# A Pharmacological Investigation on CNS Activity of Chloroform Extract of *Syzygium samarangense* Leaves

"This dissertation is submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy"


**Submitted by**

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November, 2017

# DECLARATION BY THE CANDIDATE

I, Md. Abrar Jamil, hereby declare that this dissertation, entitled **"A Pharmacological Investigation on CNS Activity of Chloroform Extract of *Syzygium samarangense* Leaves"** submitted to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the degree of Bachelor of Pharmacy, is a genuine & authentic research work carried out by me. The contents of this dissertation, in full or in parts, have not been submitted to any other Institute orUniversity for the award of any Degree or Diploma of Fellowship.

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# CERTIFICATION BY THE SUPERVISOR

This is to certify that the dissertation, entitled **"A Pharmacological Investigation on CNS Activity of Chloroform Extract of *Syzygium samarangense* Leaves"** is a research work done under my guidance and supervision by Md. Abrar Jamil (ID: 2014-1-70-030), in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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# ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the dissertation, entitled **"A Pharmacological Investigation on CNS Activity of Chloroform Extract of *Syzygium samarangense* Leaves"** is a bona fide research work done by Md. Abrar Jamil (ID: 2014-1-70-030), in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.

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## ***Dedication***

*This research paper is dedicated to my respected Parents and loving Friends*

## Abstract

Current study was designed to find out CNS activity from Chloroform extract of leaves of *Syzygium samarangense*. The study was conducted in-vivo using *Swiss albino* mice model. With the help of open-field and hole-board method, CNS activity was inspected with the decline of locomotor activity on mice. Crude extract was administered to mice at a dose of 100mg/kg and 200mg/kg body weight. All the results of our experiments were statistically significant ($p<0.05$, $p<0.01$, $p<0.001$). In CNS activity tests, the movement of mice decreased in a dose-depending manner comparing to the standard, Diazepam. In conclusion, we can say that our present findings suggest that Chloroform extracts of *Syzygium samarangense* leaves contain potent CNS Depressant principles. It can also be said that the obtained results provide a support for the use of this plant in traditional medicine and its further investigation.



**Keywords:** *Syzygium samarangense*, Chloroform extract, CNS, Open-field test, Hole-board experiment

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# Chapter 1

# Introduction

## 1.1 Nervous System

The Nervous System is what helps all parts of the body to communicate with each other. The body sends and receives messages using both electrical and chemical signals, as well as reacting with changes to both the outside and inside of the body. The Nervous System is what controls your sense of; touch, sight, smell, sound, taste and is what controls your movement. There are two parts to the Nervous System. One part being the Central Nervous System, which consists of just the brain and the spinal cord, and the other part being the Peripheral Nervous System, which is all the other nerves of the body. When a message comes into the brain from anywhere in the body, the brain tells the body how to react. Ex. When we eat a piece of chocolate (stimulus), your sensory receptors detect the stimulus (chocolate). From there your sensory neurons carry the electrical impulses to the spinal cord, where your connector neurons continue to carry the electrical impulses to the brain, where it is processed. After being processed in the brain, motor neurons carry the electrical impulses to the muscles in your arm, which then causes you to pick up more chocolate and eat it (response). (weebly.com,2017)

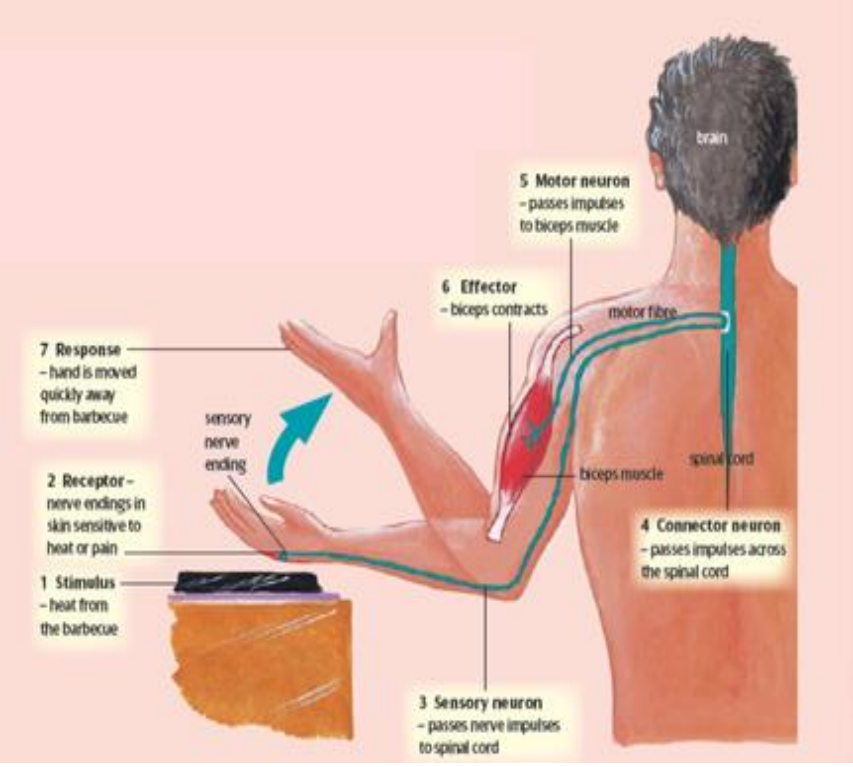


**Figure 1.1 : Nervous system responses (weebly.com,2017)**

## 1.2 Neurons

Neurons are the main building blocks of the nervous system are the nerve cells called Neurons. Neurons are all different shapes, depending on what their job is and where they are located in the body. All Neurons have finger-like projections called dendrite, as well as a long fibre called an axon. In most cases the axon is covered with a specialised membrane, called myelin sheath, which helps to increase the speed in which impulses travel along the fibres. There are bumps all along the axon, with each bump sitting near a dendrite from another neuron. In between the bump and the dendrite is called a synapse. The synapse is what allows messages to jump from one neuron to the other, using special chemical signals called neurotransmitters. (weebly.com,2017)

There are three types neurons:

1. Sensory Neurons: Sensory neurons collect information from the sensory receptors such as; the eyes, nose, ears, tongue and skin towards the central nervous system.
2. Motor Neurons: Motor Neurons carry messages away from the central nervous system to the rest of the body, being muscles and glands.
3. Inter Neurons: Most inter neurons are found in the central nervous system and are in charge of sending information between sensory neurons and motor neurons.

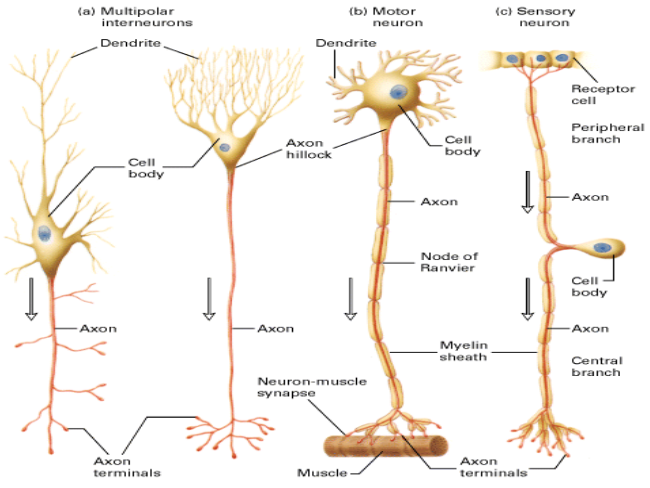


**Figure 1.2 : Neurons (weebly.com,2017)**

## 1.3 Types of Nervous System

There are two major categories of our nervous system.

1. Central Nervous System (CNS)
2. Peripheral Nervous System (PNS)

There are two categories of Peripheral Nervous System.

1. Somatic Nervous System:

   It controls all of our voluntary muscle movements. Everything from choosing to kick a ball to scratching an itch. Every time we choose to move our body we are using motor neurons in the somatic nervous system.

2. Autonomous Nervous System:

   It controls all of the automatic functions of our body. Our heart rate, lungs, internal organs, etc.

The Autonomous Nervous System is divided into 2 categories.

1. Sympathetic Nervous System - Fight or Flight response.
2. Parasympathetic Nervous System - Response for relaxation.

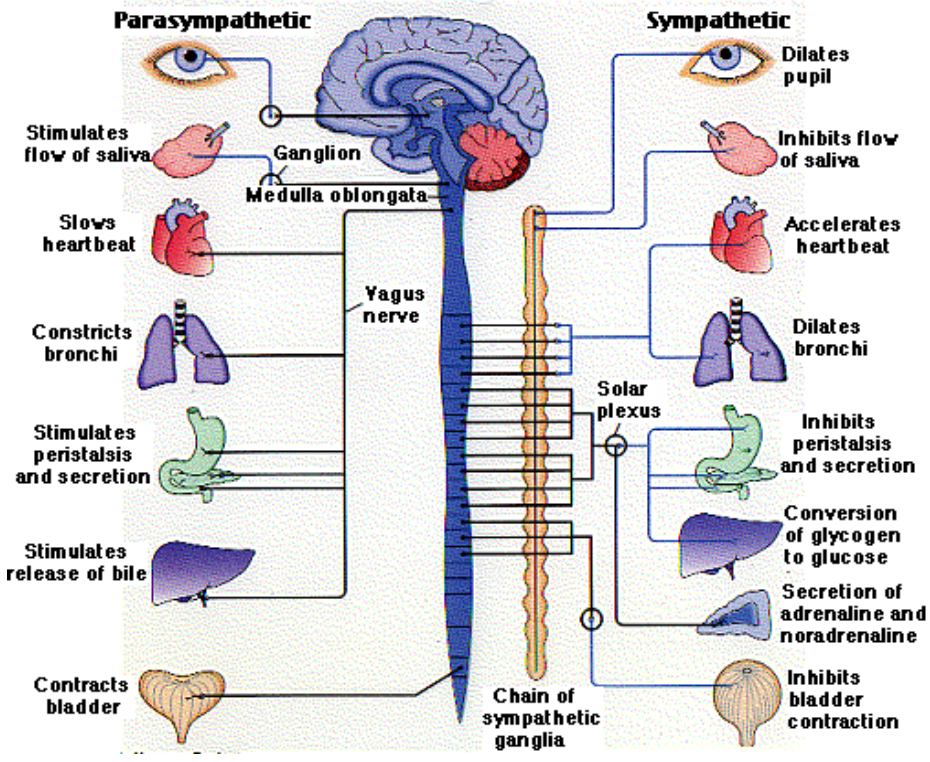


**Figure 1.3 : Autonomous Nervous System (weebly.com,2017)**

## 1.4 Central Nervous System

The central nervous System is the processing centre for the nervous system, and consists of just the brain and spinal cord, that both sends and receives information to and from the Peripheral Nervous System. (weebly.com,2017)

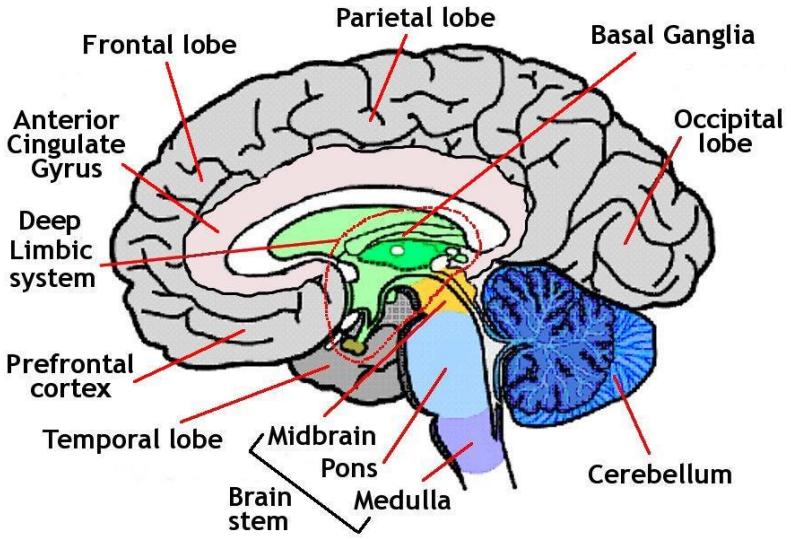


**Figure 1.4 : Central Nervous System**

### 1.4.1 Brain

Although only making up two percent of the body's weight, the brain is the powerhouse of the body working non-stop to keep the body functioning and under control at all times. The brain is soft, jelly-like organ that contains countless of neural cross connections. The brain is made up of three sections when it comes to the Nervous System. (weebly.com,2017)

- ✓ Forebrain
- ✓ Midbrain
- ✓ Hindbrain

#### 1.4.1.1 Forebrain

The forebrain is the largest and most complex part of the brain, and consists of the cerebrum, which is the area of the brain with all the grooves and folds normally seen in pictures, as well as other structures beneath the surface. The cerebrum is the part of the brain that practically makes us who we are. It consists of; our intelligence,

memory, personality, emotion, speech, and ability to feel and move. These certain processes are divided into four parts of the brain called 'lobes'. The four lobes are; Frontal lobe, Parietal lobe, Occipital lobe, and Temporal lobe. The four lobes are situated within the two halves of the brain, the left halve and the right halve, which is called hemispheres. both halves of the brain are connected by a band of fibres that run along the middle of the brain between both halves, which allows both sides of the brain to communicate with each other.

The left side of the brain is considered to be the logical, analytical, and objective side, whereas the right side of the brain is considered to be more intuitive, creative, and subjective.
The outer layer of the brain is called the 'cortex', which is also known as grey matter, and is in charge of all the information collected by our five senses that comes into the brain from our spinal cord to the cortex.

The inner part of the forebrain contains the thalamus, hypothalamus, and the pituitary gland. The thalamus carries messages from the sensory organs to the cortex, the hypothalamus controls pulse, thirst, appetite, sleep patterns, and other processes that happen in the body automatically. **(**weebly.com,2017)

### 1.4.1.2 Midbrain

The Mid brain is located under the middle of the forebrain and acts as a master coordinator, as it controls all the messages going in and out of the brain and the spinal cord

### 1.4.1.3 Hindbrain

The Hindbrain sits underneath the back of the cerebrum and consists of the Cerebellum, Pons, and Medulla. The cerebellum, also known as the 'little brain', as it looks like a smaller version of the cerebrum, and is responsible for balance, movement, and co-ordination.

The pons and medulla, as well as the brain stem is often called the brainstem. The brainstem takes in, sends out and coordinates all of the brains messages, as well as controlling most of many of the body's automatic functions like, breathing, heart rate, blood pressure, swallowing, digesting and blinking. (weebly.com,2017)

### 1.4.2 Spinal Cord

The spinal cord is a cylindrical shape bundle of nerve fibres that is connected to the brain. The spinal cord runs along down the middle of your back, in your spinal column extending from your neck to your lower back. The spinal cord nerves are in charge of transmitting information from your organs and external stimuli to your brain, and send information from the brain to other areas of the body. The grouped bundle of nerves fibres that run along your spinal column are split into two pathways. Ascending nerve tracks carry sensory information from the body to the brain, whereas descending nerve tracks send information according to motor function from the brain to the rest of the body. (weebly.com,2017)

## 1.5 CNS Depression

Central nervous system depression or CNS depression refers to physiological depression of the central nervous system that can result in decreased rate of breathing, decreased heart rate, and loss of consciousness possibly leading to coma or death.CNS depression is specifically the result of inhibited brain activity. (En.wikipedia.org, 2017)

## 1.6 Symptoms of CNS Depression

Symptoms of CNS depression or depressant overdose range from a loss of coordination to unresponsiveness. The symptoms will vary depending on the dosage taken, the size of the individual, and their medical history. The signs and symptoms will also vary depending on the types of substances involved.

Severe cases of CNS depression can lead to delirium, coma, and death. According to Mothers Against Prescription Drug Abuse (MAPDA), opioids are responsible for most overdose deaths. (Suzanne Falck, 2017)

- Mild symptoms of CNS depression include:
  - ✓ Lack of coordination
  - ✓ Muscle weakness
  - ✓ Lethargy
  - ✓ Dizziness
  - ✓ Disorientation
  - ✓ Impaired spatial sense
  - ✓ Slurred speech or stutter
  - ✓ Slight shortness of breath or shallow breathing
  - ✓ Slightly reduced heart rate
  - ✓ Constipation
  - ✓ Dry mouth
  - ✓ Restlessness and agitation
  - ✓ Euphoria
  - ✓ Blurred, altered, or double vision
- Severe CNS depression symptoms include:
  - ✓ Reduced heart rate
  - ✓ Reduced breathing rate, at less than 10 breaths per minute
  - ✓ Extreme confusion or memory loss
  - ✓ Nausea and vomiting
  - ✓ Poor judgement
  - ✓ Blue lips or fingertips
  - ✓ Irritability and aggressiveness
  - ✓ Clammy, cold skin
  - ✓ Sudden and intense mood swings
  - ✓ Slowed reflexes

## 1.7 Psychotropic Drugs

Any drug capable of affecting the mind, emotions, and behaviour. Some legal drugs, such as lithium for bipolar disorder, are psychotropic. Many illicit drugs, such as cocaine, are also psychotropic. Also known as psychodynamic drug. (MedicineNet,2017)

## 1.8 Types of Psychotropic drugs

1. Psychoactive drugs affect the central nervous system in various ways by influencing the release of neurotransmitters (chemical messengers within the nervous system, such as acetylcholine, serotonin, dopamine, norepinephrine), or mimicking their actions.
2. Psychoactive drugs are classified as stimulants, hallucinogens, or depressants based on their effects.
3. Stimulants:
    a. excite and enhance mental alertness and physical activity
    b. reduce fatigue
    c. suppress hunger
    d. cocaine, caffeine, ephedrine are well-known, plant-derived stimulants
4. Hallucinogens:
    a. produce changes (distortions) in perception , thought, and mood that depart from ordinary reality.
    b. often induces a dreamlike state
    c. peyote, marijuana (Cannabis), and LSD are examples of hallucinogens

5. Depressants:
    - ✓ CNS depressants are external substances that work to depress the CNS by slowing brain function. Many CNS depressants work by increasing the activity of the neurotransmitter gamma-amino butyric acid (GABA), a chemical that inhibits or slows the delivery of messages between cells. (Suzanne Falck, 2017)
    - ✓ It causes dull mental awareness, reduce physical performance, induce sleep or trance-like state.

- ✓ Opium and its derivatives, morphine and heroin are classic examples of depressants
- ✓ Narcotic is also induces central nervous system depression, resulting in numbness, lethargy, and sleep. This would include opiates, alcoholic beverages, and kava. In familiar use, narcotic is inferred to include psychoactive compounds that are dangerously addictive.

(unlv.edu,2017)

## 1.9 Medicinal Plant

Medicinal plants, medicinal herbs, or simply herbs have been identified and used from prehistoric times. Plants make many chemical compounds for biological functions, including defence against insects, fungi and herbivorous mammals. Over 12,000 active compounds are known to science. These chemicals work on the human body in exactly the same way as pharmaceutical drugs, so herbal medicines can be beneficial and have harmful side effects just like conventional drugs. However, since a single plant may contain many substances, the effects of taking a plant as medicine can be complex.

The earliest historical records of herbs are found from the Sumerian civilisation, where hundreds of medicinal plants including opium are listed on clay tablets. The Ebers Papyrus from ancient Egypt describes over 850 plant medicines, while Dioscorides documented over 1000 recipes for medicines using over 600 medicinal plants in De materia medica, forming the basis of pharmacopoeias for some 1500 years.

Drug research makes use of ethnobotany to search for pharmacologically active substances in nature, and has in this way discovered hundreds of useful compounds. These include the common drugs aspirin, digoxin, quinine, and opium. The compounds found in plants are of many kinds, but most are in four major biochemical classes, the alkaloids, glycosides, polyphenols, and terpenes.

Medicinal plants are widely used to treat disease in non-industrialized societies, not least because they are far cheaper than modern medicines. And innumerable drugs manufactured these days have been originated from various medicinal plants. Global

sales from exported drugs and medicines by country in 2016 totaled US$318.6 billion. Overall, the value of drugs and medicine exports were up by an average 0.4% for all exporting countries since 2012 when drugs and medicines shipments were valued at $317.3 billion. Year over year, there was a -1.5% decline from 2015 to 2016. Among continents, European countries accounted for the highest dollar value worth of drugs and medicine exports during 2016 with shipments amounting to $251.9 billion or 79% of the global total. In second place were North American exporters at 9.8% while 9.4% of worldwide drugs and medicine shipments originated from Asia. (Workman, 2017)

## 1.10 Natural Products as Medicine

Collectively, plants produce a remarkably diverse array of over 100,000 low molecular mass natural products, also known as secondary metabolites. Secondary metabolites are distinct from the components of intermediary (primary) metabolism in that they are generally non-essential for the basic metabolic processes of the plant. Most are derived from the isoprenoid, phenyl propanoid, alkaloid or fatty acid/ polyketide pathways. This rich diversity results in part from an evolutionary process driven by selection for acquisition of improved defence against microbial attack or insect/ animal predation. (Pichersky, 2000)

Natural compounds can be lead compounds, allowing the design and rational planning of new drugs, biomimetic synthesis development and the discovery of new therapeutic properties not yet attributed to known compounds (Hamburger and Hostettmann.,1991).

In addition, compounds such as muscarine, physostigmine, cannabinoids, yohimbine, forskolin, colchicine and phorbol esters, all obtained from plants, are important tools used in pharmacological, physiological and biochemical studies.

(Williamson et al.,1996).

## 1.11 Benefits of Natural Products

The use of natural products with therapeutic properties is as ancient as human civilisation and, for a long time, mineral, plant and animal products were the main sources of drugs (De Pasquale, 1984). The Industrial Revolution and the development of organic chemistry resulted in a preference for synthetic products for pharmacological treatment. The reasons for this were that pure compounds were easily obtained, structural modifications to produce potentially more active and safer drugs could be easily performed and the economic power of the pharmaceutical companies was increasing. Furthermore, throughout the development of human culture, the use of natural products has had magical-religious significance and different points of view regarding the concepts of health and disease existed within each culture. Obviously, this approach was against the new modus vivendi of the industrialised western societies, in which drugs from natural resources were considered either an option for poorly educated or low income people or simply as religious superstition of no pharmacological value. However, even if we only consider the impact of the discovery of the penicillin, obtained from micro-organisms, on the development of anti infection therapy, the importance of natural products is clearly enormous. About 25% of the drugs prescribed worldwide come from plants, 121 such active compounds being in current use. Of the 252 drugs considered as basic and essential by the World Health Organisation (WHO), 11% are exclusively of plant origin and a significant number are synthetic drugs obtained from natural precursors. Examples of important drugs obtained from plants are digoxin from Digitalis spp., quinine and quinidine from Cinchona spp., vincristine and vinblastine from Catharanthus roseus, atropine from Atropa belladona and morphine and codeine from Papaver somniferum. It is estimated that 60% of anti-tumour and anti-infectious drugs already on the market or under clinical trial are of natural origin (Yue-Zhong Shu, 1998). The vast majority of these cannot yet be synthesised economically and are still obtained from wild or cultivated plants.

## 1.12 Plants having Psychotropic Properties

- ✓ Atropa belladonna (belladonna), Solanaceae, hallucinogen
- ✓ Cannabis sativa (marijuana), Cannabaceae, hallucinogen
- ✓ Datura spp. (jimsonweed), Solanaceae, hallucinogen
- ✓ Erythroxylon coca (coca), Erythroxylaceae, stimulant
- ✓ Lophophora williamsii (peyote), Cactaceae, hallucinogen
- ✓ Mandragora officinarum (mandrake), Solanaceae, hallucinogen
- ✓ Nicotiana spp. (tobacco), Solanaceae, stimulant/depressant
- ✓ Papaver somniferum (Opium poppy), Papaveraceae, depressant
- ✓ Piper methysticum (kava), Piperaceae, depressant
- ✓ Banisteriopsis sp. (ayahuasca), Malphiginaceae, hallucinogen

(unlv.edu,2017)

## 1.13 Traditional Medicinal Plant Used in Bangladesh

The rural population of Bangladesh has traditionally depended on folk medicinal healers for treatment of their ailments. These healers use medicinal plants as their primary source of medicinal formulations. Rural patients are more dependent on traditional or folk medicinal healers for treatment of urinary tract infections (UTIs) and sexually transmitted diseases (STDs) for a number of reasons including lack of access to modern medical facilities, clinging to traditional approaches, and finally hesitancy to relate this form of illnesses in front of unknown doctors. Since the traditional healer usually resides in the same village or in an adjoining area, the patient is more comfortable in seeking them for treatment. An ethnomedicinal survey was conducted among the traditional healers of various ethnic groups and in several regions of the country to obtain information on medicinal plants used to treat UTIs and STDs. Interviews were conducted in the local dialect or language about plant parts used, ailments treated, formulations, and dosages.

- ✓ Thirty-one species were reported by traditional healers as being used for UTIs, including leucorrhea, frequent or infrequent urination, cloudy urination and burning sensations during urination.

- ✓ Ten species were reported to be used against STDs like syphilis and gonorrhea. (Hossain, 2010)

Folk medicinal practitioners (Kavirajes) of Bangladesh are consulted for treatment of various ailments by a substantial segment of the rural and urban population of the country. The major element that distinguishes the folk medicinal practitioners from other forms of medical practices is their use of simple formulations of medicinal plants for treatment. The plant(s) used by the Kavirajes for treatment of any specific ailment vary considerably in the various parts of the country, and such differences exist even among Kavirajes of adjoining villages.

An ethnomedicinal survey was conducted among the Kavirajes of two villages, namely Babla and Terbaria, which lies in Tangail district in the central portion of the country. Each village had one practicing Kaviraj. Leaves constituted the major plant part used, being used 48.7% of the time. From the number of plants used, it appeared that gastrointestinal tract disorders formed the major complaint of the patients with 5 plants used for treatment of various complaints like constipation, diarrhea, indigestion, and loss of appetite. Four plants each were used for treatment of pain, and skin disorders (scabies, eczema), and as blood purifier. Four plants were used for treatment of diseases in cattle.

Among other ailments treated by the Kavirajes were tuberculosis, sexual disorders, urinary problems, infections, fever, hepatic disorders, kidney problems, pneumonia, stomach stones, diabetes, swellings, debility, helminthiasis, hypertension, vitamin C deficiency, tumor, and poisoning. One plant was used to maintain the body in good health and so served as a preventive measure instead of a curative effect. Since a number of allopathic medicines have been derived from medicinal plants, the plants reported in the survey can, following scientific inquiry, form novel sources of newer drugs. (Mollik et al., 2009)

## 1.14 Necessity of Herbal Drug Research in Bangladesh

Most of the people of our country have no or little access to allopathic medicine due to their uncompromisable low income in respect of high cost of allopathic medicine. A survey conducted in 1990 in different villages of Bangladesh shows that on average of 14% if people suffering illness approach qualified allopathic doctors, 29% contact unqualified village doctors, 10% contact mollahs, 29% contact quack and 19% contact homeopaths.

The survey indicates an extensive use of medicinal plants, most of which are served in a crude and substandard form, by our people. The use of such crude and substandard herbal drug is dangerous and may threaten public health. Thus the analysis of plants for exploring the bounty of chemical entities and their biological screening is the current need for standardization of herbal medication. (Ghani, 1998)

Since Bangladesh is a country of low economic growth, a proper health care system can be established by supplying low cost medicines to its population. This may be only possible by utilizing our natural resources of medicinal plants and their constituents. So, scientific exploration and standardization of these potential crude drugs is an urgent need to revolutionize our drug sector. Besides, Bangladesh imports a large quantity of pharmaceutical raw materials including medicinal plants and semi-processed plant products to produce drugs and medicines. During the last five years Bangladesh has spent more than 1500 core Taka for importing chemicals, raw materials and semi-processed drugs of plant origin from neighbouring and other countries and this trend is growing upwards day by day. This huge foreign exchange can be saved if the indigenous medicinal plants or its semi processed products are utilized by the manufacturer to satisfy their need. (Ghani, 1998)

## 1.15 Plant Profile

### 1.15.1 Botanical Name

*Syzygium samarangense* (Blume) Merr. & L. M. Perry

### 1.15.2 Synonyms

- ✓ *Eugenia javanica*
- ✓ *Eugenia samarangensis*
- ✓ *Jambosa javanica*
- ✓ *Jambosa samarangensis*
- ✓ *Myrtus javanica*
- ✓ *Myrtus samrangensis*

(Theplantlist.org, 2017)

### 1.15.3 Taxonomic Hierarchy of *Syzygium samarangense*

**Domain:** Eukaryota

**Kingdom:** Planate

**Division:** Tracheophyta

**Class:** Magnoliopsida

**Order:** Myrtales

**Family:** Myrtaceae

**Genus:** *Syzygium*

**Species:** *Syzygium samarangense*

(Itis.gov, 2017)

### 1.15.4 Vernacular Names

| | |
|---|---|
| **Bangla** | Jamrul |
| **English** | Wax apple, Love apple, Java apple, Mountain apple, Cloud apple, Water apple |
| **Indonesian** | Jambu air |
| **Jamaican** | Jamaican apple, Otaheti apple |
| **Malay** | Water guava |
| **Malayalam** | Chambekka |
| **Philippines** | Makopa |
| **Sri Lankan** | Jumbu |
| **Taiwan** | Belfruit |
| **Thai** | Chomphu |
| **Vietnamese** | Man |

(Peter et al., 2011)

## 1.16 Plant Morphology

- ✓ **Stem**

The tree, 16 to 50 ft. (5-15 m) tall, has a short trunk 10 to 12 inches (25-30 cm) thick, and open, wide spreading crown, and pinkish-gray, flaking bark.

**Figure 1.5: Stem of *Syzygium samarangense***

✓ **Leaves**

The opposite leaves are nearly sessile, elliptic-oblong, rounded or slightly cordate at the base; yellowish to dark bluish-green; 4 to 10 inches (10-25 cm) long and 2 to 4 3/4 in (5-12 cm) wide; very aromatic when crushed.

**Figure 1.6: Leaves of *Syzygium samarangense***

✓ **Flowers**

Flowers, borne in drooping panicles of 3 to 30 at the branch tips or in smaller clusters in the axils of fallen leaves, are fragrant, yellowish-white, 3/4 to 1 1/2 in (2-4 cm) broad, 4-petalled, with numerous stamens 3/5 to 1 in (1.5-2.5 cm) long.

**Figure 1.7: Flowers of *Syzygium samarangense***

✓ **Fruits**

The waxy fruit, usually light-red, sometimes greenish-white or cream-colored, is pear- shaped, narrow at the base, very broad, flattened, indented and adorned with the 4 fleshy calyx lobes at the apex; 1 1/3 to 2 in (3.4-5 cm) long, 1 3/4 to 2 1/8 in (4.5-5.4 cm) wide. The skin is very thin, the flesh white, spongy, dry to juicy, sub-acid and very bland in flavor.

**Figure 1.8: Fruits of *Syzygium samarangense***

✓ **Seeds**

There may be 1 or 2 somewhat rounded seeds 3/16 to 5/16 inches (0.5-0.8 cm) wide, or none.

**Figure 1.9: Seeds of *Syzygium samarangense***

### 1.17 Biology

Shoot growth proceeds in flushes which are more or less synchronous, depending on the climate. The juvenile period lasts for 3-7 years. Bearing of clonal trees starts after 3-5 years.

There are definite flowering seasons, often two, sometimes three in a year, but the timing varies from year to year. *Syzygium samarangense* commonly flowers early or late in the dry season; the flowers appear to be self-compatible and the fruit ripens 30-40 days after anthesis. (Orwa et al., 2009)

## 1.18 Ecology

The trees are at home in fairly moist tropical lowlands up to 1200 m elevation. *Syzygium samarangense* grows best in areas with a fairly long dry season. This does not mean that this species is drought resistant. The species require a sufficient water supply and are often planted along streams or ponds. (Orwa et al., 2009)

## 1.19 Traditional Claims of *Syzygium samarangense* Plant Parts

- **Leaves:** It is used as astringent, to treat fever and halt diarrhea. Powdered leaves are used for cracked tongues. Juice of leaves is used in baths and lotion. It is also used in diabetes, cough and headaches.
- **Fruits:** It is used in diabetes, stomatitis aphthosa, diuretic, emmenagogue, abortifacient and febrifuge. Decoction of fruits is used in fever.
- **Root-bark:** The root bark decoction is used in dysentery and amenorrhea and also used as abortifacient.
- **Root:** It is used as diuretic and is given to alleviate edema. Malayans use powdered dried root preparations for itching.
- **Bark:** Juice of bark is used to treat wounds and the bark is used as astringent in mouthwash preparations for the treatment of thrush.
- **Stem:** Decoction of stem is used to treat diarrhea

(Peter et al., 2011)

## 1.20 Aim and Objectives

The purpose of this study was to evaluate pharmacological effect of Methanolic extract of leaves of *Syzygium samarangense* plant on the Central Nervous System. The aim was to-

- ✓ Assess general locomotor levels and anxiety in *Swiss albino* mice model by Open Field Test
- ✓ Analyse neophilia, anxiety, and stress responses in *Swiss albino* mice model by Hole Board Experiment

Traditionally, this plant has been used to treat a variety of diseases leading to the fact that it must have some potential medicinal properties. Thus, the principle objective of this study was to explore the possibilities of deriving medicinal agents from this plant for the treatment of various diseases.

# Chapter 2

# Literature Review

## 2.1 Anti-hyperglycemic activities

A scientific study was done to evaluate anti-hyperglycemic potential of methanolic extract of the leaves of three plants from Bangladesh in which "*Syzygium samarangense*" was included which's fruits are edible and the leaves of this plant are used for treatment of cold, itches, and waist pain. The extracts at different doses were administered one hour prior to glucose administration and blood glucose level was measured after two hours of glucose administration using glucose oxidase method. All the three plants showed significant oral hypoglycemic activity and the fall in serum glucose levels were dose dependant for every individual plant. Among the three plants, the methanolic extract of leaves of " *S. samarangense*" was proved to be the most potent in demonstrating anti- hyperglycemic effects. (Shahreen et al., 2012)

An investigation was done by the ethanolic extracts of " *Syzygium aqueum*" for its anti- hyperglycemic activity. This study revealed its effectiveness in inhibiting the carbohydrate hydrolysing enzymes at significant level than the commercial drug acarbose. The findings provide a strong rationale to establish " *S. aqueum*" capability as an anti- hyperglycemic agent. ( Manaharan et al, 2012)

## 2.2 Analgesic, Anti-inflammatory and CNS activities

This study was aimed to evaluate the analgesic, anti--inflammatory and CNS activities of the methanolic extract of " *Syzygium samarangense*" leave in mice. The analgesic activity was examined by acetic acid induced writhing and formalin tets, the anti--inflammatory activity was done by using carrageenan induced hind paw edema model, and the CNS depressant activity was evaluated by observing the reduction of locomotor and exploratory activities in the open field and hole cross tests. The results of the study suggested that the methanolic extract of " *S. samarangense*" leave has remarkable analgesic, moderate anti--inflammatory and significant CNS effects. ( Mollika et al., 2014)

A pharmacological study was performed to observe anti--inflammatory activity Aurentiacin chalcone isolated from *Syzygium samarangense*, in an inflammatory animal model. Intraperitoneal injection of Aurentiacin suppressed the release of pro-

inflammatory cytokines. The result suggested that Aurentiacin showed anti--inflammatory activity related to the inhibition of NF-κB activation. (Kim et al., 2012)

## 2.3 Anti-microbial activities

An experiment was done to evaluate the anti-microbial properties of two " *Syzygium*" species, against certain bacterial and fungal strains using disc diffusion method. All the test extracts exhibites significant anti-microbial activity on certain pathogens. Among the test extracts " *S. samarangense*" was found to be effective drug on both Gram positive and Gram negative bacteria. ( Ratnam, Raju, 2008)

## 2.4 Anti-motility activities

This study was under taken to rationalize the use of the plant " *Syzygium samarangense*" in hyper motility states of the gut. The hexane extract of this plant was found to dose- dependently relax the spontaneously contracting isolated rabbit jejunum. The findings of this experiment indicate that the presence of compounds withspasmolytic and calcium antagonist activity may be responsible for the medicinal use of the plant in diarrhoea. ( Ghayur et al., 2006)

## 2.5 Anti-bacterial and Anti- fungal properties

In an experiment six bioactive compounds were evaluated from *Hibiscus sabdariffa* and *Syzygium samarangense* juice extracts. Both juices had high amounts of saponins, with *Syzygium samarangense* having higher content. Microbial counts in the juices were in the range of 104 cfu ml-1 of ethanolic extract. The juice extracts showed significant anti-microbial activities against Escherichia coli, *Salmonella typhi* and Candida albicans, implying that the juices possess both anti-bacterial and anti-fungal properties. ( Edema, Alaga, 2012)

## 2.6 Anti-cholinesterase activities

A study shows that a Dihydrochalcone flavonoid isolated from *Syzygium samarangense* shows potency in anti--cholinesterase activity. The chemical showed 98.5% inhibitory activity against acetylcholinesterase and 68.0% inhibitory activity against butyrylcholinesterase. (Amor, Villaseñor and Nawaz, 2005)

## 2.7 Cytotoxic, Anti-oxidant and Anti- microbial activities

A study was done to evaluate the cytotoxic, anti-oxidant and anti-microbial activity of aqueous fraction of *Syzygium samarangense* leaf extract. The powder of *Syzygium samarangense* leaf were extracted with methanol, the aqueous fraction was used to evaluate cytotoxic, anti-oxidant and anti-microbial activities, the cytotoxic activity was measured by brine shrimp lethality bioassay. The results of study indicated the presence of cytotoxic and poor anti-oxidant properties of aqueous extract. (Tabassum, 2016)

## 2.8 Activity and influencing factors analysis of Catalase

An experiment was done to study the catalase (CAT) activity and influencing factors of *Syzygium samarangense* fruit to provide theoretical references for its postharvest freshness by using spectrophotometry method. Findings of the study indicated that the CAT activity of *Syzygium samarangense* fruit was significantly affected by temperature, pH, organic solvent and metal ions. The storage life of the fruit could be prolonged at low temperature with rational use of organic solvent. (Zhang et al, 2014)

## 2.9 Protective effects in induced inflammation

A study was done to analyze the protective effects of Vescalagun from pink waxapple fruit against Methylglyoxal induced inflammation and carbohydrate metabolic disorder in rats. The excessive formation of Methylglyoxal due to unbalanced glucose metabolism may interact with various biomolecules. Results showed that VES

reduced the value of oral glucose tolerance test, cardiovascular risk index, AGEs, and tumor necrosis factor-α contents while increasing C-peptide and d-lactate contents significantly in rats orally administered MG and VES together. On the basis of the experiment data, a mechanism was shown by which prevention of β-cell damage, is proposed to explain the bioactivities of VES in anti- glycation and in the alleviation of MG-induced carbohydrate metabolic disorder in rats. ( Chang, Shen, Wu, 2013)

## 2.10 Anti-oxidant and Anti-inflammatory activities

A study was done with many species of Myrtaceae are cultivated in home gardens for their edible fruit, and have been used in traditional medicine to treat several inflammatory conditions. Fruit phenolics are important dietary anti-oxidant and anti--inflammatory constituents. It was investigated that the anti-radical activity, total phenolic content (TPC), and total anthocyanin content (TAC) of 14 underutilized Myrtaceae fruits, in which *S. samarangense* inclides, and HPLC-PDA method was developed to do this test. (Reynertson et al, 2008)

## 2.11 Anti-aging and Anti-inflammation

A study was done to identify novel cosmetic ingredients from subtropical plants by screening 21 parts of 12 plant species collected from the Agricultural Research Institute in which *S. Samarangense* was included. The leaves and branches of *S. samarangense* also had the highest total phenolic content. Results revealed that *S. samarangense* leaves potently inhibited the LPS-stimulated NO production concentration-dependently with an IC50 of 152.3 μg/mL. These results suggest that these subtropical plants possess several biological activities that may be potent inhibitors of the skin aging and inflammatory processes. Further investigations will focus on cell-based in vitro assays and chemically identifying the major active components mediating the anti--aging and anti--inflammation. (Kim et al., 2016)

## 2.12 Hepato protective activities

In a study, fruits of *Syzygium samarangense* and two other plants were used on alcohol-induced liver injury in mice. Chronic treatment with alcohol showed elevation of various parameters in the mice that led to damage in the hepatocytes. *Syzygium samarangense* fruit normalized various biochemical parameters. This indicated that *S. samarangense* might possess hepatoprotective effect that could cure liver injuries due to alcohol. (Zhang et al., 2016)

## 2.13 Immunomodulatory Effect

A pharmacological study was performed with the sixteen flavonoids which was isolated from acetone extract leaves of *Syzygium samarangense* for immunomodulatory effects. Human Peripheral Blood Mononuclear Cells (PBMC) were used as test models and cell proliferation was assessed by $^{3}$H-thymidine uptake. Four of the flavonoids exhibited suppression of PBMC cells through cytotoxic effect in a dose-dependent manner. The inhibitory mechanisms might have involved the impairment of IL-2 and IFN-γ production. (Kuo, Yang and Lin, 2004)

## 2.14 Chemical Constiuents

- ✓ Two flavonol glycosides have been isolated and characterised from leaves of *Syzygium samarangense*. One is the rare mearnsitrin (1) while the second, 2′-C-methyl-5′-O-galloylmyricetin-3-O-a-l-rhamnopyranoside (2), is new. Detailed spectral data were analyzed further. (Nair et al, 1999)
- ✓ Investigators have found several chemical constituents upon performing various assays of different Syzygium samarangense plant parts.
- ✓ Leaves contain Lupeol (triterpenoid); Betulin (triterpenoid); Epi-betulinicacid (triterpenoid); 2, 4-dihydroxy-6-methoxy-3-methylchalcone; 2-hydroxy-4, 6-dimethoxy-3-methylchalcone; 2, 4-dihydroxy-6-methoxy-3, 5-dimethylchalcone; 2, 4-dihydroxy-6-methoxy-3-methyldihydrochalcone; 7-hydroxy-5-methoxy-6, 8-dimethylflavanone; 2-hydroxy-4, 6-dimethoxy-3-methyldihydrochalcone; 2,4-dihydroxy-6-methoxy-3,

5-dimethyldihydrochalcone; Sitosterol; Alpha-carotene and Beta-carotene.

- ✓ Leaf oil is largely composed of Monoterpenes (30% Sesquiterpenes, 9% Caryophyllene).
- ✓ Aerial parts contain Ursolic acid, Jacoumaric acid Arjunolic acid, Mearnsitrin, 2-C-Methyl-5-O-Galloylmyricetin-3-O-α-l-Rhamnopyranoside, Desmethoxymatteucinol, 4, 6-Dihydroxy-2-Methoxy-3, 5-Dimethylchalcone, Methyl 3-epi-betulinate, Oleanolic acid, Desmethoxymatteucinol, 5-O-Methyl-4-desmethoxymatteucinol, Oleanic acid.
- ✓ Quercetin glycosides are also present in this plant which include〕 Reynoutrin, Hyperin, Myricitrin, Quercitrin, Quercetin and Guaijaverin.
- ✓ It also contains Flavanone - (S)-pinocembrin, and Phenolic acids- Gallic acid and〕 Ellagic acid. (Peter et al., 2011)

# Chapter 3

# Research Methodology

## 3.1 Collection and Preparation of *Syzygium samarangense* extract

### 3.1.1 Collection of the *Syzygium samarangense* leaves

The leaves of *Syzygium samarangense* were collected from the Botanical Garden located at Mirpur - 1, Dhaka, Bangladesh.

### 3.1.2 Preparation of *Syzygium samarangense* extract

#### 3.1.2.1 Drying of the collected leaves of *Syzygium samarangense*

The plant materials were washed with water properly to remove the adhering dirt. All unwanted plant parts were discarded. The leaves were then spread on large polythene bags and placed for shadow drying for about 1 week. The leaves were turned upside down after every 1 day for proper drying of both sides of the leaves.

#### 3.1.2.2 Grinding and Storage of the Dried Sample

The dried leaves were ground to acoarse powder with the help of a high capacity mechanical grinder (Grinding Mill). This causes breakdown of plant parts into smaller pieces, thus exposing the internal cellular structure of the plant parts. This facilitates the penetration of solvents into the cells of the plant parts to extract the chemical constituents. Before grinding of the plant sample, the grinder was thoroughly cleaned to make sure that no contamination occurred by the remnant of the previously triturated materials.

After grinding, the powdered sample was kept in clean closed glass containers till extraction. The net weight of dry powder was 720gm.

### 3.1.2.3 Maceration of the dried powdered sample

From the total amount of powder, 240gm powder was soaked in Chloroform for the further processes of extraction.

The powder was soaked in 1 Liter of Chloroform for 7 days. The preparation was kept in an amber colored bottle. The bottle was regularly shaken to facilitate the complete exhaustion of the chemical constituents into the solvent.

### 3.1.2.4 Filtration and Retrieval of the extract

After the completion of maceration process, the solution was filtered in three consecutive steps. At first, the filtration was done by using sterile cotton cloth, then by sterile cotton filter and lastly by No. 1 Whatman filter papers. Later on, the solvent was evaporated completely by Heidolph Rotary Evaporator. The yield was collected in a beaker and preserved in the refrigerator with the mouth sealed with plastic.

**Figure 3.1 : Hiedolph rotary evaporator**

## 3.2 Standard Drug

Diazepam was used for this study purpose which was supplied from Square Pharmaceuticals Ltd.

## 3.3 Research Animal

For the research purpose, 30 *Swiss albino* mice were collected from ICDDR, B. The average weight of the mice were 20-25 gm. Optimum environmental conditions were maintained to rear the mice. The conditions were 12-hours light/dark cycle, 55-65% relative humidity, and 24.0 ± 2.0°C temperature. Also, the mice were supplied with ample food-pelletssupplied by Animal Research Facility, ICDDR, B and filtered water.

**Figure 3.2 : Swiss albino mice**

### 3.4 Ethical Approval

Institutional Animal Ethical Committee approved the guidelines which were followed forcarrying out the study.

### 3.5 Pharmacological Study of Plant Extract

CNS Depressant activity was studied in mice model to determine the medicinal activity of *S. samarangense*leaf extract.

The CNS depressant action of *Syzygium samarangense* leaves extract was observed by comparing with the standard Diazepam in the experimental rodents. CNS depressant activity was assessed by using two techniques. They were:

- Open Field Test and
- Hole board Experiment

## 3.5.1 Method design of CNS Experiments

For both the experiments, 24 mice were selected randomly and then divided into 4 groups. Each group consisted of 6 mice and they were termed Group 1 to Group 4.

Group 1 – Control (Distilled Water)

Group 2 – Standard (Diazepam)

Group 3 – Chloroform 100 mg/kg

Group 4 – Chloroform 200 mg/kg

Before the experiment, the mice were weighed and marked accordingly. The dose of the sample and the standard drug were administered per body weight. A specific treatment was set for each group.

## 3.5.2. Preparation of standard and sample solution

For the preparation of Chloroform extract solution at doses 100 mg/kg and 200 mg/kg per body weight of mice, the extract was weighed based on the weight of the experimented mice and sonicated in a unidirectional way by the addition of 3 ml of distilled water. A small amount of CMC was slowly added as a suspending agent for proper mixing. To stabilize the suspension, it was stirred adequately.

For the preparation of positive control group, Diazepam (1mg/kg) was taken and a 3 ml suspension was prepared.

**Table 3.1: Test samples used in the estimation of CNS activity of *Syzygium samarangense* plant**

| **Group** | **Treatment** | **Dose** | **Route of Administration** |
|---|---|---|---|
| Group 1 (Control) | Distilled Water | 10 ml/kg | Orally |
| Group 2 (Standard) | Diazepam | 1 mg/kg | Orally |
| Group 3 (Extract) | SSC | 100 mg/kg | Orally |
| Group 4 (Extract) | SSC | 200 mg/kg | Orally |

### 3.5.3 Open Field Test

The Open Field test was performed according to Gupta using a cubic box measuring 1m x 1m x 1m. (Gupta et al, 1971)

The top of the cube was uncovered. The rodent was placed in the middle of the bottom surface of the box and its movements were recorded over the course of minutes to hours as it moved around and explored the arena.

The flow chart of theprocedure for assessment of CNS depressant effect of the Chloroform extract of leaves of *Syzygium samarangense* by Open Field test is shown below:

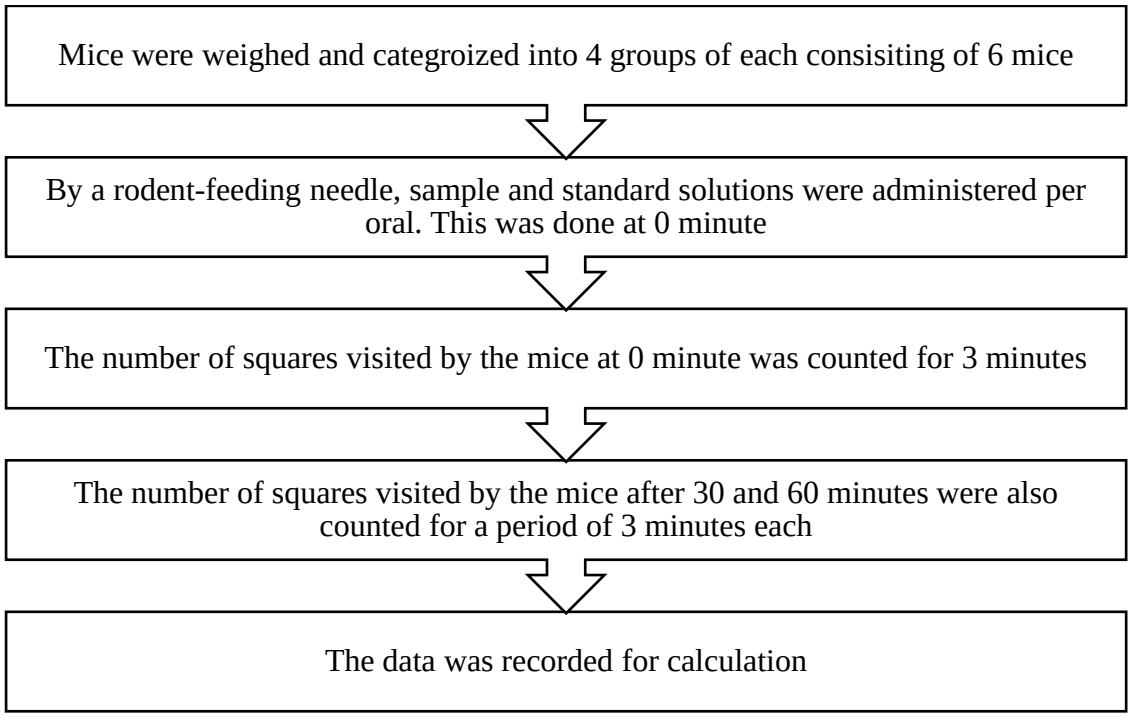


**Fig 3.3: Flow chart showing the process of Open Field test for the determination of CNS activity on mice**

### 3.5.4. Hole board Experiment

The Hole board experiment was done following Takagi's method on a quadripedal holed board with an enclosure of 40 cm x 40 cm x 35 cm and the test chamber holes having the diameter of 3 cm each. (Takagi et al., 1971)

The rodent was placed in the center of the board and its movements were recorded over the course of minutes to hours as it moved around and explored the arena.

The flow chart of the procedure for assessment of CNS depressant effect of the Chloroformic extract of leaves of *Syzygium samarangense*by Hole board experiment is shown below:

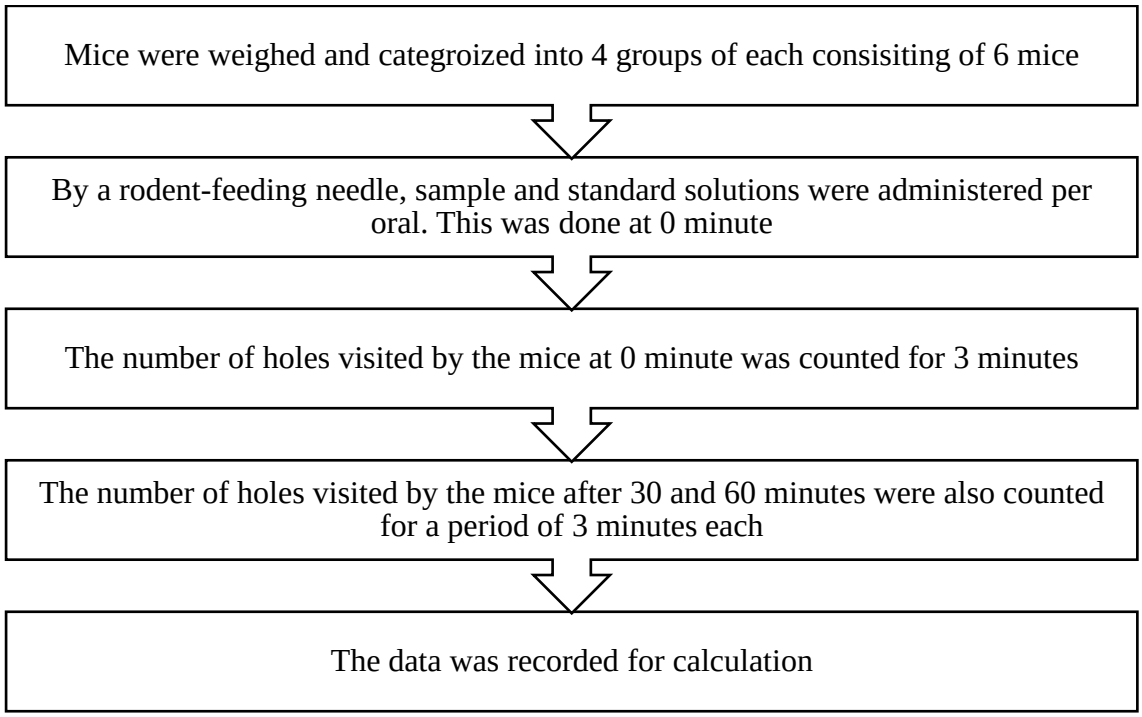


**Fig 3.4: Flow chart showing the process of Hole board experiment for the determination of CNS activity on mice**

# Chapter 4

# Result

# &

# Discussion

## 4.1 Results

### 4.1.1 Open-Field Test

At doses 100 mg/kg and 200 mg/kg, experimental leaf extracts were administered to mice. As a result, the movements of the mice got reduced significantly ($p < 0.05/ 0.01/ 0.001$) in a dose-dependent manner. From Table 6.1, significant levels of decrease in movement of mice after 30 and 60 minutes of extract solution administration can be observed. The standard drug, Diazepam, also exhibited a significant decrease in locomotion in the mice model after 30 and 60 minutes of administration.

**Table 4.1: Data of Open Field Test to determine CNS Activity of Chloroform extract of *Syzygium samarangense*leaves in *Swiss albino* mice model**

| Group | Treatment | Dose, Route | Number of Movements | | |
|---|---|---|---|---|---|
| | | | 0 min | 30 min | 60 min |
| **Group – 1 (Control)** | Distilled Water | 10 ml/kg, p.o | 137.5 ± 44.64 | 126 ± 32.78 | 159.67 ± 15.47 |
| **Group –2 (Standard)** | Diazepam | 1 mg/kg, p.o | 137.5 ± 44.64 | 36.17 ± 26.09*** | 68.83 ± 39.40*** |
| **Group – 3 (Extract)** | SSC | 100 mg/kg | 37.17 ± 16.36** | 69.17 ± 21.23** | 34.33 ± 15.65*** |
| **Group – 4 (Extract)** | SSC | 200 mg/kg | 48 ± 45.06** | 60.67 ± 37.97** | 37.5 ± 26.04*** |

SSC refers to *Syzygium samarangense* in Chloroform extract. Values were expressed as Mean ± SD (n=6); One-Way Analysis of Variance (ANOVA) trailed by Dunnett's Test. * P<0.05, ** P<0.01 and *** P<0.001 were considered significant.

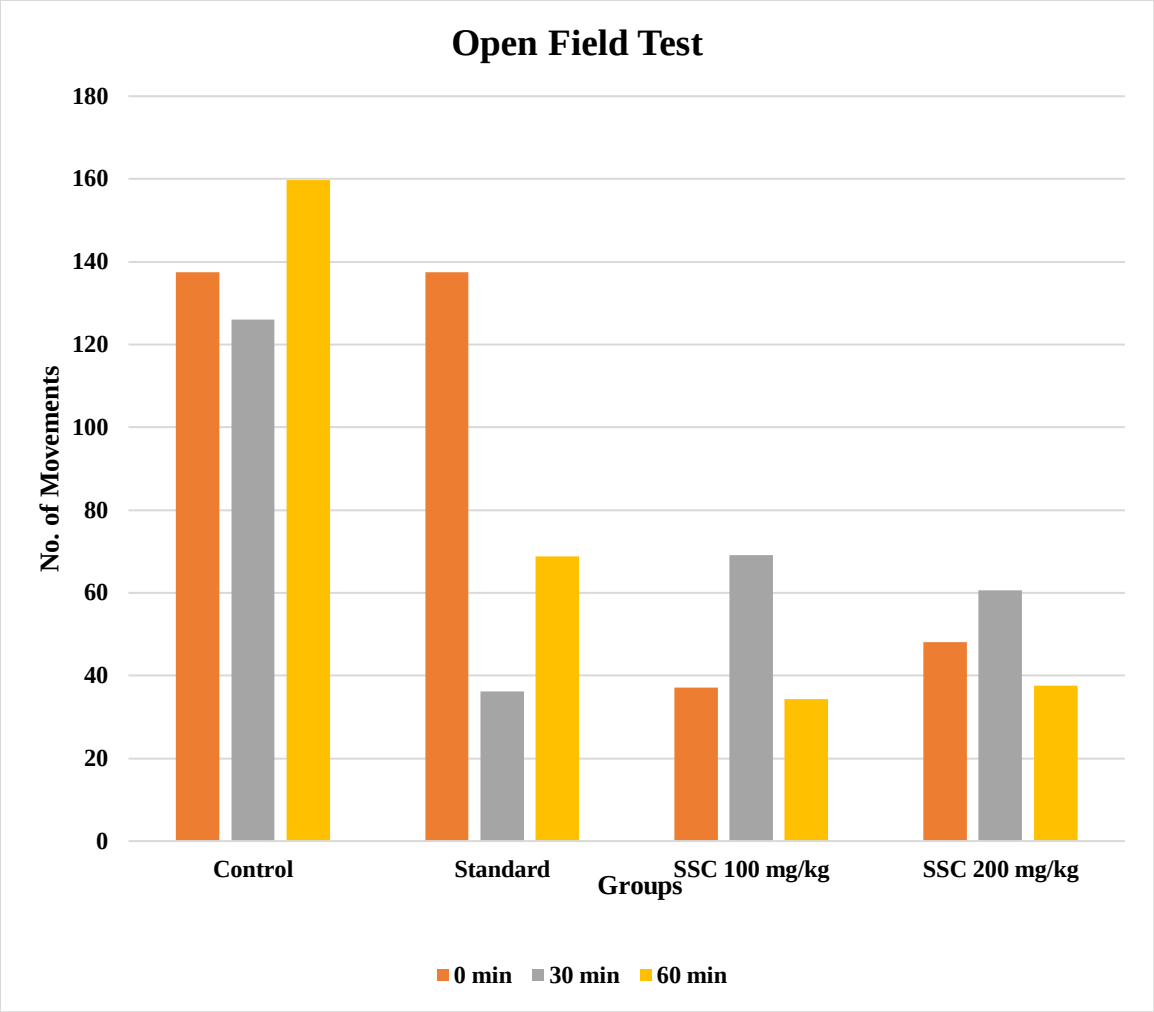


**Figure 4.1: Graph for Open Field Test**

### 4.1.2 Hole board Experiment

At doses 100 mg/kg and 200 mg/kg, experimental leaf extracts were administered to mice. As a result, the movements of the mice got reduced significantly ($p < 0.05/ 0.01/ 0.001$) in a dose-dependent manner. From Table 6.1.2, significant levels of decrease in locomotion of mice after 30 and 60 minutes of extract solution administration can be observed. The standard drug, Diazepam, also exhibited significant decrease in locomotion in the mice model from after 30 and 60 minutes of administration.

**Table 4.2: Data of Hole board Experiment to determine CNS Activity of Chloroform extract of *Syzygium samarangense* leaves in *Swiss albino* mice model**

| Group | Treatment | Dose, Route | Number of Movements | | | |
|---|---|---|---|---|---|---|
| | | | -30 min | 0 min | 30 min | 60 min |
| **Group – 1 (Control)** | Distilled Water | 10 ml/kg, p.o | 20.83 ± 7.03 | 23.67 ± 5.16 | 18.33 ± 2.80 | 19.17 ± 2.93 |
| **Group – 2 (Standard)** | Diazepam | 1 mg/kg, p.o | 10.67 ± 3.56 | 8.00 ± 5.54*** | 7.50 ± 1.87*** | 4.00 ± 1.90*** |
| **Group – 3 (Extract)** | SSC | 100 mg/kg, p.o | 16.67 ± 3.83 | 10.67 ± 6.23** | 7.83 ± 4.07*** | 6.17 ± 2.86*** |
| **Group- 4 (Extract)** | SSC | 200 mg/kg, p.o | 36.83 ± 12.35* | 16.33 ± 6.02 | 6.17 ± 2.32*** | 2.83 ± 1.94*** |

SSC refers to *Syzygium samarangense* in Chloroform. Values were expressed as Mean ± SD (n=6); One-Way Analysis of Variance (ANOVA) trailed by Dunnett's Test. * P<0.05, ** P<0.01 and *** P<0.001 were considered significant.

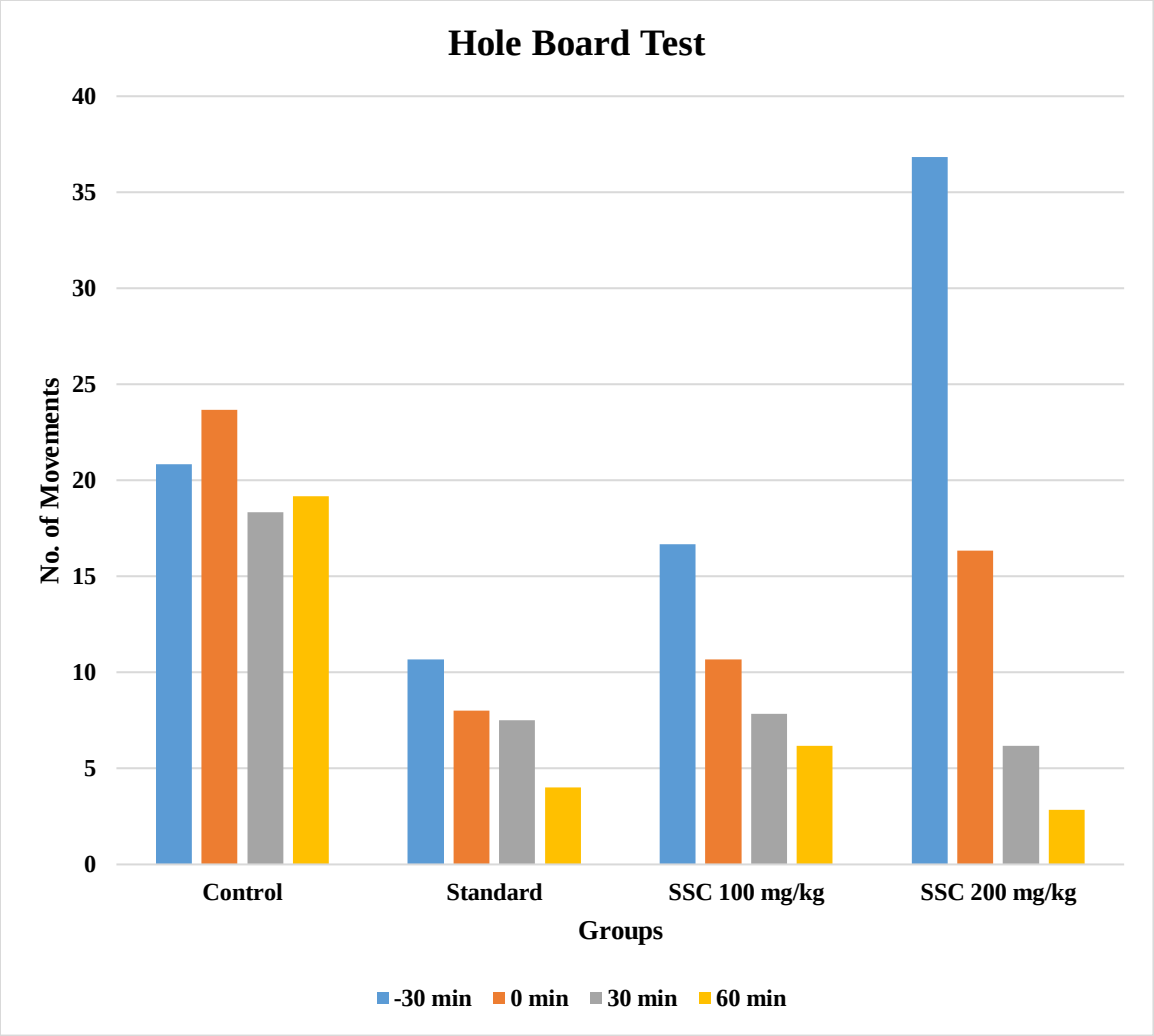


**Figure 4.2: Graph for Hole Board Test**

## 4.2 Discussion

The studies were performed to evaluate the CNS activity of Methanolic extract of *Syzygium samarangense* leaves. From Table 4.1 and 4.2, we can observe that the extract showed asignificant decrease in locomotion in mice model after 30 and 60 minutes of observation.

Locomotor activity is considered as a potential parameter for assessing CNS stimulatory or depressant effect of a plant extract. Increase in locomotor activity indicates CNS stimulatory effect and decrease in the same is indicative of CNS depressant activity. Thus, it can be said that Methanolic leaf extracts of *Syzygium samarangense* exhibit CNS depressant activity.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. Different anxiolytic, muscle relaxant, sedative-hypnotic drugs exert their action through $GABA_A$, therefore it is possible that extracts of *Syzygium samarangense* may act by potentiating GABA-ergic inhibition in the CNS via membrane hyperpolarization which leads to a decrease in the firing rate of critical neurons in the brain or may be due to direct activation of GABA receptor by the extract. (Kolawole et al., 2007)

Some studies suggest that compounds like flavonoids, saponins and tannins are useful in many CNS disorders. Earlier investigation on phytoconstituents suggests that many flavonoids and neuroactive steroids were found to be ligands for the $GABA_A$ receptors in the central nervous system; which led to the assumption that they can act as benzodiazepine-like molecules. (Verma et al., 2010)

Phytochemical investigations of *Syzygium samarangense* show that the leaves are rich in tannins and flavonoids mostly (Peter et al., 2011) which may be responsible for its CNS depressant activity. Also, a study was conducted stating that the methanolic extract of the bark of *Syzygium samarangense* also possess a very potent CNS depressant action. (Mollika, 2013) So, perhaps, the common constituents between the two plant parts might be exerting the same CNS depression activity.

# Chapter 5

# Conclusion

From the ancient time people used plants as medicines which have serve as natural source of treatment and therapies. Today scientists are using these renewable sources to produce a new generation of therapeutic solution. Many plants have pharmacological properties against various types of diseases but they are well known to common people. Medicinal plants are in dispensable source of medicinal preparation both preventive and curative. Careful and planned investigations of the plant are needed in order to develop new drug that would meet the criteria of modem treatment.

The *Syzygium samarangense*is a plant of natural gift that possesses many therapeutic activities. The research work was aimed to investigate the possible in vivo pharmacological investigations of the chloroform extract of the leaves of this plant in *Swiss albino* mice. Two tests were performed to observe the CNS activity – the open field test and the hole board test. From our result, it came out that the extract exhibits a significant ($p<0.001$) depressant activity at 30 and 60 minutes after dose administration.

In the end, we expect that further comprehensive investigation will be conducted as well as illustration of active components and pre-formulation studies will be initiated for development of the potential dosage form from this crude extract.

# Chapter 6

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