Investigation of *in vivo* antidiabetic, analgesic, and CNS depressant properties of *Lagerstroemia thorelli* leaf extract

By:

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
BRAC University
April 2024

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Investigation of *in vivo* antidiabetic, analgesic, and CNS depressant properties of *Lagerstroemia thorelli* leaf extract" submitted by Raisha Rajib (20146011), of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on April, 2024

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Ethics Statement

This study involved animal trials and the ethical permission had been granted from respective authority.

Abstract

Plants in the Lythraceae family are well-known for having anti-inflammatory, analgesic, and antidiabetic qualities. However, through a comprehensive literature search it was found that the antidiabetic, analgesic, and CNS depressant properties of *Lagerstroemia thorelli (L. thorelli)* have not yet been investigated. This research involved the use of the ethanol leaf extract of *Lagerstroemia thorelli* at doses of 200 mg/kg, 400 mg/kg, and 600 mg/kg in Swiss albino mice. The antidiabetic effect was assessed in alloxan-induced diabetic mice, the analgesic activity was detected using the acetic acid-induced writhing test, and the CNS depressant effect was determined using the hole cross method. The plant extract exhibited a dose-dependent, statistically significant ($P<0.01$) antidiabetic, remarkable analgesic and CNS depressant properties. Thus, the present study suggests that extract of *Lagerstroemia thorelli* could be an effective treatment for diabetes.

Keywords: Medicinal plant, *Lagerstroemia thorelli*, leaf extract, antidiabetic, analgesic, CNS depressant

Dedication

This is dedicated to my parents, my family and my good friends for their love, motivation and support.

Acknowledgement

First and foremost, all the praise and admiration to Almighty Allah for blessing me and giving me the patience, knowledge, dedication, good health, strength and the opportunity to complete this project and to work towards my goal of obtaining my Bachelor's degree in Pharmacy.

A project is never the result of one person's labor. Without any guidance and guidelines, it cannot be completed.

For this, I would like to share my appreciation and offer my sincere gratitude to my supervisor, Dr. Raushanara Akter, Professor at the School of Pharmacy, BRAC University, from the bottom of my heart for her unwavering and continuous support. I am eternally grateful and indebted to her for her guidance, advice, instruction and valuable time. From the very beginning to the end, she has continuously given me her patience as well as supportive advice. Without her guiding hand, I would not be able to complete my project.

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Lastly, I will be forever indebted to my parents for their continuous love, support and encouragement throughout my entire life.

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List of Acronyms

Mg	Milligram
Gm	Gram
Kg	Kilogram
mL	Milliliter
dL	Deciliter
CNS	Central nervous system
BGL	Blood glucose level
SEM	Standard error of mean
L.thorelli	*Lagerstroemia thorelli*
L.Speciosa	*Lagerstroemia Speciosa*
L.indica	*Lagerstroemia indica*

Chapter one: Introduction

1.0 Introduction

1.1 Overview on medicinal plants

The usage of plants as curative agents has continued for over thousands of years. Alongside provision of food, shelter and clothing plants have traditionally been used as medicines. Typically, plants possessing therapeutic properties or exerting pharmacological effects on the human and animal body are referred to as medicinal plants. Around the world, about 70,000 medicinal plants are used for treatment (Rahman et al., 2022). Almost all parts of plants can be used for medicinal purposes. The roots, stem, barks, flowers, leaves, fruits, seeds as well as the whole plants and their extract can have medicinal properties. Initially, these medicinal plants are transformed into crude drugs in the form of powders, tinctures, poultices, teas along with other herbal formulations. Bangladesh is a rich resource for medicinal plants. Currently there are 722 species of medicinal plants in Bangladesh according to Bangladesh Agricultural Research Institute (BARI) (Rahman et al., 2022). These plants are being used to treat various diseases, especially in local communities in villages.

1.2 Discovery and traditional uses of medicinal plants

In the beginning, people looked instinctively for drugs in nature for cures of various ailments (Kelly, 2010). In ancient times, most medicinal plants were discovered through trial and error. Thus, the earliest drugs were discovered. The oldest medicinal plant is called Ephedra which was used as an anti-fatigue drug. On a Sumerian clay slab from Nagpur, the oldest written evidence of medicinal plants usage for preparation of drugs was found, which was written around 5000 years ago. The slab contained information of 250 different medicinal plants

including poppy, mandrake, henbane. Moreover, around 882 herbal remedies of various diseases were mentioned in Egyptian Ebers Papyrus in 1550 BC (Kelly, 2010). To treat ailments and prevent disease, rural and tribal people of Bangladesh have used plants and natural remedies as their first choice of medicine. Rural areas comprise around 75% of the country's population, among which almost 80% of the population relies on ethnomedicine which is plant-based (Ahmed, 2009). The medicinal plants used in such traditional systems include Tejpatra (*Cinnamomum tamala*) for treatment of diabetes mellitus, Sarpagandha (*Rauwolfia serpentina*) for treatment of hypertension and for curing bronchial asthma, Haridra (*Curcuma longa*) can be used (Roy et al., 2001) (Table 1.1). In the Unani medicinal system, plants such as *Ricinus communis, Abrus precatorius, Semiecarpus anacardium L.* etc., are used to make medicine to treat various diseases such as arthritis, tetanus, infections etc. (Arunachalam et al., 2023). However, the commercial cultivation of medicinal plants that began in the early 90's, concentrated around Natore district (Palash et al., 2021). In recent years commercial medicine is being produced from medicinal plants such as Tulsi (*Ocimum tenuiflorum*), Basok (*Justicia adhatoda*) to treat common ailments such as cold, cough etc. (Palash et al., 2021).

Table 1.1: Traditional medicinal plants in Bangladesh (Mohammad Nazmul Hasan et al., 2010)

Scientific name	**Local name**	**Therapeutic uses**	**Pictures**
Cinnamomum tamala	Tejpata	Diabetes, wound healing, antimicrobial	
Rauwolfia serpentina	Sarpagandha	Hypertension, snake bite, pimple	
Ocimum tenuiflorum	Tulsi	Cold, cough, skin disease, Jaundice	
Justicia adhatoda	Basok	Cough, chronic asthma, leprosy, cold	
Curcuma longa	Haridra	Bronchial asthma, diabetes, anti-inflammatory	

1.3 Significance of medicinal plants in drug discovery and development

Medicinal plants have a significant role in drug discovery and development involving phytochemical, botanical, molecular as well as various biological techniques. One of the first examples of this implementation occurred in the early 19th century by isolating morphine from opium (Kinghorn, 2001). Similarly, due to discovery of drugs from various medicinal plants, isolation and characterization of pharmacologically active compounds from these plants accelerated. Moreover, these identified compounds from medicinal plants have shown potential affinity or selective activity towards different molecular targets that are important for various diseases. For example, indirubin, isolated from *Baphicacanthus cusia* selectively inhibits cyclin-dependent kinases (Kinghorn, 2001). Additionally, artemisinin derived from *Artemisia annua* is used to treat type-1 diabetes and cancer, curcumin from *Curcuma longa* works as an antioxidant and anti-inflammatory agent and *Althaea officinalis* extracts have anti-inflammatory properties (Nasim et al., 2022)

1.4 Advantages of natural drugs over synthetic drugs

In the current healthcare environment, uses of drugs which are synthetic as well as drugs which are of natural variant can be seen. Modern medicine system applies the use of synthetic drugs more over traditional medicine. However, there exists advantages of natural drugs made of plants over synthetic drugs. Synthetic drugs are called so because of artificial modification of them from naturally occurring sources. Many antidiabetic, analgesic and CNS depressant drugs are made synthetically. These drugs can exhibit therapeutic properties as well as adverse effects. Compared to natural drugs, synthetic drugs are more potent in their activity. However, with more potency comes the increasing risk of toxicity. For example, toxicity associated with synthetic drugs and its side or adverse effects are the cause of around 8% of hospital admission in the United States of America resulting in 100000 deaths each year (Karimi et al., 2015).

Compared to synthetic drugs, natural drugs show fewer toxic effects. In fact, the entire plant itself is composed of various different complex substances that as a whole may show some effects that cannot be replicated by isolated active compounds. Moreover, natural medicinal plants and drugs made of them are readily available to the people. This is especially significant for underprivileged people as it is difficult for them to obtain conventional medicines such as synthetic drugs (Karimi et al., 2015). For a country like Bangladesh, whose healthcare sector is behind those of developed nations, natural drugs can be a key to bridge those gaps.

1.5 Overview of Diabetes mellitus

As a heterogeneous disease, diabetes is defined by elevated blood glucose or blood sugar levels, which can happen when the pancreases cannot make enough insulin to control blood glucose levels, a condition known as hyperglycemia. Chronic hyperglycemia of diabetes is detrimental to the health of the patients by causing long term microvascular complications. Diabetes can manifest as a variety of symptoms mainly frequent urination (often at night), thirst, hunger, tiredness, numbness in hands or feet, slow healings and more frequent infections (Centers for Disease Control and Prevention, 2023). Diabetes can be classified as either type 1 or type 2 diabetes on the basis of availability of insulin alongside gestational diabetes which can occur during pregnancy. Type 1 diabetes occurs when the pancreas is unable to produce insulin whereas type 2 diabetes occurs due to insufficient insulin production or utilization. Type 1 diabetes mellitus or T1DM is otherwise known as insulin dependent diabetes mellitus (IDDM). The primary mechanism underlying this condition is illustrated in Figure 1, wherein insulin deficiency and hyperglycemia are caused by T-cell-mediated autoimmune destruction of pancreatic β-cells and lymphocytic infiltration. Type 2 diabetes, also referred to as non-insulin dependent diabetes mellitus (NIDDM), can arise in a patient as a result of two distinct insulin-related abnormalities. Firstly, insulin resistance due to destruction of various cellular pathways

causes reduced response of various organs such as liver, muscle or adipose tissue towards insulin. Secondly, the β-cell dysfunction is another key factor behind T2DM (Sameer et al., 2020).

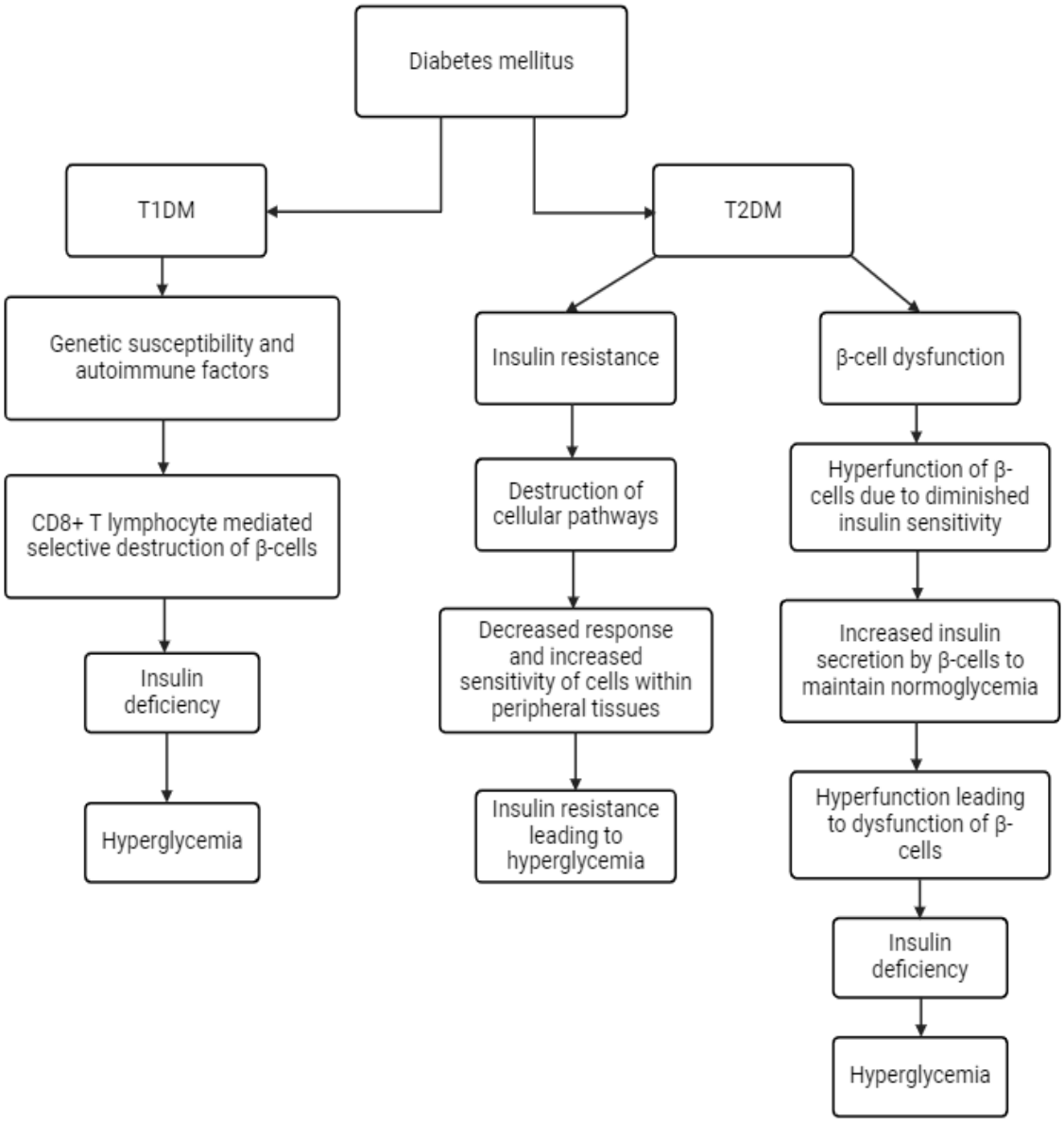

Figure 1.1: Mechanism of diabetes mellitus (Sameer et al., 2020)

1.5.1 Medicinal plants with antidiabetic property in Bangladesh

In Bangladesh, medicinal plants are often used to treat diabetes due to the cost-effectiveness as well as due to availability. The frequency of usage of the medicinal plants significantly increases in the rural areas. *Abroma augusta, Anthocephalus cadamba, Bombax ceiba, Bunium persicum, and Carica papaya* are among the many medicinal plants that are capable of treating diabetes in Bangladesh *(Table 1.2)*. The methanol extract of *Abroma augusta* can act as a protective agent for type 2 diabetes against nephropathy and cardiomyopathy associated with it (Khanra et al., 2015). Flavonoids present in the methanolic extract of *Anthocephalus cadamba* exhibit hypoglycemic activity (Himanshu Gurjar et al., 2010). Moreover, mangiferin found in *Bombax ceiba* can enhance insulin release to treat hyperglycemia (Bhargava & Shah, 2020). Various extracts of *Bunium persicum* including aqueous, hydro-alcoholic, n-hexane and ethyl acetate show increased insulin secretion as well as inhibit the activity of α-amylase significantly (Sagar & Joshi, 2024).

Table 1.2: Medicinal plants with antidiabetic property available in Bangladesh (Rahman et al., 2021)

Name of species	**Name of families**	**Local name**	**Parts used**
Abroma augusta	Sterculiaceae	Ulotkombol	Leaf, bark, root
Anthocephalus cadamba	Rubiaceae	Kadam	Stem, bark
Bombax ceiba	Bombacaceae	Shimul	Bark, root
Bunium persicum	Apiaceae	Kalo jeera	Seed, whole plant

1.6 Overview of analgesics

Analgesics are defined as medications that decrease pain without changing consciousness or sensory awareness, nor preventing the conduction of nerve impulses (Hena & Znad, 2018). The two main categories of analgesic medications are opioids and nonopioids. Here, opioids can influence the central nervous system but nonopioids affect the peripheral nervous system. Morphine, codeine and naloxone are examples of opioid analgesics while NSAIDs (non-steroidal anti-inflammatory drugs), cyclooxygenase inhibitors and paracetamol are examples of nonopioid analgesic drugs (Vardanyan & Hruby, 2006). Application of analgesic has improved cognitive, behavioral, motivational as well as physical wellbeing.

1.6.1 Medicinal plants with analgesic property in Bangladesh

Prior to the development of commercial analgesic drugs, medicinal plants were used to treat symptoms related to pain. There are several thousand medicinal plants available in Bangladesh. Among them, the number of plants with analgesic properties are quite significant. As mentioned in table 1.3, *Ananas comosus* displays analgesic activity by inhibiting pro-inflammatory mediators (Ajayi et al., 2022). Due to the presence of flavonoids, tannins, and phenolic compounds, *Callophyllum inophyllum* acts as an analgesic agent and cannabidiol found in *Cannabis sativa* has one of the highest analgesic effect of medicinal plants (Ninà Robertina Nalimanana et al., 2022; Liktor-Busa et al., 2021).

Table 1.3: Medicinal plants with analgesic property available in Bangladesh (Uddin & Islam, 2020)

Name of species	**Name of families**	**Local name**	**Parts used**
Ananas comosus	Bromeliaceae	Anarash	Leaf extracts
Callophyllum inophyllum	Clusiaceae	Sultan chapa	Leaves extracts
Cannabis sativa	Cannabinaceae	Ghaja	Leaves, flowers and fruits
Hibiscus rosa sinensis	Malvaceae	Joba	leaves
Spilanthes acmella Murr	Asteraceae	Shormoni	whole plant, leaves

1.7 Overview of CNS depressants

CNS depressants drugs are referred to as those drugs that interact with activity of the brain and reduce its irritability or excitement by causing the brain activity to decrease. It induces sedation and can be used to treat anxiety or seizures or to induce sleep or to treat insomnia. CNS depressant drugs are broadly classified into two groups, one is opioids CNS depressants and the other one is non-opioids CNS depressants. Opium, morphine, codeine falls under opioids CNS depressants and non-opioids CNS depressants can include alcohol, barbiturates, benzodiazepines etc. *(*Davis et al., 2002*).* Mechanism of CNS depressant drugs varies based on the classification of the drugs. Different classes of drugs interact with the receptor site or site of actions differently. Although both barbiturates and benzodiazepine drugs work at the GABA (γ-Aminobutyric acid) receptors, their interaction with the receptor is different (Ghit et al., 2021). Barbiturates bind to a site of $GABA_A$ receptor which can activate the chloride channel, leading to increase in the duration of opening of the chloride channels and causing

hyperpolarization of the cells. Thus, causing CNS depression. In contrast to barbiturate drugs, benzodiazepines increase the frequency of chloride channels opening. Thus, it induces hyperpolarization of the cells leading to CNS depression (Davis et al., 2002).

1.7.1 Medicinal plants with CNS depressant property available in Bangladesh

There is an abundance of plants in Bangladesh that have exhibited effects on CNS in human or animal bodies. Some of these plants as described in table 1.4 include *Acorus calamus* which reduces stress and anxiety by reversing neurotoxicity induced by stress, *Rauwolfia serpentina* induces CNS depression by exerting antagonistic effect on dopamine and many more (Table 4) ((Ashwin Rohan Rai et al., 2023; Kapalka, 2010).

Table 1.4: Medicinal plants with CNS depressant property available in Bangladesh (Uddin & Zidorn, 2020)

Names of species	**Names of family**	**Local names**	**Parts used**
Acorus calamus	Acoraceae	Bach	Rhizome, leaves
Amaranthus viridis	Amaranthaceae	Notey shak	Leaves
Rauwolfia serpentina	Apocynaceae	Sarpagandha	Leaves, root
Tabernaemontana divaricata	Apocynaceae	Tagar	Leaves, root, flower

1.8 About *Lagerstroemia thorelli*

Lagerstroemia thorelli is a flowering plant known as crape myrtle or Jarul in Bangladesh. This plant is a part of the Lythraceae family (Table 1.5). The family Lythraceae is a family of various flowering plants which includes 32 genera and 620 species. The fruits and flowering period for this plant is from April to September (Kotnala et al., 2013).

Taxonomical classification:

Table 1.5: Taxonomical classification of Lagerstroemia thorelli

Rank	**Scientific name**
Kingdom	Plantae
Phylum	Magnoliophyta
Class	Magnoliopsida
Order	Myrtales
Family	Lythraceae
Genus	*Lagerstroemia*
Species	*Lagerstroemia thorelli*

1.8.1 Morphology of *Lagerstroemia thorelli*

Lagerstroemia thorelli is a medium sized ornamental plant growing throughout Bangladesh typically reaching 15 meters or 49 feet tall. This plant has a relatively short trunk with bushy crown and pale yellowish-gray bark. The leaves of this plant are elliptical in shape and opposite and the size can range from 10.0 Ã— 5.5 cm. However, the most notable feature of this plant

is the purple or lilac colored 6 petaled flower which fades to white color (Figure 1.2). The plant gets its signature name crape myrtle from the crepe like crinkled structure of its flowers (Kotnala et al., 2013).

Figure 1.2: Lagerstroemia thorelli

1.8.2 Overview of therapeutic properties of *Lagerstroemia* genus

The *Lagerstroemia* genus contains many chemicals that are responsible for its various pharmacological properties. Although substantial research has not been done on *Lagerstroemia thorelli* and its constituents, research has been conducted on other species. One of the most common species of this genus is *Lagerstroemia speciosa*. The leaves of this species contain alanine, lageracetal, ellagic acid, isoleucine alpha amino butyric acid, amyl alcohol, beta sitosterol, methionine, 3,3,4-tri-O-methylellagic acid, new tannin-lager tannin, 3-O-

methyllagic acid but does not contain any alkaloids, glucosides, sterols or any flavonoids which can display antioxidant, antitussive, anti-inflammatory, antidiabetic or hypoglycemic, antimicrobial effects (Kotnala et al., 2013). On the other hand, *Lagerstroemia indica* contains alkaloids, cardiac glycosides, sterols, tannins, triterpenes, saponins, flavonoids (flavanones, dihydroflavonols and chalcones), phenolic glycosides (strosides A-C), reducing compounds and anthraquinones which can have potential analgesic, antipyretic, anti-inflammatory, antioxidant, anticancer, antimicrobial, hypoglycemic effects (Al-Snafi, 2019).

1.9 Rationale of the project

The *Lagerstroemia thorelli* species is a member of the Lythraceae family and *Lagerstroemia* genus. Other species of this genus have shown to have antidiabetic, analgesic, anti-inflammatory, antioxidant and cytotoxic activities. Members of this genus contain different classes of compounds such as flavanones, phenols, polyphenols, tannins, alkaloids, dihydroflavonols, and chalcones. Research has shown that these chemical constituents are capable of producing antidiabetic, analgesic and CNS depressant effects. Since, *Lagerstroemia thorelli* also belongs to the same family and genus it might contain similar chemical constituents that have similar effect *in vivo* as other members of the same *Lagerstroemia* genus. However, literature review of any available academic studies did not reveal any adequate information about the *in vivo* antidiabetic, analgesic and CNS depressant potentials of *Lagerstroemia thorelli*. Therefore, it validated the importance of investigating such topic. Thus, *Lagerstroemia thorelli* plant was chosen to investigate the *in vivo* antidiabetic, analgesic and CNS depressant effect due to insufficient research done on this plant with the selected extract and method.

1.10 Aim and objectives of the project

Aim:

This project aims to investigate and discover the antidiabetic, analgesic, and CNS depressant potential of *Lagerstroemia thorelli.*

Objectives:

- To investigate antidiabetic property of ethanol extract of *Lagerstroemia thorelli*
- To investigate analgesic property of ethanol extract of *Lagerstroemia thorelli*
- To investigate CNS depressant property of ethanol extract of *Lagerstroemia thorelli*
- To evaluate the potential role of *Lagerstroemia thorelli* in antidiabetic, analgesic, and CNS depressant drug discovery and development

Chapter two: Methodology

2. Methodology

2.1 Collection of plant material

The ethanol extract of *Lagerstroemia thorelli* was provided by Dr. Shahana Sharmin, former-assistant Professor at the School of Pharmacy, BRAC University. Healthy green leaves of *Lagerstroemia thorelli* were collected from Nabiganj Upazila in Habiganj district, Sylhet division, Bangladesh. The specimen was collected, identified and was given the accession number DACB-87494.

Figure 2.1: Leaves of Lagerstroemia thorelli

2.2 Preparation and extraction of plant material

The ethanol extract of *Lagerstroemia thorelli* was prepared from its leaves. Fresh leaves were collected, washed and dried to prepare for the extraction process. An electric blender in the laboratory was used to ground the dried leaves into a coarse powder, which was then utilized to make the ethanolic extract. Ethanol was used as a solvent in the preparation of the *Lagerstroemia thorelli* extract, which was then concentrated to get the ethanolic crude extract. The phytochemical screening of the extract indicated the presence of flavonoids, phenolic compounds, tannins, glycosides, carbohydrates, resins and steroids. The extract of *Lagerstroemia thorelli* was then diluted to different concentrations of 200 mg, 400 mg and 600 mg. The preparations were labeled as *L. thorelli*-200 mg/kg, *L. thorelli*-400 mg/kg and *L. thorelli*-600 mg/kg.

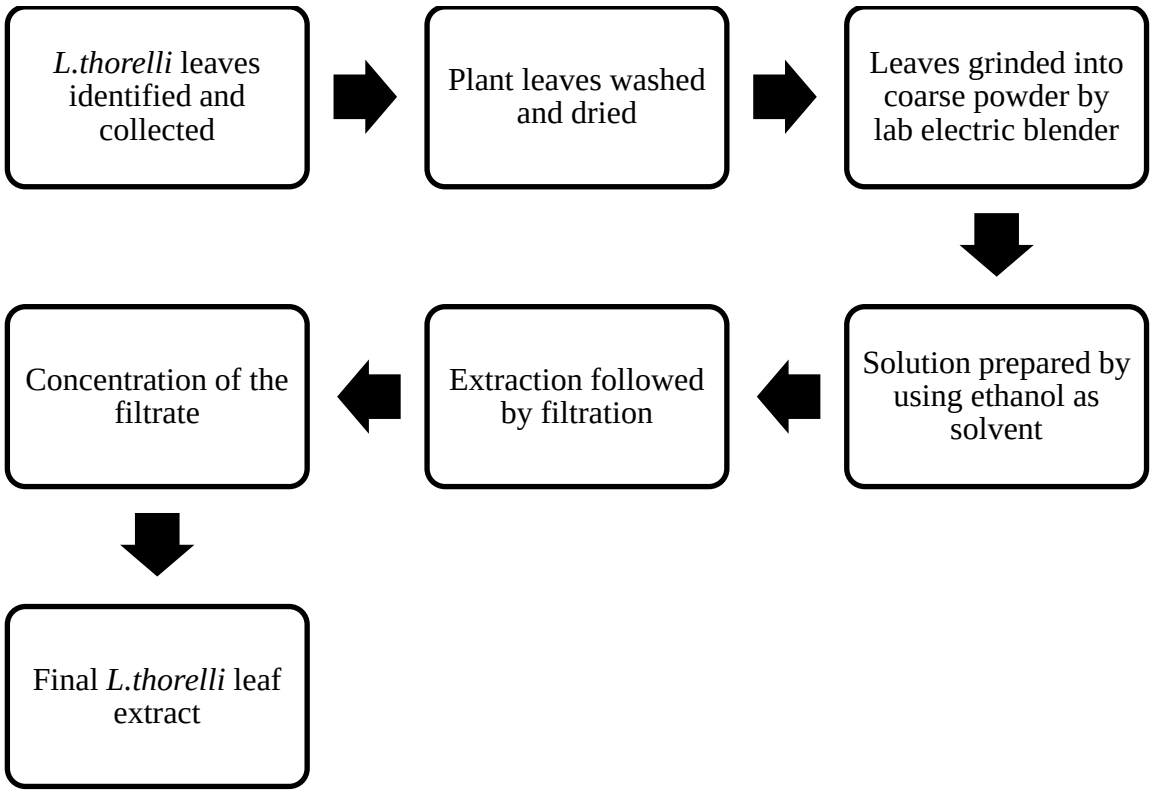

Figure 2.2: Extraction of Lagerstroemia thorelli leaves

2.3 Experimental animals

For conducting the various experiments, Swiss albino mice were selected and used for the therapeutic investigation. These experimental animals were collected from Jahangirnagar University animal lab and ICDDRB, Bangladesh. The mice were selected based on similar baseline characteristics with their average weight being from 29 to 34 gm. The mice were kept in ideal conditions to avoid any environmental stress. Relative humidity around 55-65% was maintained in their enclosure. Light-dark cycles of 12 hours as well as temperature around 24.0±0°C were also kept to maintain the ideal conditions (Khatoon et al., 2014).

Figure 2.3: Swiss albino mice

2.4 Drugs and chemicals

In this investigation, analytical-grade chemicals and reagents were employed. Square Pharmaceuticals PLC provided the glibenclamide, diclofenac-Na, and diazepam medications that were utilized in this investigation. Regular saline solution was bought from Beximco Pharmaceuticals Ltd. Chemical reagents, including acetic acid were purchased from Merck, Germany, alloxan from India, and Tween 80 from BDH Chemicals, UK.

2.5 Evaluation of antidiabetic effect

In this experiment, the mice were divided into 6 groups, each group containing 6 mice. The six groups include the control group, diabetic control group, standard group, group-I (200 mg/kg of *Lagerstroemia thorelli*), group-II (400 mg/kg of *Lagerstroemia thorelli*) and group-III (600 mg/kg of *Lagerstroemia thorelli*) based on the dose of the extract (Table 2.1). The mice of each group were marked and their weight taken. This data was used to calculate the doses of test samples and control groups. Other equipment such as disposable 1 mL sterile syringe with 100 divisions, tuberculin syringe with ball shaped end and digital balance are used.

Standard solution: 5 mg/kg of glibenclamide was administered to the mice at 0.5 mL volume orally.

Extract suspension: It was prepared at 200 mg/kg, 400 mg/kg and 600 mg/kg doses by adding tween 80 as a suspending agent with normal saline and was administered to the mice at 0.5 mL volume orally.

Table 2.1: Groups and treatments of antidiabetic experiments

Groups	**Reagents and treatments**
Control group	Normal saline 10 mL/Kg
Diabetic control group	Normal saline (0.9%)+alloxan 150 mg/Kg
Standard group	Glibenclamide 5 mg/Kg
Group-I	*Lagerstroemia thorelli* extract 200 mg/Kg
Group-II	*Lagerstroemia thorelli* extract 400 mg/Kg
Group-III	*Lagerstroemia thorelli* extract 600 mg/Kg

2.5.1 Assessment of hypoglycemic effect on alloxan-induced diabetic mice

In this method, diabetes is deliberately induced in mice to determine the antidiabetic potential of *Lagerstroemia thorelli.* The control group of mice was given normal saline (0.9%) at 10 mL/Kg. Here, mice in the diabetic or negative control group received an intraperitoneal injection of 0.9% solution of normal saline and alloxan at a dosage of 150 mg/Kg to induce diabetes following a 16-hour fast. After 72 hours the mice were checked and those whose fasting blood glucose levels were higher than 200 mg/dL were selected for this experiment (Tanquilut et al., 2009). Glibenclamide at 5 mg/Kg dose was administered as standard. The antidiabetic effect was observed for a period of 14 days or 2 weeks (Figure 6).

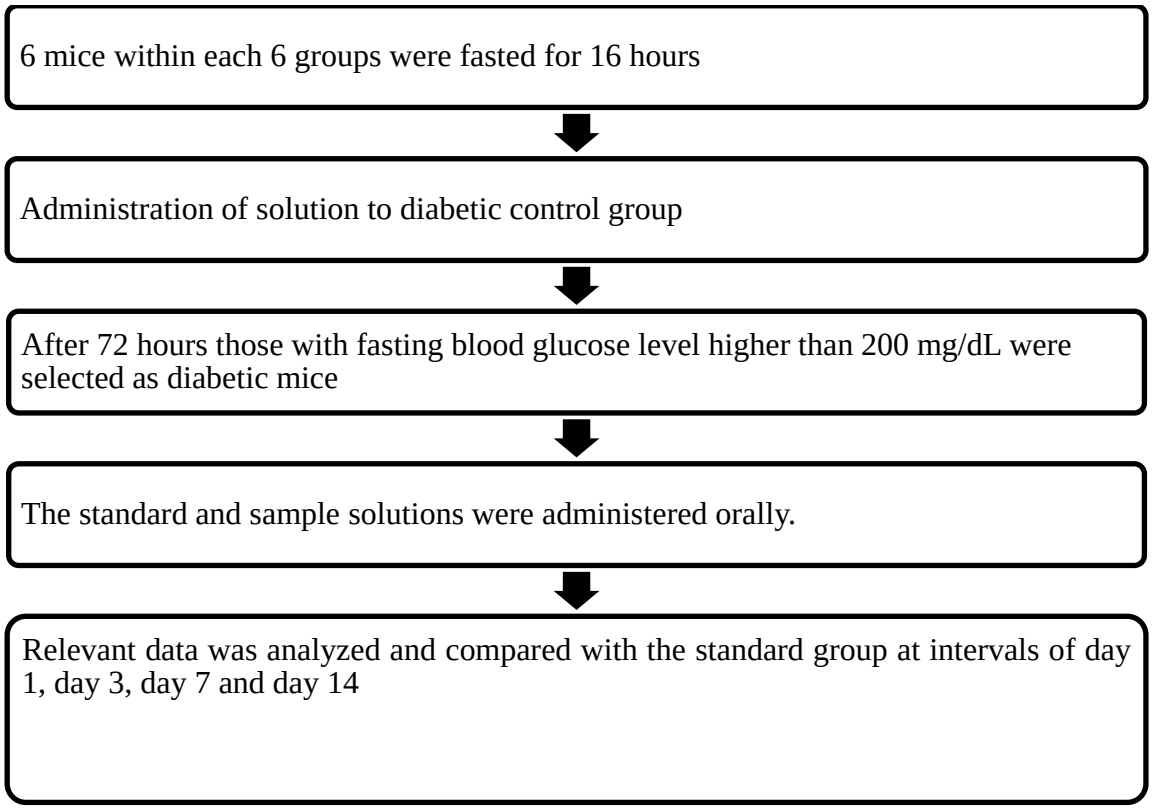

Figure 2.4: Procedure of antidiabetic effect of Lagerstroemia thorelli extract on alloxan-induced diabetic mice (Tanquilut et al., 2009)

2.6 Investigation of analgesic property

In this experiment, the mice were divided into 5 groups, with each group containing 6 mice. These 5 groups include the control group, the standard group with diclofenac-Na, group-I (200 mg/kg of *Lagerstroemia thorelli*), group-II (400 mg/kg of *Lagerstroemia thorelli*) and group-III (600 mg/kg *Lagerstroemia thorelli) (Table 2.2)* To conduct the experiment, each mouse was marked and had their weight taken, to accurately calculate the dosage of test samples and control groups. Normal saline (0.9%) was used to prepare the standard solution. Equipment such as 1 mL sterile disposable syringe (100 divisions), tuberculin syringe with ball shaped end and digital balance were used.

Standard solution: 10 mg/kg of diclofenac-Na was dissolved in normal saline (0.9%) water and was administered to the mice at 0.5 mL volume orally.

Extract suspension: It was prepared at doses of 200 mg/kg, 400 mg/kg and 600 mg/kg by adding tween 80 as a suspending agent with normal saline and was administered to the mice at 0.5 mL volume orally.

Table 2.2: Groups and treatments of analgesic experiments

Groups	**Treatments**
Control group	1% Tween 80 in water (10 mL/Kg)
Standard group	Diclofenac-Na (10 mg/kg)
Group-I	*Lagerstroemia thorelli* extract 200 mg/Kg
Group-II	*Lagerstroemia thorelli* extract 400 mg/Kg
Group-III	*Lagerstroemia thorelli* extract 600 mg/Kg

2.6.1 Analgesic effect evaluation using acetic acid induced writhing method

This method is used to assess the pain-relieving potential of different substances, including medicinal plants. This chemical process begins by initiating sensation of pain in animal models by administering substances that can cause irritation, thereby producing pain. One of the substances is acetic acid which induces a motion called writhing, that is an abnormal and erratic movement or contraction of the body (Khatun et al., 2011). The analgesic and anti-nociceptive ability of the plant can be determined if it reduces or inhibits the number of writhing in mice. There was administration of 1% tween 80 in water to the control group, diclofenac-Na to the standard group as well as three different extract doses at 200 mg/kg, 400 mg/kg and 600 mg/kg were administered to the group I, II and III, respectively. After 30 minutes of receiving treatments, 0.6% acetic acid was administered intraperitoneally at a dose of 10 mL/Kg to induce writhing. The total amount of writhing was calculated for 30 minutes after 5 minutes of administration of acetic acid solution (Figure 2.5). Here, 2 partial writhings were counted as one full writhing. To determine success of the treatment, percentage of inhibition is used as a key indicator. It can be calculated by the following formula according to Khatun et al., (2011).

$$\textbf{Percentage of inhibition} = \frac{A-B}{A} \times 100$$

Where, A= Average number of writhing of the control group; B= Average number of writhing of the test group

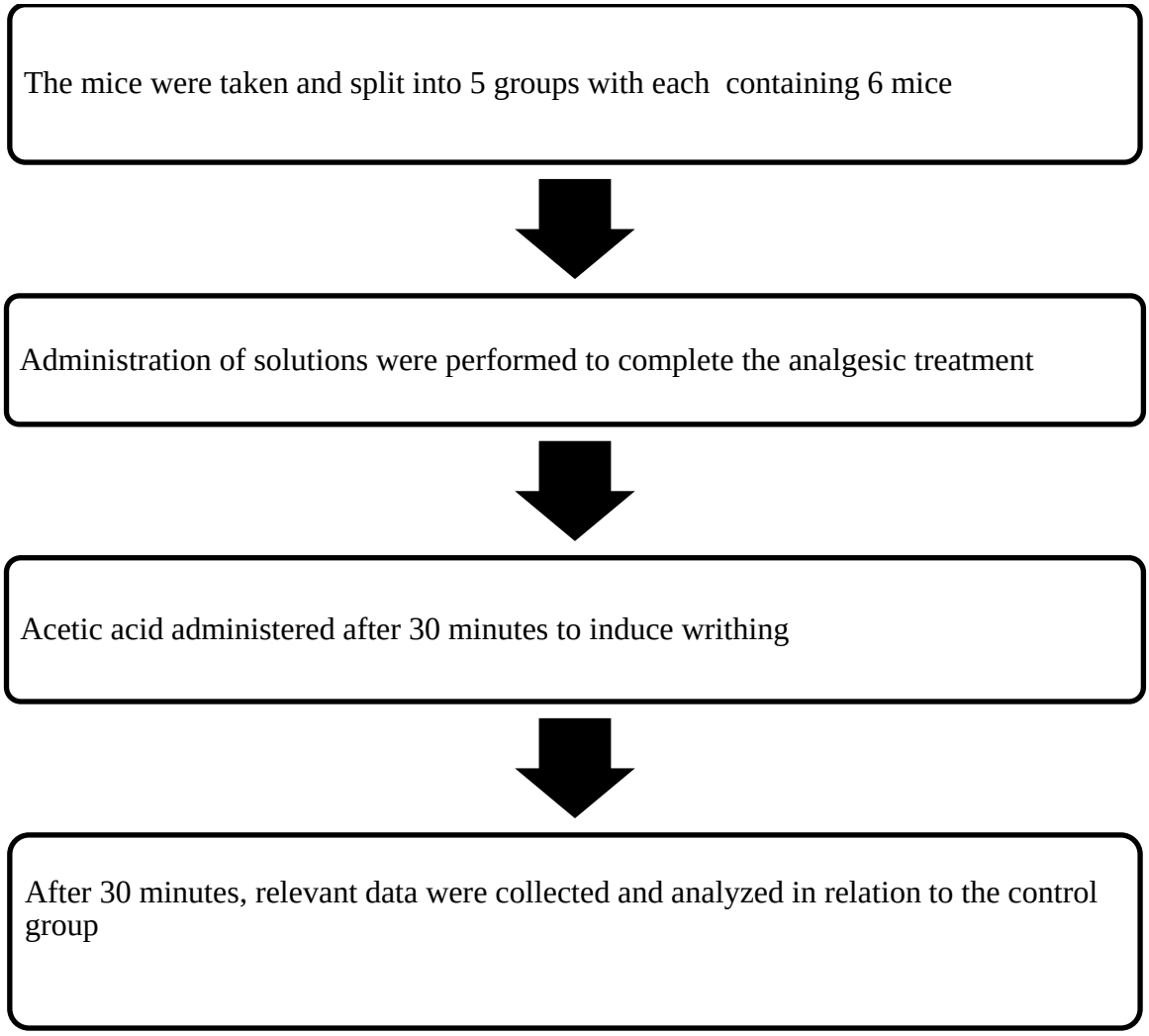

Figure 2.5: Procedure of acetic acid induced analgesic and anti-nociceptive test (Khatun et al., 2011)

2.7 Evaluation of CNS depressant effect

In this experiment, the mice were divided into 5 groups with each group containing 5 mice. These five groups include the control group, the standard group and 3 groups with different doses of *Lagerstroemia thorelli* plant extract: 200 mg/kg (group I), 400 mg/kg (group II) and 600 mg/kg (group III), respectively (Table 2.3). The doses to be administered for both the standard and the test group is determined by the body weight of mice. To prepare the standard solution normal saline (0.9%) water was used. Equipment such as 1 mL sterile disposable

syringe (100 divisions), tuberculin syringe with ball shaped end and digital balance are also used.

Standard solution: 1 mg/kg of diazepam was dissolved in normal saline (0.9%) water and was administered to the mice at 0.5 mL volume orally.

Extract suspension: It was prepared at doses of 200 mg/kg, 400 mg/kg and 600 mg/kg by adding 1% of tween 80 as a suspending agent with normal saline and was administered to the mice at 0.5 mL volume orally.

Table 2.3: Groups and treatments of CNS depressant experiments

Groups	**Treatments**
Control group	1% Tween 80 in water (10 mL/Kg)
Standard group	Diazepam (1mg/Kg)
Group-I	*Lagerstroemia thorelli* leaf extract 200 mg/Kg
Group-II	*Lagerstroemia thorelli* leaf extract 400 mg/Kg
Group-III	*Lagerstroemia thorelli* leaf extract 600 mg/Kg

2.7.1 Investigation of CNS depressant effect using Hole cross method

This is one of the standard methods for determining the CNS depressant effect of any substances or medicinal plant extract. This method utilizes hole cross apparatus where a mouse can pass through each hole one at a time. The number of times that a mouse passes each hole is counted. Thus, this method can be used to determine locomotor activity as well as time course of motor activity (Takagi et al., 1971). In this test, after the treatment with the control, standard

and test solutions, the movement of mice of each group is carefully observed and counted. Here, after the administration of 200 mg/kg, 400 mg/kg and 600 mg/kg *Lagerstroemia thorelli* extract, the effect of it can be seen on the motor activity of the mice. Data on the locomotor activity of the mice were collected throughout the experiment at regular intervals of 0,30,60,90,120 minutes and the interpretation of the result was compared with the standard (Figure 2.6). If the movement of mice through the hole after sample administration decreases compared to the control, CNS depressant effect can be confirmed.

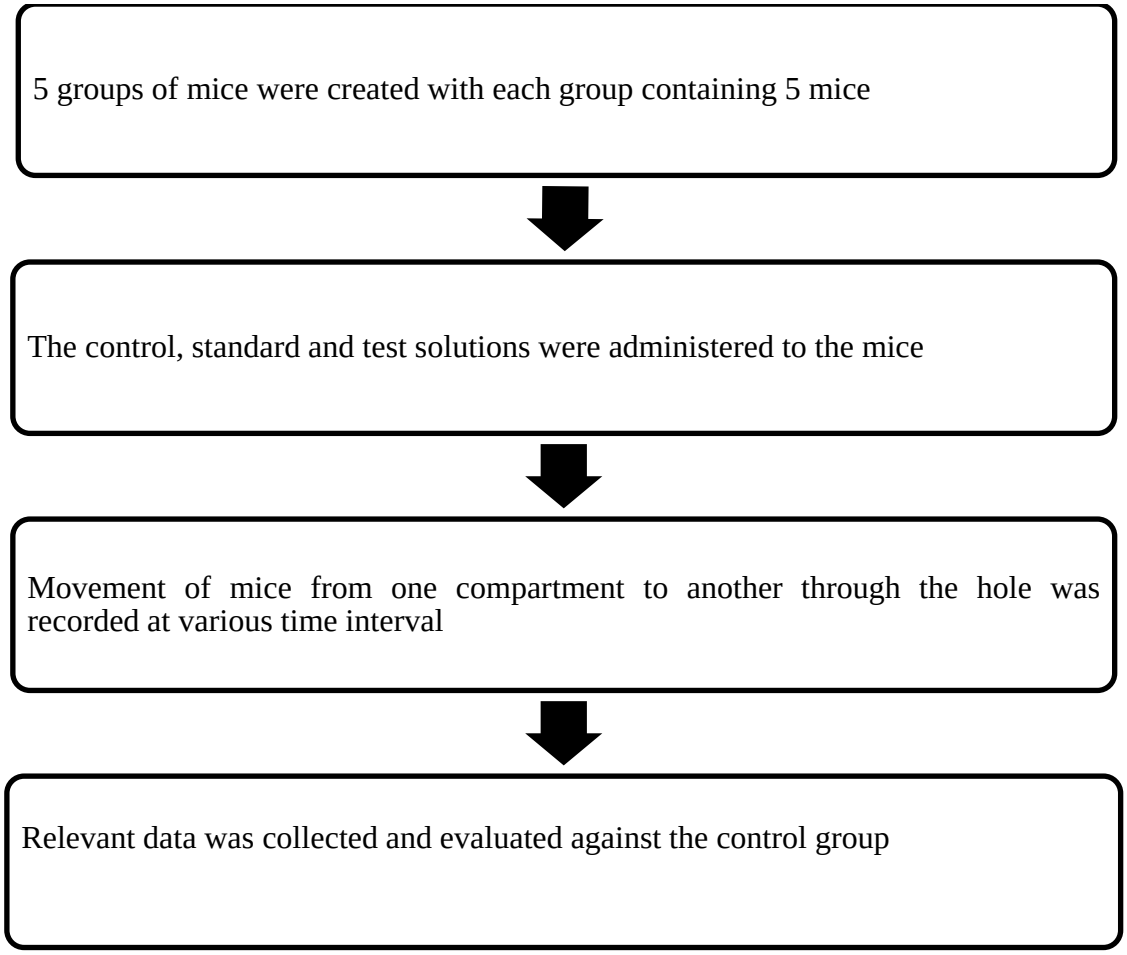

Figure 2.6: Hole cross method (Takagi et al., 1971)

2.8 Statistical analysis

All the data and the values gathered from these experiments are presented as mean ± standard error of mean (SEM). These statistically obtained data were analyzed and verified by one-way Analysis of Variance (ANOVA) followed by Dunnett's test.

Chapter three: Results

3. Results

3.1 Results of antidiabetic effect of *Lagerstroemia thorelli* extract on mice

The dose dependent effect of *Lagerstroemia thorelli* extract on blood glucose level was determined through a period of 14 days with 3 different doses of *Lagerstroemia thorelli* and is presented in Table 3.1.

Table 3.1: Effect of Lagerstroemia thorelli extract on blood glucose level

Groups	**Doses**	**Day 1**	**Day 3**	**Day 7**	**Day 14**
Normal control (Normal saline 0.9%)	10 ml/kg	102.33±1.05	97±1.73	95.83±1.33	94.17±1.83
Negative control (Normal saline 0.9% +Alloxan)	150 mg/kg	221±1.63	223.33±1.98	223±2.37	221.17±1.92
Standard (Glibenclamide)	5 mg/kg	227.33±1.74	195.67±1.60*	177.67±2.44*	140±0.58*
Group-I	200 mg/kg	217±1.21	201.67±1.69*	191.67±1.11*	182.83±1.30*
Group-II	400 mg/kg	217.17±2.59	196.33±3.52*	178.33±1.98*	162±1.18*
Group-III	600 mg/kg	219.5±3.60	182.5±2.84*	160±2.77*	147.5±1.88*

The values are demonstrated as mean±SEM (n=6), * significant (P<0.01) compared to control

Interpretation:

By performing the blood glucose level (BGL) test after alloxan-induced diabetes in mice, the effect of *Lagerstroemia thorelli* on diabetes was determined. The antidiabetic effect of the *Lagerstroemia thorelli* was found to be dose dependent. At day 14, BGL was at 221.17±1.92 mg/dL for negative control group and 140±0.58 mg/dL for standard group compared to group-I which showed a reduction in the BGL from 217±1.2 mg/dL in day 1 to 182.83±1.30 mg/dL in day 14. Similarly, a more significant decrease in BGL was observed for group-II from 217.17±2.59 mg/dL on day 1 to 162±1.18 mg/dL on day 14. However, group-III showed the most significant change in BGL from 219.5±3.60 mg/dL on day 1 to 147.5±1.88 mg/dL on day 14 (Table 3.1). Here, the antidiabetic ability increased with the concentration of the plant extraction.

3.2 Results of analgesic effect of *Lagerstroemia thorelli* extract on mice

Analgesic effects of plant extract can be determined using various methods. In this study, acetic acid-induced writhing test was used to evaluate the analgesic effect of *Lagerstroemia thorelli* extract which is presented in Table 10. This test was performed through the administration of 0.6% acetic acid at the dose of 10 mg/kg in mice, 30 minutes after receiving the standard and the plant extract. Here, acetic acid induced writhing in the experimental mice.

Table 3.2: Effect of Lagerstroemia thorelli on acetic acid induced writhing test

Groups	**No. of writhing**	**Percentage of writhing inhibition**
Control	27.33±1.05	
Diclofenac-Na	4.83±0.31	82.31%
Group-I	23.17±0.83	15.24%
Group-II	17.5±0.62	35.97%*
Group-III	12.33±0.76	54.87%*

All values are expressed as mean±SEM (n=6). * Significant (P<0.01) compared to control

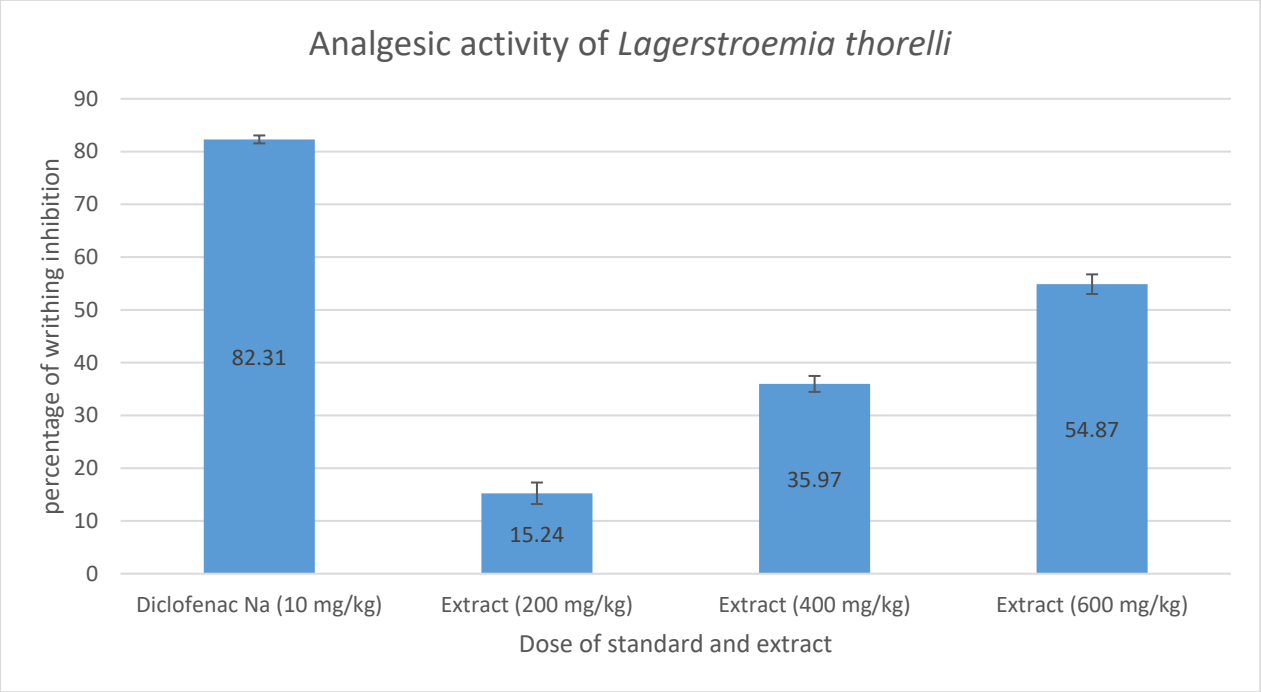

Figure 3.1: Analgesic effect of Lagerstroemia thorelli by percentage of writhing inhibition with SEM

Interpretation:

The results showed a clear dose dependent analgesic effect of *Lagerstroemia thorelli*. Here, the analgesic effect of diclofenac-Na was the highest, as it produced a writhing inhibition of 82.31%. In case of the plant extract, a dose of 200 mg/kg inhibited 15.24% of the writhing and a dose of 400 mg/kg comparatively exhibited greater inhibition by reducing the writhing to 35.97%. However, in comparison to the aforementioned groups of plant extract, the greatest inhibition in writhing was demonstrated by a dose of 600 mg/kg which reduced the writhing by 54.87% (Figure 3.1).

3.3 Results of CNS depressant effect of *Lagerstroemia thorelli* extract on mice

CNS depressant ability of *Lagerstroemia thorelli* can be determined through different tests conducted on mice *in vivo*. The test used here was hole cross test. This test measures the decrease in the locomotion of the animals. Here, the number of times a mouse passes a hole at various time intervals was documented and then interpreted (Table 11).

Table 3.3: CNS depressant ability of *Lagerstroemia thorelli* ethanol extract on hole cross test

Groups	**Doses**	**0 Minutes**	**30 Minutes**	**60 Minutes**	**90 Minutes**	**120 Minutes**
Control	1% tween 80 in water (10ml/kg)	27.6±0.51	24.8±0.37	23.2±0.49	20.8±0.37	18.8±0.37
Diazepam	1 mg/kg	19.6±0.51*	15.2±0.37*	9.2±0.37*	4.8±0.37*	1.8±0.58*
L.thorelli-200	200 mg/kg	26.8±0.37	23.8±0.37	20.8±0.37*	18.8±0.37*	16.2±0.8
L.thorelli-400	400 mg/kg	27.6±0.81	20.4±0.51*	15.4±0.51*	12.8±0.58*	11±0.45*
L.thorelli-600	600 mg/kg	27.6±0.81	16.4±0.51*	13.8±0.49*	12±0.32*	10.8±0.37*

All values are expressed as mean±SEM (n=6) * significant (P<0.01) compared to control

Interpretation:

Here, the CNS depressant ability of *Lagerstroemia thorelli* was quite clear as evident by the decrease in number of movement. Compared to the control group, the group of animals injected with the plant extract showed considerable decrease in movement. In the case of *Lagerstroemia thorelli*-200 mg/kg, the number of movements decreased from 26.8±0.37 to 16.2±0.8 in the first 2 hours. Similarly, *Lagerstroemia thorelli*-400 mg/kg also decreased the locomotor activity in mice from an initial 27.6±0.81 to 11±0.45 in 120 minutes. Finally, the most

significant reduction in locomotion of mice could be seen for 600 mg/kg of *Lagerstroemia thorelli*-600 mg/kg from 27.6±0.81 to 10.8±0.37 within 2 hours.

Chapter four: Discussion

4. Discussion

Belonging to the Lythraceae family, *Lagerstroemia thorelli* has potential to be an effective medicinal plant like the other members of its family such as *Lagerstroemia speciosa (L. speciosa), Lagerstroemia indica (L. indica) and Lagerstroemia parviflora (L. parviflora)* which has shown analgesic, antipyretic, anti-inflammatory, antioxidant, anticancer, antimicrobial and hypoglycemic ability (Kotnala et al., 2013). After thorough literature review, it was found that no previous study was done to observe the antidiabetic, analgesic and CNS depressant effect of *Lagerstroemia thorelli.* However, ethanol leaf extract of *Lagerstroemia indica* demonstrated significant antidiabetic effect (Chang et al., 2023). Similarly, ethanol leaf extract of *Lagerstroemia speciosa* also had shown antidiabetic and analgesic ability (Al-Snafi, 2019).

This study revealed that the ethanol leaf extract of *Lagerstroemia thorelli* showed 36.3% reduction of blood glucose level at 14 days in alloxan-induced diabetic mice which is more significant than *Lagerstroemia speciosa* aqueous leaf extract which showed 30% reduction of BGL in alloxan-induced diabetic mice in 15 days (Al-Snafi, 2019). *Lagerstroemia speciosa* is known to contain compounds responsible for antidiabetic effects such as flavonoids, tannins, and phenols. Similarly, phytochemical analysis of *Lagerstroemia thorelli* indicated the presence of flavonoids and tannins. Flavonoids can exert a hypoglycemic effect through controlling liver gluconeogenesis (Yi et al., 2023). Similarly, ellagitannin which is known as Lagerstroemin can exert an antidiabetic effect in the *Lagerstroemia* genus (Al-Snafi, 2019). Thus, presence of flavonoids and tannins in the *Lagerstroemia thorelli* ethanol leaf extract also exhibited antidiabetic effect in mice.

The analgesic effect of *Lagerstroemia thorelli*, was displayed through acetic acid-induced writhing test performed on three different doses of 200 mg/kg, 400 mg/kg and 600 mg/kg. The writhing test is typically performed to assess both the central and peripheral analgesic action (Hussain et al., 2015). Release of free arachidonic acid from tissue phospholipid triggers localized inflammatory reactions responsible for writhing induced by acetic acid (Mamun et al., 2011). The results showed significant dose-dependent pain reduction. Moreover, the percentage of writhing inhibition at 400 mg/kg dose was 54.87% for the ethanol leaf extract of *Lagerstroemia thorelli* much higher than 16.68% for the flower extract of *Lagerstroemia speciosa* (Al-Snafi, 2019). The analgesic effect of *Lagerstroemia thorelli* can be due to presence of tannins, steroids and phenolic compounds in the extract. All these constituents can exert an analgesic effect in mice to stop or reduce acetic acid induced writhes (Abdulmalik et al., 2011).

Lastly, *Lagerstroemia thorelli* had also shown notable dose dependent CNS depressant effect by reducing mice movement. But, in phenobarbitone sodium induced sleeping time test, *Lagerstroemia speciosa* delayed onset of sleep (Sharmin et al., 2018). The flavonoids (flavanones, dihydroflavonols and chalcones) present in the plant might be a key indicator of its CNS depressant potential (Al-Snafi, 2019). The hole cross test was chosen to determine the CNS depressant ability of *Lagerstroemia thorelli.* In most CNS depressant drugs, the action is elucidated through potentiating inhibition of $GABA_A$ receptor, leading to membrane hyperpolarization and subsequent decrease in CNS activity. This could potentially be the mechanism behind the CNS depressant activity of *Lagerstroemia thorelli* leaf extract Mamun et al., 2011).

Chapter five: Conclusion and future perspectives

5. Conclusion and Future perspectives

Bangladesh has a wide variety and sources of medicinal plants with diverse pharmacological activities. Based on this study, it can be said that the ethanolic leaf extract of *Lagerstroemia thorelli* possesses natural antidiabetic, analgesic, and CNS depressant -activities *in vivo,* at doses up to 600 mg/kg. This could explain the use of this plant in traditional medicinal systems in Bangladesh. The potential of the leaf's extract was determined by using alloxan alloxan-induced diabetic mice test, acetic acid-induced writhing test, and hole cross test. However, the therapeutic potential of flowers, bark and fruits of *Lagerstroemia thorelli* is yet to be determined. Considering the pharmacological effects of different parts of various members of this genus, different parts of *Lagerstroemia thorelli* might also possess similar pharmacological activities. Thus, more research is needed to further characterize the active compounds responsible for the antidiabetic, analgesic, and CNS depressant properties of *Lagerstroemia thorelli*.

Future perspectives

Lagerstroemia thorelli has shown great potential to be a medical miracle. However, further investigations and research into the chemical constituents and pharmacological properties of *Lagerstroemia thorelli* are needed to ensure its safety and efficacy as well as its therapeutic potential. In the future, the possible studies that can be done are:

- Investigation of other parts of *Lagerstroemia thorelli* with different extracts such as acetone, water, methanol etc.
- Performing formalin tests to elucidate analgesic properties. Conducting different tests to observe CNS depression such as open field tests.

- Investigation and evaluation of other pharmacological properties on leaf extract of *Lagerstroemia thorelli* such as anti-viral, antitussive and anti-pyretic etc.
- Performing clinical trials to confirm the antidiabetic, analgesic, or CNS depressant effects of *Lagerstroemia thorelli*
- Performing preformulation research for developing any potential dosage forms.

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