดเชื้อของระบบทางเดินหายใจ ☐ มี ☐ ไม่มี ☐ ไม่ทราบ ☐ ไม่แน่ใจ
- โรคหอบหืด ☐ มี ☐ ไม่มี ☐ ไม่ทราบ ☐ ไม่แน่ใจ
- โรคภูมิแพ้ ☐ มี ☐ ไม่มี ☐ ไม่ทราบ ☐ ไม่แน่ใจ
- โรคไซนัส ☐ มี ☐ ไม่มี ☐ ไม่ทราบ ☐ ไม่แน่ใจ
- โรคความดันโลหิต ☐ มี ☐ ไม่มี ความดันโลหิตที่วัดได้.....

ท่านมีโรคประจำตัวคือ.....และหรือ เคยเข้ารับการผ่าตัด.....

ยารักษาโรคประจำตัวที่ใช้เป็นประจำ

ชนิด	ขนาด	ปริมาณ
.....	.....	.....
.....	.....	.....

2) ที่คิดว่าสุขภาพร่างกายของท่านตอนนี้เป็นอย่างไร

☐ เจ็บป่วย ☐ ปกติตามเคย ☐ แข็งแรงดี ☐ แข็แรงดีมาก

3) ท่านเคยแพสิ่งต่อไปนี้ หรือไม่

☐ สารเคมี..... ☐ อาหาร..... ☐ น้ำหอม ☐ เกสรดอกไม้

☐อื่น ๆ โปรดระบุ.....

4) ท่านเคยประสบอุบัติเหตุร้ายแรง หรือไม่

☐ เคยที่อวัยวะ.....เมื่อ..... ☐ ไม่เคย

5) เวลานอนตามปกติ.....ชั่วโมง

6) ท่านมีปญหาเรื่องนอนหลับในช่วง 1 เดือนที่ผ่านมา หรือไม่

☐ มี ☐ ไม่มี ☐ ไม่ทราบ ☐ ไม่แน่ใจ

7) ท่านมีปญหาการได้ยิน หรือไม่

☐ มี ☐ ไม่มี

8) ท่านมีปญหาในการดมกลิ่น หรือไม่

☐ มี ☐ ไม่มี

9) ท่านได้รับการฝังเครื่องกระตุ้นหัวใจ

☐ มี ☐ ไม่มี

10) ท่านคิดว่าสุขภาพจิตของท่านเป็นอย่างไร ☐ เจ็บป่วย ☐ ไม่ดี ☐ ดี

11) ท่านสูบบุหรี่หรือไม่ ☐ ไม่เคยแลย ☐ สูบ ☐ เคยสูบแต่หยุดสูบแล้ว

12) ท่านดื่มสุรา เครื่องดื่มที่มีแอลกอฮอลหรือไม่ ☐ไม่เคยเลย ☐ บ่อยครั้ง ☐ บางครั้ง

ท่านดื่มน้ำอัดลมหรือไม่ ☐ ไม่เคยเลย ☐ บ่อยครั้ง ☐ บางครั้ง

ท่านดื่มชากาแฟหรือไม่ ☐ ไม่เคยเลย ☐ บ่อยครั้ง ☐ บางครั้ง

..... *Pretesting* **Health status (English version)**

..... *Screening*

Date.....

Please answer this questionnaire with honesty

1. Personal information

Sex..... Age.....Wight.....kg Height.....cm Obesity.....kg/m^2

Vitals; Temperature.....C Respiration.....per min Pulse.....per min

BP Systolic.....mmhg BP Diastolic .....mmhg Telephone Number

2. Health Information

2.1 Do you suffer from any of the following illnesses?

- Neurological diseases.

☐ Yes ☐ No ☐ Not that I know/unsure.....

- Epilepsy

☐ Yes ☐ No ☐ Not that I know/unsure.....

- Infection

☐ Yes ☐ No ☐ Not that I know/unsure.....

- Asthma

☐ Yes ☐ No ☐ Not that I know/unsure.....

- Allergy

☐ Yes ☐ No ☐ Not that I know/unsure.....

- Sinus

☐ Yes ☐ No ☐ Not that I know/unsure.....

- High/ Low Blood Pressure

☐ Yes ☐ No ☐ Not that I know/unsure.....

Do you have any previous health problems or surgery? Please specify.....

Are you on any regular medication?.....

2.2 How good is your health?

☐ Sick ☐ Normal ☐ Healthy ☐ Very healthy

2.3 Have you ever been allergic to any of the following?

☐ Chemical ☐ Food..... ☐ Perfume..... ☐ Pollens.....

2.4 Have you ever experienced any critical accident?

☐ Yes, internally..... If yes, when?..... ☐ never

2.5 How long do you normally sleep a night?.....Hours

2.6 Do you have any sleeping problem during this past month?

☐ Yes ☐ No

2.7 Do you have any hearing problem?

☐ Yes ☐ No

2.8 Do you have any smelling disorder?

☐ Yes ☐ No

2.9 Have you been installed any pacemaker?

☐ Yes ☐ No

2.10 How is your mental health?

☐ Sick ☐ Not well ☐ ok ☐ Good ☐ Very good

2.11 Have you ever smoked cigarette?

☐ Never ☐ Yes ☐ Yes, but not anymore

2.12 Do you drink alcohol?

☐ No ☐ Consistently ☐ Consistently but quit already

2.13 Do you drink these follows regularly?

- Pop soda

☐ Yes, what's the quantity per day?.....☐ No ☐ Sometimes, How often?.....

- Tea, Coffee

☐ Yes, what's the quantity per day?..... ☐ No ☐ Sometimes

- Tonic beverage

☐ Yes, what's the quantity per day?..... ☐ No ☐ Sometimes

APPENDIX B

Edinburgh Handedness Inventory Test

Date.....

แบบทดสอบถนัดมือขวา (ภาษาไทย)

ให้ท่านอ่านกิจกรรมในแต่ละข้อแล้วให้คะแนนตามความเป็นจริงมากที่สุดโปรดตอบทุกข้อ ตามมือข้างที่ถนัดหากไม่เคยมีประสบการณ์ในกิจกรรมนั้น ๆ ให้เว้นช่องว่างไว้

วิธีการให้คะแนน

+ ในช่องมือข้างที่ถนัดขณะทำกิจกรรมนั้นซึ่งมืออีกข้างพอที่จะทำได้บ้าง

++ ในช่องมือที่ถนัดข้างเดียวโดยที่มืออีกข้างที่ไม่สามารถทำกิจกรรมนั้นได้เลย

+/+ ในทั้ง 2 ช่องถ้าสามารถทำกิจกรรมในแต่ละข้อนั้นได้ดีทั้ง 2 มือเท่า ๆ กัน

กิจกรรม	ข้างขวา	ข้างซ้าย
1.เขียนหนังสือ		
2. วาดรูป		
3. โยนหรือปาของ		
4. ใช้กรรไกร		
5. ถือแปรงสีฟัน		
6. ถือมีดหั่นของ		
7. ถือช้อน		
8. กวาดพื้น		
9. ถือก้านไม้ขีดไฟ		
10. มือข้างที่ถือฝาขณะเปิดฝากล่องหรือขวด		
คะแนนรวม		

..... ผู้ประเมิน

การคิดคะแนน $\frac{\text{ผลรวมของช่องข้างขวา – ช่องข้างซ้าย}\times 100}{\text{ผลรวมทั้งหมด}}$

เกณฑ์ ได้คะแนนต่ำกว่า -40 แสดงว่าถนัดมือซ้าย

ได้คะแนนระหว่าง -40- +40 แสดงว่าถนัดทั้งสองข้าง

ได้คะแนนมากกว่า +40 แสดงว่าถนัดข้างขวา

Date.....

Edinburgh handedness inventory test (English version)

Please indicate your preferences in the use of hands in the following activities by putting +in the appropriate column. Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, put ++ checks. If in any case you are really indifferent, put + in both columns. Some of the activities listed below require the use of both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in parentheses. Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

Activities	Right	Left
1 Writing		
2. Drawing		
3 Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking Match (match)		
10. Opening box (lid)		

Scoring:

Add up the number of checks in the “Left” and “Right” columns and enter in the “TOTAL” row for each column. Add the left total and the right total and enter in the “Cumulative TOTAL” cell. Subtract the left total from the right total and enter in the “Difference” cell. Divide the “Difference” cell by the “Cumulative TOTAL” cell (round to 2 digits if necessary) and multiply by 100; enter the result in the “Result” cell. Below -40 = left-handed, Between -40 and +40 = ambidextrous, Above +40 = right-handed

APPENDIX C

Score Sheet for Odor Test (Butanol Threshold)

Score sheet for odor test (butanol threshold)

Date.....

Step	Concentration	1	2	3	4	5
11	2.25×10^{-5}	B	W	B	B	W
10	6.77×10^{-5}	B	B	W	W	B
9 (Start)	2.03×10^{-4}	W	B	W	B	B
8	6.09×10^{-4}	W	B	W	B	B
7	1.82×10^{-3}	W	W	B	B	B
6	5.48×10^{-3}	B	W	B	B	B
5	0.0164 %	B	B	B	B	W
4	0.049 %	W	B	B	B	W
3	0.148 %	W	B	B	B	B
2	0.44 %	W	B	B	B	B
1	1.33 %	B	W	B	B	W
0	4 %	B	W	B	B	W
score						

B = smell buthanol W = smell water

Key : ✓correct ✕ incorrect

APPENDIX D

Odor Familiarity

แบบประเมินความพึงพอใจที่มีต่อกลิ่น

Date.....			

คุณเคยมีอาการเหล่านี้หลังจากการดมกลิ่นบางหรือไม่

(สามารถตอบได้มากกว่า 1 ข้อ)

☐ ปวดศีรษะ / เวียนศีรษะ ..... ☐ คลื่นไส้ / อาเจียน .....

☐ น้ำมูกไหล ..... ☐ อาการแพ้ .....

☐ หายใจติดขัด..... ☐ ไม่มีอาการใด ๆ .....

คุณรู้สึกอย่างไรเมื่อได้ดมกลิ่นของสารหอม

คะแนน/กลิ่น	พอใจมาก 5	พอใจ 4	ปานกลาง 3	ไม่พอใจ 2	ไม่พอใจมาก 1

Odor familiarity

Date.....

Have you ever had these symptoms after inhalation? (Answer more than one item)

☐ Headaches / Dizziness ..... ☐ Nausea / Vomiting .....

☐ Runny nose..... ☐ Allergy .....

☐ Respiratory difficulty..... ☐ No symptoms.....

How do you feel the smell of the following volatile compounds?

Score/Odor	Very pleasant 5	Pleasant 4	Moderate 3	Unpleasant 2	Very Unpleasant 1

APPENDIX E

Case Record Autonomic Nervous System

Case record autonomic nervous system

Date.....

Activity	No	Times	Blood pressure		Pulse	Temp	RR	Note
			Systolic	Diastolic				
	1							
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	1							
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							

APPENDIX F

Case Record Electroencephalographic

Case record electroencephalographic

Date.....

Gender .....

Age .....

DOB.....

Handed .....

EEG operator:.....

No.	Procedure	Duration	Time	EEG recorded file	Sequence file	Bad channel/Remark
1	Apply EEG Cap	30 min				
2	EEG baseline (Eye open)	5min				
3	EEG baseline (Eye close)	5 min				
4	Sweet Almond (Eye close)	8 min				
5	Essential oil (Eye close)	8 min				

Note

.....

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.....

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APPENDIX G

Emotional Record

Emotional Record

Date.....

ในนาทีนี้ท่านมีความรู้สึกตามหัวข้อต่อไปนี้อย่างไรให้ท่านทำเครื่องหมายลงบนเส้นจากน้อยไปหามาก ค่าความเที่ยงและความตรงของแบบประเมิน (Cronbach's a value) เท่ากับ 0.752

รู้สึกดี (Good)

รู้สึกไม่ดี (Bad)

รู้สึกกระปรี้กระเปร่า (Active)

รู้สึกเฉื่อยชาง่วงซึม (Drowsy)

รู้สึกสดชื่น (Fresh)

รู้สึกผ่อนคลาย (Relaxed)

รู้สึกเครียด (Stressed)

รู้สึกอึดอัด (Frustrated)

รู้สึกเคลิ้มเคลิ้มรัญจวนใจ (Romantic)

รู้สึกหงุดหงิด (Annoyed)

รู้สึกจิตใจสงบนิ่ง (Calm)

รู้สึกรังเกียจขยะแขยง (Disgusted)

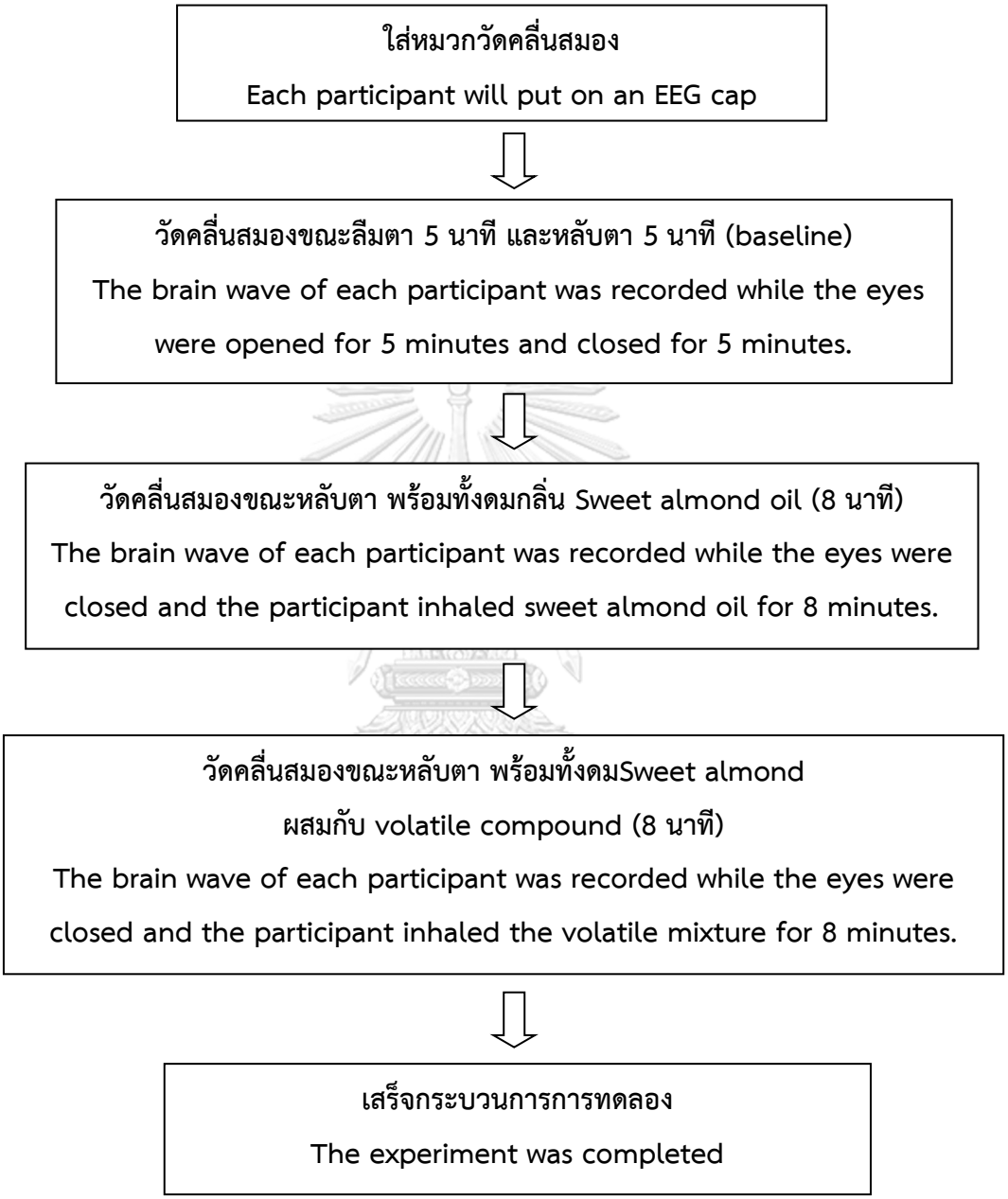
ท่านมีอาการข้างเคียงหลังดมกลิ่นหรือไม่ระบุ.....

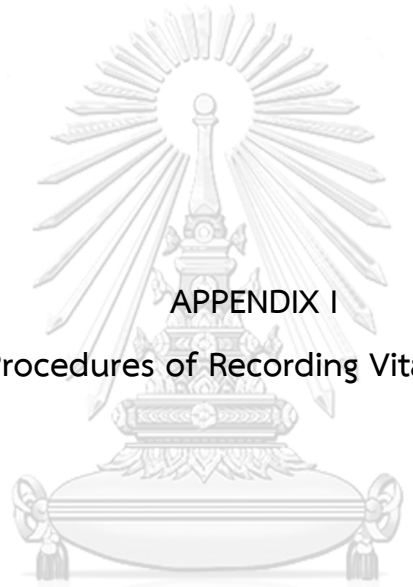
APPENDIX H

EEG Procedures of Measuring EEG Brainwave

ขั้นตอนการเก็บข้อมูลการวัดคลื่นสมอง

EEG procedures of measuring EEG brain wave



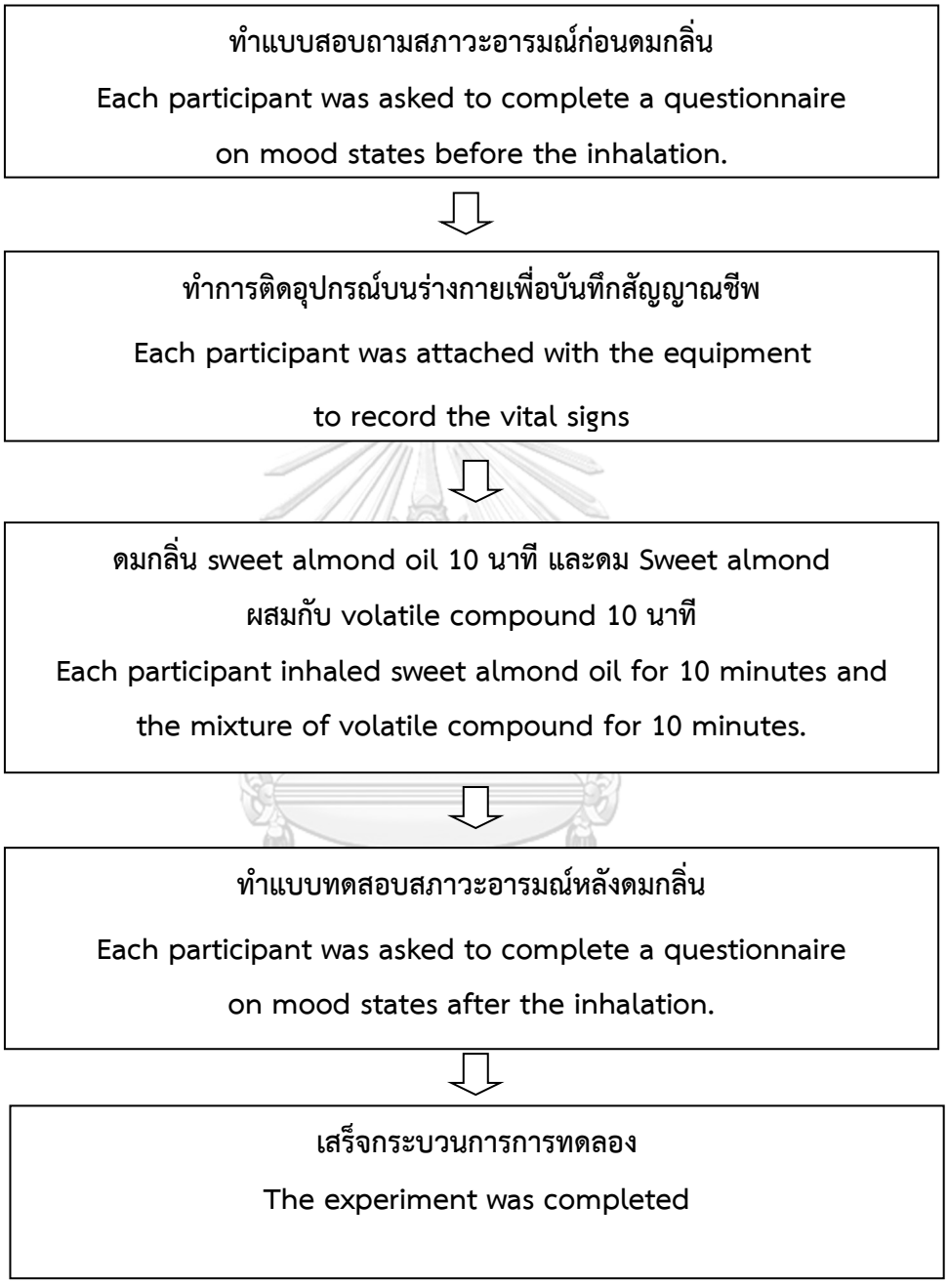


APPENDIX I

Procedures of Recording Vital Signs

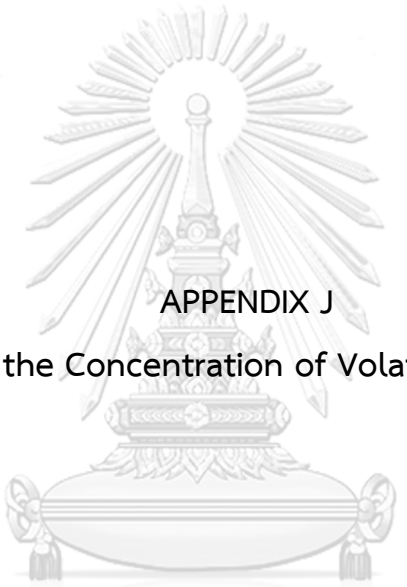
ขั้นตอนการเก็บข้อมูลระบบประสาทอัตโนมัติ

Procedures of recording vital signs



APPENDIX J

Pretesting the Concentration of Volatile Compounds



Pretesting the concentration of volatile compounds

Date.....

Concentration of volatile compound/ sweet almond oil	2%	4%	6%	8%	10%	12%
1. (+)-Borneol						
2. (+)-Camphor						
3. Methyl eugenol						
4. Methyl chavicol						

แบบประเมินระดับความเข้มข้นน้ำมันระเหย

Date.....

ระดับความเข้มข้นสาร ระเหย/น้ำมันสวีทอัลมอนด์	2%	4%	6%	8%	10%	12%
1. พิมเสน						
2. การบูร						
3. เมทิลยูจินอล						
4. เมทิลชาวิคอล						

APPENDIX K

Certificate of Approval of Ethics Review Committee for Research Involving Human Research

Certificate of Approval of Ethics Review Committee for Research Involving Human Research Subjects, Health Science Group, Chulalongkorn University on 10 March, 2020 with ethics number COA No. 074/2020.

AF 02-12

The Research Ethics Review Committee for Research Involving Human Research Participants, Group I, Chulalongkorn University
Jamjuree 1 Building, 2nd Floor, Phyathai Rd., Patumwan district, Bangkok 10330, Thailand,
Tel: 0-2218-3202, 0-2218-3049 E-mail: eccu@chula.ac.th

COA No. 074/2020

Certificate of Approval

Study Title No. 272.2/62 : EFFECTS OF SELECTED AROMA COMPOUNDS ON PHYSIOLOGICAL ACTIVITIES AND EMOTIONS

Principal Investigator : MR. AKARAT SIVAPHONGTHONGCHAI

Place of Proposed Study/Institution : College of Public Health Sciences, Chulalongkorn University

The Research Ethics Review Committee for Research Involving Human Research Participants, Group I, Chulalongkorn University, Thailand, has approved constituted in accordance with Belmont Report 1979, Declaration of Helsinki 2013, Council for International Organizations of Medical Sciences (CIOM) 2016, Standards of Research Ethics Committee (SREC) 2013, and National Policy and guidelines for Human Research 2015.

Signature: Prida Tasanapradit
(Associate Prof. Prida Tasanapradit, M.D.)
Chairman

Signature: Nuntaree Chaichanawongsaroj
(Associate Prof. Nuntaree Chaichanawongsaroj, Ph.D.)
Secretary

Date of Approval : 10 March 2020 Approval Expire date : 9 March 2021

The approval documents including;

1) Research proposal
2) Participant Information Sheet and Consent Form
3) Researcher
4) Questionnaires

Protocol No. 272.2/62
Date of Approval 10 MAR 2020
Approval Expire Date 9 MAR 2021

The approved investigator must comply with the following conditions:

1. *The research/project activities must end on the approval expired date of the Research Ethics Review Committee for Research Involving Human Research Participants, Health Sciences Group, Chulalongkorn University (RECCU). In case the research/project is unable to complete within that date, the project extension can be applied one month prior to the RECCU approval expired date.*
2. *Strictly conduct the research/project activities as written in the proposal.*
3. *Using only the documents that bearing the RECCU's seal of approval with the subjects/volunteers (including subject information sheet, consent form, invitation letter for project/research participation (if available).*
4. *Report to the RECCU for any serious adverse events within 5 working days*
5. *Report to the RECCU for any change of the research/project activities prior to conduct the activities.*
6. *Final report (AF 02-14) and abstract is required for a one year (or less) research/project and report within 30 days after the completion of the research/project. For thesis, abstract is required and report within 30 days after the completion of the research/project.*
7. *Annual progress report is needed for a two- year (or more) research/project and submit the progress report before the expire date of certificate. After the completion of the research/project processes as No. 6.*

VITA

NAME	AKARAT SIVAPHONGTHOGCHAI
DATE OF BIRTH	29 December 1979
PLACE OF BIRTH	Saraburi, Thailand
INSTITUTIONS ATTENDED	Bachelor's degree in Social Work from Faculty of Social work and Social welfare, Huachiew Chalerprakiet University, 2003 Master's Degree in Public Health Sciences, Chulalongkorn University Thesis title: Wall inscription on herbal medicine and hermit exercise at Sala Ruesee Wat Matchimawas Worawihan, Songkhala province, Thailand, 2013
HOME ADDRESS	72 Phahonyotin 4, Phahonyotin rd., Samsen-nai Phayathai Bangkon 10400
PUBLICATION	Sivaphongthongchai A., Palanuvej C., Ruangrungsi N. (2012) Wall Inscription at Sala Ruesee Wat Matchimawas, SongKhla: (Compilation, Renovation and Explanation) Proceeding of the 1st International Conference on Herbal Medicines Herbal Remedies: The Art of Sciences, pp. 132-140. The Effects of d-Camphor Inhalation on Psychophysiological Parameters among Healthy Participants, Journal of Public Health and Development (J Public Hlth Dev), Vol. 20 No. 3 (2022): September-December Oral presentation: Effects of d-Borneol and d-Camphor

Inhalations on Emotional States and Brain Wave Activities in Healthy Participants “3rd Edition of International Conference on Traditional Medicine, Ethnomedicine and Natural Therapies” (TRADITIONAL MEDICINE 2022) during the month of May 18-19, 2022

AWARD RECEIVED

The student council president in Public Health Sciences, Chulalongkorn University from 2016 to 2019

An outstanding student in Public Health Sciences, Chulalongkorn University in 2018

One of 50 extraordinary Kundalini yoga teachers from 3HO luminary program in New Mexico, USA in 2020

One of 10 projects worldwide selected to receive Kundalini Border Grant so that Kundalini Yoga teachers can teach Kundalini Yoga to an underserved population from KRI and IKYTA, USA in 2022