In vivo studies of analgesic, antidiabetic, and CNS depressant properties of *Pterocarpus indicus* 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.)

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Declaration

It is hereby declared that

1. The thesis report 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 “In-vivo studies of analgesic, antidiabetic, and CNS depressant properties of *Pterocarpus indicus*” submitted by Farzana Tabassum (20146015), of Spring, 2020 has been accepted as satisfactory in the 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 permission had been granted from relevant authority.

Abstract

The species *Pterocarpus indicus* belongs to the Fabaceae family, locally known as Padauk. Plants belonging to this family can treat rheumatic pain, insomnia, stress, and an increased heartbeat. However, through a literature search, it was seen no one has investigated the analgesic, antidiabetic, and CNS depressant properties of the ethanol leaf extract of *P. indicus*. This research aimed to investigate therapeutic properties like analgesic, antidiabetic, and CNS depressants of *Pterocarpus indicus* leaf extract using Swiss albino mice at doses of 200 mg/kg, 400 mg/kg, and 600 mg/kg. The antidiabetic effect was evaluated on alloxan-induced diabetic mice, the acetic acid-induced writhing test was used for the analgesic activity, and the hole cross method was employed for the CNS depressant effect. The extract showed significant anti-diabetic activity ($P<0.01$), notable analgesic and CNS depressant effects. Hence, the findings suggest that the extract of *Pterocarpus indicus* could be effective in diabetes treatment.

Key words: Medicinal plant, *Pterocarpus indicus.*, Analgesic, Antidiabetic, CNS depressant, mice.

Dedication

Dedicated to my late father, mother, younger sisters, and to my friends for their support and encouragement throughout my journey.

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Before anything else, I would like to express my gratitude to Allah (SWT), the best planner, who has bestowed on me knowledge, opportunities, strength, and a dedicated supervisor for completing this degree.

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List of Acronyms

gm	Gram
mg	Milligram
Kg	Kilogram
cm	Centimeter
mL	Milliliter
dL	Deciliter
COX-1	Cyclooxygenase 1
COX-2	Cyclooxygenase 2
Conc	Concentration
DM	Diabetes Mellitus
GDM	Gestational diabetes Mellitus
HPA	Hypothalamic-pituitary-adrenal axis
5-HT	5-hydroxytryptamine
BGL	Blood glucose level
OTC	Over the counter drugs
ADHD	Attention deficit hyperactivity disorder
PTSD	Post-traumatic stress disorder
HPLC	High performance liquid chromatography
GC-MS	Gas chromatography-mass chromatography
NMR	Nuclear Magnetic Resonance

Chapter 1

1. Introduction

1.1 An overview of history of medicinal plants

Medicinal plants are an invaluable resource for the healthcare system to fight with various diseases and in developing safe and effective drugs. Phytochemicals like flavonoids, phenols, quinones, coumarins and tannin alkaloids are produced by plants which have the potential to act against viruses, bacteria, fungi, etc. Notably, medicinal plants are precursors for synthesizing a novel drug and so to discover new therapeutic properties in a plant and to find the best aid plants leaves, barks, roots, seeds, fruits, and flowers are used from time to time. According to the archaeological finds, medicinal plants were in use before 60,000 years approximately (Yuan et al., 2016). Around 5000 years ago, the Sumerians first wrote a list of medicinal plants with their usage documented in a slab of clay. In a book named 'Herbals', different therapeutic properties of medicinal plants were written by different ancient physicians. Later on, this documentation was continued in the early Middle Ages, early modern ages and the 19th and 20th centuries by various scholars in various books. *De materia medica* by the Greek physician Pedanius Dioscorides has thousands of medicinal recipes using over six hundred plants (Petrovska, 2012). In the Middle Ages, compilation of five books of medicines named "The Canon of Medicine" was done by Avicenna a Muslim Persian physician and philosopher. This book is known as an encyclopedia of medicine which consists of principles of medicines, drugs developed with their natural origins, pathology, health condition, formulary (The Canon of Medicine., n.d.). Due to the advancement of science and technology, active ingredients of medicinal plants were purified by scientists. Morphine from *Papaver somniferum* was isolated by scientist Friedrich in the year 1806 (Hosseinzadeh et al., 2015). In

the modern era, many developed countries have created their own dataset of medicinal plants known as Materia Medica. According to IUCN, the number of flowering plant species used as medicinal plants is about 50,000 to 80,000 around the world (Chen et al., 2016). In this era natural products have earned consumers' confidence around the world over chemically synthesized products.

1.1.1: Traditional uses of medicinal plants found in Bangladesh

Medicinal plants are nature's gift to mankind. In bushes, forests, and along water bodies, medicinal plants grow in abundance which are used in treatment. In the last few decades systemic approaches to find new medicinal plants and use of them have exceptionally increased in developed countries as well as in developing countries. According to WHO, it is reported that China ranks first in using medicinal plants as 80% of their medicaments are produced from plants. In addition to that, Ayurveda practice in India, Unani in the Indo-Pakistan subcontinent, traditional African medicine of Africa, Kabiraji practice in Bangladesh.

Bangladesh, being situated in a sub-tropical monsoon region, is suitable for plant growth while experiencing six seasons. Different medicinal plants are collected from different areas of Bangladesh mostly from the largest mangrove forest Sundarban. It is more likely that five hundred species of 6500 plants in Bangladesh have medicinal value (Rahman et al., 2022). Bangladesh has a vast list of medicinal plants for instance, Malabar nuts (*Justica adhatoda*), Garlic (*Allium sativum*), Aloe vera (*Aloe vera*), *Malabar spinach* (*Basella alba*) , Green chiretta (*Andrographis paniculata*), False daisy (*Eclipta alba*), Shameplant (*Mimosa pudica*), Tulsi (*Ocimum tenuiflorum*) (P. A. Rahman, 2020). Rose periwinkle (Catharanthus *roseus)*, Neem (*Azadirachta indica*), Lemon grass (*Cymbopogon citratus*), Haritaki (*Terminalia bellirica*), Pathor kuchi (*Kalanchoe pinnata*) (Borkatullah et al., 2023) (Table 1.1).

As an easy to grow plant, Aloe vera is widely popular among the population who prefers organic products for dermatological purposes. The word aloe vera is derived from “Alloeh” which is an Arabic word. Aloe Vera is known as “The plant of immortality” by the Egyptians (Surjushe et al., 2008). Aloe Vera is a shrubby, perennial, xerophytic plant belonging to the Liliaceae family. It has about 75 active constituents (Surjushe et al., 2008). Traditionally, it is used to treat sun burns, bacterial infection, fungus infection, skin burns,acne vulgaris, constipation, wrinkles, psoriasis vulgaris, mucositis, inflammation, wounds, frostbites,etc.

In Ayurvedic practice, the Ashoka plant is largely utilized by the practitioners. *Saraca asoca* (Ashoka plant) is a medium sized evergreen flowering plant belonging to the Fabaceae family. In the old days, bark of ashoka plants along with other herbs were used to treat menstrual disorders and hormonal imbalance. To control heavy bleeding ashoka is used (Singh, 2023). Leaves and flowers are used to reduce inflammation and remove kidney stones. Moreover, it contributes in bringing down tumor cells in case of skin cancer, helps in osteoporosis, heart diseases, breast cancer, detoxification, and relieves pain (Singh, 2023).

In tropical and subtropical countries, false daisy is one of the popular medicinal herbs which belongs to the Asteraceae family. It is a small herbaceous plant which has a wide range of therapeutic values. Traditionally, it is used for respiratory disorders, burns, wounds, jaundice, liver enlargement, diabetes, hair fall, acidity, blood tonic, body pain, chicken pox (Timalsina & Devkota, 2021).

Green chiretta is an herbaceous plant that grows throughout the season in the Acanthaceae family. Although it is a plant from tropical Asian countries in isolated patches, it has various habitats like hillsides, coastlines, and plain land. Green chiretta is a commonly used herbal tonic in Bangladesh for treating common cold, flu, jaundice, diabetes (Reddy & Bhadra, 2020).

This plant is also used to treat digestive problems like gastritis, indigestion, heartburn, stomach pain and others.

Malabar nuts also known as Bashok are found in our subcontinent. It is a smaller shrub belonging to the Acanthaceae family. Commonly its leaves are used for remedy. Malabar nuts are used to treat common cold, cough, asthma, congestion and uremia (Basu, 2021). Furthermore, this plant is used for hypertension, purifying blood, decreasing heart rate, in treating digestive problems, boosting immunity and in reducing inflammation (Basu, 2021).

Malabar spinach, scientifically known as *Basella alba* belongs to the family Basellaceae. Due to its medicinal properties like anti-ulcerant, anti-inflammatory, antidiabetic, anticancer, CNS depressant activity, antibacterial, gastroprotective activity it is termed as "Upodika" by ayurvedic medicine (Chaurasiya et al., 2021). This plant helps to treat vomiting, crack heels, and catarrh. Moreover, it is considered as a safe laxative for pregnant women, children (Chaurasiya et al., 2021).

In case of Ayurvedic and Homeopathic practice, *Azadirachta indica* (Neem) is widely used. Due to a wide range of therapeutic properties, most of the parts are used. Traditionally, neem leaves are used to treat skin problems like ringworm, eczema, acne, worms. It is used in preventing bleeding gums, bad breath, boosting the immune system, and purifying blood (Rakshak & Rakshak, 2024).

The scientific name of rose periwinkle is *Catharanthus roseus* from Apocynaceae family. This plant has a rich history of medicinal use in treating diabetes, Hodgkin's disease, high blood pressure, ocular inflammation, insect bites, and lung congestion. Additionally, it helps to boost cerebral blood flow, reduce urinary retention (Das et al., 2017).

Shankasur is a multipurpose plant commonly known as peacock flower. *Caesalpinia pulcherrima* (Shankasur) belongs to the Fabaceae family. From ancient times, it was used to induce abortion, reduce inflammation, treat diarrhea, gallbladder problems, urinary tract problems, stomach-aches, fever, cold (Sharma & Rajani, 2011).

Sweet wormwood, botanically known as *Artemisia annua* from the Asteraceae family, is characterized by lots of medicinal properties. According to Ayur Times (2019), sweet wormwood has a history of treating illness for more than 2000 years. Traditionally it was used to treat malaria, dengue fever, indigestion, bloating, systemic lupus erythematosus, psoriasis. Moreover, it helps in relieving headaches, anxiety, and stimulating digestion (Powers, 2022) (Table 1.1).

Table 1.1: Medicinal plants with their traditional uses

Species name	**Local name**	**Family**	**Therapeutic uses**	**Reference**
Aloe vera	Aloe vera	Liliaceae	Treat sunburn, skin burns, bacterial and viral infections	(Surjushe et al., 2008).
Saraca asoca	Ashoka	Fabaceae	Treat menstrual disorders, hormonal imbalance, and tumors	(Singh, 2023)
Eclipta prostrata	False daisy	Asteraceae	Treat respiratory disorders, jaundice, and chicken pox	(Timalsina & Devkota, 2021)

Andrographis paniculata	Green chiretta	Acanthaceae	Common cold, indigestion, and diabetes	(Reddy & Bhadra, 2020)
Justicia adhatoda	Bashok/ Malabar nuts	Acanthaceae	Asthma, congestion, and uremia	(Basu, 2021)
Basella alba	Malabar spinach	Basellaceae	Gastritis, CNS depressant, vomiting, and crack heels	(Chaurasiya et al., 2021)
Azadirachta indica	Neem	Meliaceae	Treat acne, eczema. Prevent gum bleeding, and purifies blood	(Rakshak & Rakshak, 2024)
Catharanthus roseus	Rose periwinkle	Apocynaceae	Treat diabetes, Hodgkin's disease, and high blood pressure	(Das et al., 2017)
Caesalpinia pulcherrima	Shankasur	Fabaceae	Induce abortion, treat liver diseases	(Sharma & Rajani, 2011)
Artemisia annua	Sweet wormwood	Asteraceae family	Treat malaria, dengue fever, and psoriasis	(Powers, 2022)

1.1.2: Availability of the plant *Pterocarpus indicus*

Pterocarpus indicus locally known as Padauk is a large deciduous tree cultivated along the roadside of Dhaka city, highlands of Chattogram city, botanical gardens, parks in Bangladesh (Ali, 2020). Due to its evergreen nature, round, drooping branches it is used as ornamental trees, windbreaks around lands. As Bangladesh is a subtropical monsoon area, riverine country, *Pterocarpus indicus* grows naturally here. *Pterocarpus indicus* belongs to the Fabaceae family. Fabaceae is one of the largest family of angiosperm flowering plants with almost 19,500 species and 770 genera around the world of which genus *Pterocarpus* has 35 species (Nadon & Jackson, 2020). From Eastern Asia- southern China to Western pacific land this plant is widely cultivated. Local name of this plant changes with different regions for instance, narra in India, Philippine, angsana in Brunei Darussalam, Indonesia, sena in Myanmar (Rojas-Sandoval, 2022). The plant can be propagated from stem cuttings, seeds easily.

Figure 1.1: Pterocarpus indicus

Taxonomical classification

Table 1.2: Taxonomy hierarchy of Pterocarpus indicus

Rank	**Scientific name**
Kingdom	Plantae
Phylum	Magnoliophyta
Class	Magnoliopsida
Order	Fabales
Family	Fabaceae
Genus	*Pterocarpus*
Species	*Pterocarpus indicus*

1.1.3: Medicinal uses of different parts of *Pterocarpus indicus*

Pterocarpus indicus is one of the iconic trees with different medicinal properties. During the 16th to 18th century, leaves and barks of this plant were used to treat kidney problems, lower blood pressure, vomiting and nausea. Root juice of padauk is used to treat syphilitic sores, red latex used to treat cancer, tumors. Moreover, a concentrated liquid preparation of bark was given to treat diarrhea, sore mouth, and gonorrhea. Extract of young leaves are used for ulcers, rashes. A concentrated liquid preparation of leaf was prepared to treat amenorrhea or to induce

menstruation after pregnancy. Roots, barks and woods of *Pterocarpus indicus* showed antibacterial, antifungal and anti-asthmatic properties in studies (Ragasa et al., 2005) (Table 1.3)

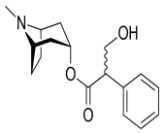
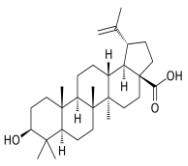
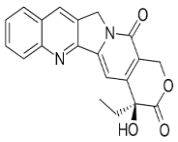
Figure 1.2: Pterocarpus indicus leaf

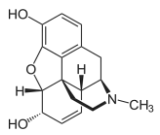
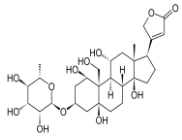
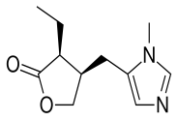
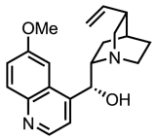
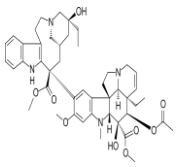
Table 1.3: Medicinal benefits of different parts of Pterocarpus indicus

Parts of *Pterocarpus indicus*	**Medicinal benefits**
Roots	Used in treating syphilitic sores
Barks	Used to treat diarrhea, sore mouth, and gonorrhea.

Leaves	To treat amenorrhea
Young leaves	Antibacterial, antifungal, and anti-asthmatic agent

Table 1.4: Drugs with their plant sources, local name, family, structure, therapeutic uses (Helmenstine, 2020).

Drug	**Plant**	**Local name**	**Family**	**Structure**	**Therapeutic uses**
Atropine	*Atropa belladonna*	Deadly nightshade	Solanaceae		Antimuscarinic agent, to treat bradycardia
Betulinic acid	*Betula alba*	Silver birch	Betulaceae		Treat Cancer, malaria, inflammation
Camptothecin	*Camptotheca acuminata*	Happy tree	Nyssaceae		Treat cancer

Morphine	*Papaver somniferum*	Opium poppy plant	Papaveraceae		To treat severe pain
Ouabain	*Strophanthus gratus*	Ouabain tree	Apocynaceae		Treat heart diseases
Pilocarpine	*Pilocarpus jaborandi*	Jaborandi	Rutaceae		Used in treating glaucoma, dry mouth
Quinine	*Cinchona calisaya*	Jesuit's Bark	Rubiaceae		Antimalarial agent, muscle relaxant, non narcotic analgesic, babesiosis
Vinblastine	*Catharanthus roseus*	Periwinkle	Apocynaceae		To treat Hodgkin's disease, testicular cancer

1.2: Prevalence and importance of nature-based drugs

Nature based drugs have become popular over the time due to its ability to modify biological activity, 3D structures, and properties of drugs. Many new lead compounds for different diseases like cancer, tumors, and malaria are being developed from natural products. Currently, the world is inclining towards nature-based drugs due to its less side effects, toxicity and good potency. According to the FDA, roughly 30% of approved drugs have natural origin. These drugs are widely used around the world for instance morphine, vinblastine, salbutamol, and aspirin (Licciardi & Underwood, 2011). Drugs can be designed in the laboratory through chemicals, AI and other scientific approaches while focusing on curing only one disease at a time but problems arise when a multipurpose drug is to be designed. In order to increase patient acceptability, medicinal plants play a crucial role in designing a drug which serves different problems at a time. As people are becoming more health conscious and aware about side effects about synthetic drugs, they are becoming attracted towards natural products. Previously, it was seen that only people from developing countries are using medicines derived from plant sources as they are cost effective, however, now the importance of nature-based drugs has been spread throughout the world. According to WHO, more than 80% of the population of developing nations uses natural products over synthetic products (Veeresham, 2012).

1.2.1: Advantages of natural products over synthetic product

Natural drug products are directly or indirectly derived from the plants. Historically, these products are used to treat wounds, infections, fever, and pain and used by most people. As a single plant can have more than one therapeutic effect it may cause unwanted effects in our body. Moreover, these products can cause occasional toxicity if the medicinal plant is not identified properly or if preparation and administration go wrong by practitioners. Due to

advancements of modern science and technology, synthetic medicines have entered the market. Synthetic drugs are the chemical entities made in the laboratory to produce a drug whose effects can be controlled. Now-a-days synthetic drugs are widely produced in batches to meet the needs of the world along with it and have also gained popularity for low costing, quick effects. Apart from prescription medication, OTC drugs have covered a large number of world markets. These OTC drugs show a significant safety profile but misuse of these drugs leads to severe adverse effects. Every year approximately 100,000 people lose their lives due to side effects. As a result, the population tends to shift towards natural products due to its less side effects (Karimi et al., 2015).

Although synthetic drugs are manufactured under strict pharmaceutical protocols, misuse of drugs may happen during distribution. Some synthetic drugs are so powerful that they may create serious toxicity and side effects in our body. During drug design, both natural and synthetic molecules can be used parallelly. Statistically, it is seen that the number of drugs produced from natural sources was higher than the synthetically produced ones, which is 42% of total drugs between the years 1981-2019 (Tzvetkov et al., 2023).

1.3: Analgesic properties of medicinal plant

The term “Analgesic” is derived from the Greek word which is used for medication that helps in pain relief (Ames, 2022). Analgesic drugs alter the brain perception of sensing pain. Three types of analgesics are classified; those are non-opioid analgesic (Acetaminophen, NSAIDs), compound analgesic (combination of non-opioid with an opioid), opioids analgesics (both natural, and synthetic) (Ames, 2022). Due to favorable climatic conditions, Bangladesh has a large number of medicinal plants among them many have analgesic properties like *Justicia gendarussa, Mussaenda philippica, Trewia polycarpa, Steudnera virosa* (Sikder et al., 2013).

Species with potential to inhibit cyclooxygenase enzyme activity

Cyclooxygenase is a class of enzymes that generates inflammation by producing prostaglandins from arachidonic acid. Prostaglandins levels rise at the site of inflammation. Although inflammation is a part of our immune system it needs to be reduced (Adelizzi, 1999). Due to variation in functions two isoenzymes of cyclooxygenase are found, COX-1 and COX- 2. To maintain homeostatic function, Cox-1 produces prostaglandins throughout the body. On the other hand, COX-2 mediates pain to the site of inflammation (Adelizzi, 1999). Traditionally, *Rosmarinus officinalis* were used for analgesic, anti-inflammatory, antirheumatic, antihepatotoxic purposes. This plant is enriched with phytochemicals like volatile oils, flavonoids, terpenoid, salicylates, caffeic acid, and rosmarinic acid. According to an experiment conducted by Emami et al. (2013), carnosol constituent of rosemary was able to produce an analgesic effect and relieve pain as it has a potential to inhibit COX-1 and COX-2 pathways. *Matricaria recutita L.* Chamomile has active constituents such as flavonoids, apigenin, luteolin, chalmuzene, alpha bisabolol which gives potential analgesic, antiinflammatory effect (McKay & Blumberg, 2006).

Table 1.5: Analgesic drugs derived from plants (Helmenstine, 2020)

Drugs name	**Plant**	**Local name**	**Family**
Borneol	Several plants **(***Blumea balsamifera, Cinnamomum camphora* **)**	Ngai camphor, camphor tree	Asteraceae, Lauraceae
Codeine	*Papaver somniferum*	Opium poppy	Papaveraceae
Morphine	*Papaver somniferum*	Opium poppy	Papaveraceae
Rotundine	*Stephania sinica*	Shrub	Menispermaceae
Salicin	*Salix alba*	White willow	Salicaceae
TetrahydroPalmatine	*Corydalis ambigua*	Flowering plant	Papaveraceae

1.4: Antidiabetic properties of medicinal plants

In case of both traditional and modern medicines, medicinal plants are extensively used for treating diabetes. Phytochemically, medicinal plants have huge number of active constituents which exhibit antidiabetic properties for instance, alkaloids (berberine, boldine, oxymatrine, piperine), flavonoids (quercetin, kaempferol, catechins, luteolin, rutin, silymarin), terpenoids (monoterpenoids, diterpenoids, pentacyclic terpenoids), phenols, ellagic acid, glycosides and many more (Salehi et al., 2019).

Antidiabetic medicinal plants are used worldwide as it is a safer option for regulating diabetes because of their low toxic effects. In Bangladesh, lot of antidiabetic medicinal plants like kalmegh (Andrographis *paniculata),* Chirata (Swertia *chirata)*, Neem (*Azadirachta indica*), Onion (*Allium cepa)*, Satamuli (Asparagus *racemosus*), Nayantara (*Catharanthus roseus*), Shada datura (*Datura stramonium L.*) etc. (Sarkar et al., 2022).

1.4.1: An overview of diabetes

According to the World Health Organization, Diabetes Mellitus is a metabolic, chronic disorder due to hormonal imbalance of the human body. It happens due to declining capability of producing insulin hormone by β- cell of pancreas. Hyperglycemia may lead to diabetic retinopathy, kidney damage, nerves damage, gangrene, corn, etc. Different forms of diabetes can be found along with the common types of diabetes like, polygenic form (Type-I, Type-II) monogenic form (MODY, neonatal diabetes), gestational diabetes and many more.

Type I diabetes

Insulin dependent diabetes or juvenile diabetes are the formal names of Type I diabetes which occurs due to incapability of producing less insulin or no insulin resulting in increasing blood glucose level. This type of diabetes happens during childhood, early childhood bearing the symptoms like weight loss, blurry vision, frequent thirst, polyuria, tiredness (Salehi et al., 2019).

Type II diabetes

The most familiar form of diabetes among the adult population is Type-II diabetes. Although it is the common one, people are unable to detect it because of minor symptoms. Human body cannot utilize the secreted insulin to produce energy or become insulin resistant. Due to genetic factors, obesity, metabolic syndrome, damaged beta-cells, this type of diabetes may occur (Salehi et al., 2019).

Gestational diabetes

Some women may not have been affected with diabetes throughout their lifetime however, they may become diabetic during their pregnancy. Being obese, prediabetes, and sedentary can be the causes of gestational diabetes. It may or may not diminish after childbirth also it might affect the child. Healthy lifestyle, continuous monitoring of glucose level in blood, taking insulin and oral medication can help in gestational diabetes management (American Diabetes Association, 2021).

Maturity Onset Diabetes of the Young

Preliminary, maturity onset diabetic of the young (MODY) was confused with Type I or juvenile diabetes. A rare type of disease with the features where a genetic feature is passed down from generation to generation, being diagnosed within the age of 25 years, destruction of β cells, not being able to resist insulin. Moreover, the function of β cells prevails (American Diabetes Association, 2021). Since it is a genetic dysfunction, symptoms are not detected at once. Healthy teens, young people might be affected with these types of diabetes while showing symptoms like blurry vision, skin infection, frequent urination, fatigue (Liao, 2018).

Neonatal Diabetes

Neonatal Diabetes is the rarest monogenic form of diabetes. Those infant bodies who are unable to produce enough insulin are affected with hyperglycemia. In some cases neonatal diabetes does not last for long at that time transient treatment is provided; however, if this one lasts forever at this time insulin has to be administered throughout the lifetime (American Diabetes Association, 2021).

1.4.2: Prevalence of diabetes patients in Bangladesh

Diabetes has spread throughout the world uncontrollably. Since 1980, diabetes among the adult population has increased exponentially from 4.7% to 8.5%. For the past three decades the number has been increasing steadily (Salehi et al., 2019). According to the World Health Organization, about 422 million people are affected with diabetes around the world of which most of them are from tropical and subtropical countries. Bangladesh is at higher risk.

According to International Diabetic federation, in the year 2000, there were about 1,759,700 who had diabetes however it was increased in 2011 to around 8,405,600 people in Bangladesh. The number of people has grown exponentially. This number skyrocketed in the last survey by 13,136,300 people. If the situation prevails like this it is estimated that this number will rise to 16,822,000 by 2030.

1.4.3: Treatment of diabetes melitus, gestational diabetes, neonatal.

At present, there is no permanent cure for diabetes; it can only be managed by medication. First line of treatment for DM, GDM is taking insulin shots in intervals. Furthermore, Metformin tablets are prescribed. Healthy lifestyles for instance, diet, exercise, weight loss can manage or prevent diabetes. According to the European Medicine Agency, a drug named 'Amglidia' is the first one to treat neonatal diabetes.

1.4.4: Earlier research for the antidiabetic effect of *Pterocarpus indicus.*

Phytochemical drugs acceptance is increasing day by day. Researchers are now more interested in investigating new flora, the genus *Pterocarpus* is one of them. This genus has 70 species along with different bioactive ingredients. *Pterocarpus marsupium* has two compounds named marsupsin and pterostilbene which showed antidiabetic activity in *in vivo* studies (Ahmad et al., 2022). *Pterocarpus indicus* is a well-known medicinal tree. In a pharmacological study it was found that extract of *Pterocarpus indicus* shows antibacterial and antifungal activity (N. Senthilkumar, 2020).

1.5: Medicinal plants with CNS depressants properties

From the primitive phase, people from walks, races, and cultures are fond of natural products over synthetic products. Many medicinal plants are used as CNS depressants from earlier times. Plants are enriched with active ingredients like alkaloids, flavonoids which exhibit medicinal properties. Plants with great quantities of alkaloids possess CNS depressant effects as they are able to interact with CNS receptors. Furthermore, flavonoids like apigenin, quercetin,

kaempferol showed potent effects on CNS as they interact with enzymes and the receptor system of the brain (Jäger & Saaby, 2011).

Female ginseng (Angelica *sinesis*), Golden shower tree (*Cassia fistula*), Sycamore fig (*Ficus sycomorus*) , Kali Musli (*Curculigo orchioides*) , Lavender (*Lavandula angustifolia*) and many other medicinal plants shows CNS depressant effects (Khazdair et al., 2017). These plants function by regulating activity of HPA, regulation of 5-HT, dopamine, and noradrenaline.

1.5.1: Types of CNS depressant

Those classes of drugs which ease the activity of the brain by increasing the secretion of GABA are known as CNS depressants. These drugs help to treat anxiety, drowsiness, insomnia, stress, and panic attacks. Depending on the medical uses there are three types of CNS depressants for instance, sedative, hypnotic, tranquilizers.

Sedative

Commonly, sedatives are used to provide a calming effect to the patient by slowing down brain activity, excitements. To treat disorders like sleeping, anxiety, panic attack, manic depression and tension, sedatives are prescribed by health practitioners. In relieving anxiety disorders barbiturates class of drugs are used for example phenobarbital, pentobarbital, amobarbital. Furthermore, Benzodiazepines like diazepam, lorazepam, and clonazepam are used as sedatives. Some short-term side effects are seen like confusion, memory loss, impaired judgements, unclear speech, etc.

Hypnotics

Those drugs which are prescribed intending to treat insomnia are known as hypnotics. Hypnotic drugs are classified into five types among three major groups for instance, benzodiazepines, melatonin receptor agonists, Z-drugs, orexin receptor agonists, antihistamines (Dietmaier, 2022). Overuse of hypnotics may cause side effects like drowsiness, sleep disorders (hypnagogic or hypnopompic), dryness of mouth and skin, weariness and nausea.

Tranquilizer

The group of drugs or medication used to treat mental disorders, anxiety, fear, muscle spasm is termed as tranquilizers or anxiolytics. According to the Editors of Encyclopedia of Britannica,1998, Two main classes of tranquilizers are their antipsychotic agents which help to reduce delusional problems, in treating symptoms of schizophrenia, in soothing an irritated person whereas antianxiety agents are used to alleviating tension, anxiety. Clonazepam, diazepam, triazolam are common types of tranquilizers.

1.5.2: Traditional treatment of insomnia, anxiety by using medicinal plants.

A sleep disorder where people are unable to sleep or have a sound sleep is known as insomnia. Condition can be of two types: acute and chronic insomnia. In case of acute insomnia happens occasionally while chronic insomnia lasts for months. Due to stress, anxiety, depression, discomfort, ADHD, menopause and other health issues, insomnia may occur. Traditional medicine for instance, infusion of passion flowers (Passiflora *caerulea*) can promote relaxation and improve sleep efficiency as it has anxiolytic properties. Furthermore, infusion of valerian

(Valeriana *officinalis*), poppy (*Papaver rhoeas*), and chamomile can be used to treat insomnia (Begum, 2023).

The feeling of uneasiness, fear, panic due to phobias, PTSD, social disorders are termed as anxiety. Sweaty hands, rapid heartbeat, numbness, dyspnea, muscle tension are the symptoms of anxiety. Kava (Piper *methysticum)*, Golden thryallis (*Galphimia glauca*), Cannabis (*Cannabis sativa*) were used to alleviate anxiety traditionally.

Table 1.6: Drugs obtained from plant sources with their family and local name (Helmenstine, 2020).

Drug class	**Drug name**	**Plant source**	**Local name**	**Family**
Antidiabetic	Metformin	*Galega officinalis*	French Lilac	Oleaceae
CNS depressant	Deserpidine	*Rauvolfia canescens*	Devil pepper	Apocynaceae
	Kawain	*Piper methysticum*	Kava kava	Piperaceae
	Papaverine	*Papaver somniferum*	Opium	Papaveraceae

	Scopolamine	*Datura stramonium*	Jimsonweed	Solanaceae
	Valepotriates	*Valeriana officinalis*	Garden heliotrope	Caprifoliaceae

Chapter two

2. Methodology

2.1 Collection and identification of the plant *Pterocarpus indicus*

During December, 2018 healthy and fresh leaves of *Pterocarpus indicus* were collected from Sundarban, Bangladesh. The specimen was identified and certified by Bangladesh National Herbarium with the accession number DACB: 46477.

2.2: Experimental animal

For *in vivo* studies of analgesic, antidiabetic and CNS depressant properties of extract of *Pterocarpus indicus* leaves, Swiss albino mice were used. The mice of 5-6 weeks age and 20-25 grams were collected from the Pharmacy Department of Jahangirnagar University and animal resource branch of ICDDRB of Bangladesh. For the research, the experimental protocol was authorized by the Animal Ethics Committee, Southeast University (SEU/Pharm/CERC/110a/2023) and was conducted in compliance with rules governing the uses of laboratory animals. For adaptation, these mice were given ideal conditions, stress free environment for one week while feeding them with rodent food and water *ad libitum*. Throughout the experiment, relative humidity of around 55-65% and temperature at 24.0±1° was maintained.

2.3: Drugs and chemical

All chemicals and reagents used in this investigation were of analytical grade. Tween 80 (BDH Chemicals, UK),acetic acid (Merck, Germany), alloxan (India) were used. Drugs like,

diclofenac Na, glibenclamide, and diazepam were purchased from Square Pharmaceuticals PLC. and normal saline solution from Beximco infusion Ltd., Bangladesh.

2.4: Therapeutic Inspection of leaf extract of *Pterocarpus indicus*

To determine the curative effects of the sample robust and valid tests were carried out-

- ➢ Analgesic or anti-nociceptive activity.
- ➢ Antidiabetic or antihyperglycemic activity.
- ➢ CNS depressant activity.

2.5: Analgesic activity of *Pterocarpus indicus* leaf extract

In this experiment, to evaluate the analgesic activity of the sample, acetic acid-induced writhing technique was performed.

Table 2.1: List of samples used in acetic acid-induced method

Groups	**Treatment**	**Doses**	**Route of administration**
Control group	1% Tween 80 in water	0.1 ml/ 10 gm body weight	Orally
Standard group	Diclofenac Na	10 mg /kg	Orally

Treatment group I	*Pterocarpus indicus* leaf extract	200 mg/kg	Orally
Treatment group II	*Pterocarpus indicus* leaf extract	400 mg/kg	Orally
Treatment group III	*Pterocarpus indicus* leaf extract	600 mg/kg	Orally

2.5.1: Acetic acid-induced writhing method

This is a chemical process of studying visceral pain in animal models by intraperitoneal administration of an irritant substance like acetic acid. The analgesic activity of medicinal plants or substances can be determined by reduced number of twisting, contraction of body (Rahman et al., 2021). The mice were split into five groups of six mice each. Control group as group I received 1% Tween 80 in water and standard group as group II received diclofenac Na. Other groups as group III, IV, V receive doses of 200, 400 and 600 mg/kg respectively of the extract. 0.6% of acetic acid was administered after 30 minutes at a dose of 10 mL/kg to induce pain sensation. The mice were monitored for writhing after 5 minutes of administration calculated for 30 minutes. For each mice, numbers of writhing were observed for 10 minutes. In some cases, partial writhing was observed so two partial writhings are considered as one full writhing (Rahman et al., 2021). Number of writhing of the experimented group with the control group was compared.

Percentage of inhibition (% of nociceptive activity) was calculated by following formula -

$$\text{Percentage of inhibition (\%)} = (A - B / A) \times 100$$

Here, A = Average no. of writhing of control group

B = Average no. of writhing of treated group

2.6 Anti-diabetic activity of *Pterocarpus indicus* leaf extract

In this experiment, to evaluate the ability of antidiabetic effect of sample extract alloxan induced diabetic method was used.

2.6.1: Anti-diabetic effect of alloxan-induced diabetic mice

Alloxan is a diabetogenic agent which damages beta cells selectively resulting in diabetes melitus in the animal body. Mice were kept on 16 hours fasting period before inducing fresh solution of alloxan was in each body intraperitoneally. Those mice who's fasting BGL were over 200 mg/dl after 3 days were selected for experiment. The mice were divided into six groups of six mice in each.

Group I (Control group): treated with normal saline 10mL/kg

Group II (Diabetic control group): treated with 0.9% of normal saline along with 150 mg/kg of alloxan.

Group III (Standard group): treated with glibenclamide of 5 mg/kg

Group IV (Test group): 200 mg/kg of *Pterocarpus indicus* leaf extract

Group V (Test group): 400 mg/kg of *Pterocarpus indicus* leaf extract

Group VI (Test group): 600 mg/kg of *Pterocarpus indicus* leaf extract

Afterwards, the antidiabetic effects of the test group are compared with standard groups at day 1, day 3, day 7 and day 14 consecutively.

2.7: CNS depressant activity of *Pterocarpus indicus* leaf extract

In this experiment, the hole cross method was used to determine the CNS depressant effect of the sample extract. The mice were divided into five groups consisting of five mice in each group.

Table 2.2: List of samples used in the experiment of hole cross method

Groups	**Treatment**	**Doses**	**Route of administration**
Control group	1% Tween 80 in water	0.1 ml/ 10 gm body weight	Orally
Standard group	Diazepam	1 mg /kg	Orally
Test group I	*Pterocarpus indicus* leaf extract	200 mg/kg	Orally
Test group II	*Pterocarpus indicus* leaf extract	400 mg/kg	Orally

Test group III	*Pterocarpus indicus* leaf extract	600 mg/kg	Orally

2.7.1: Hole cross method

The purpose of the hole cross method was to determine the sedative effect of sample extract explained by (Takagi et al.1971). A box made up of wooden material with a size of 30 cm × 20 cm × 14 cm was built with a steel partition in middle. At the height of 7.5 cm, a hole was made of 3 cm diameter so that only one mouse can pass through at specific time. As each group received their individual administration, their locomotion was observed and counted carefully at a regular interval of 0, 30, 60, 90, and 120 minutes.

Chapter three

3. Results

3.1 Evaluation of analgesic/nociceptive activity in acetic acid-induced writhing test

The ethanol extract of *Pterocarpus indicus* exhibited reduced number of abdominal contractions stimulated by 0.6% acetic acid at a dose of 10 mg/kg in acetic acid induced writhing test after oral administration. Different concentrations of extract were administered to evaluate the analgesic activity of the sample.

Table 3.1: The dose-dependent analgesic effect in acetic acid-induced writhing test

Groups	**No. of writhing**	**Percentage of inhibition**
Control group	27.33±2.58	No inhibition
Diclofenac Na	4.83±0.75	82.31%
Pterocarpus indicus leaf extract *(*200 mg/kg)	22.16±1.47	18.90% *
Pterocarpus indicus leaf extract (400 mg/kg)	16±2	41.46% *

Pterocarpus indicus leaf extract (600 mg/kg)	11.83±1.47	56.70% *

All values are demonstrated as mean ±STD (n=6). * Significant (P<0.01) to control

Figure 3.1: identification of writhing of mice by acetic acid-induced writhing test

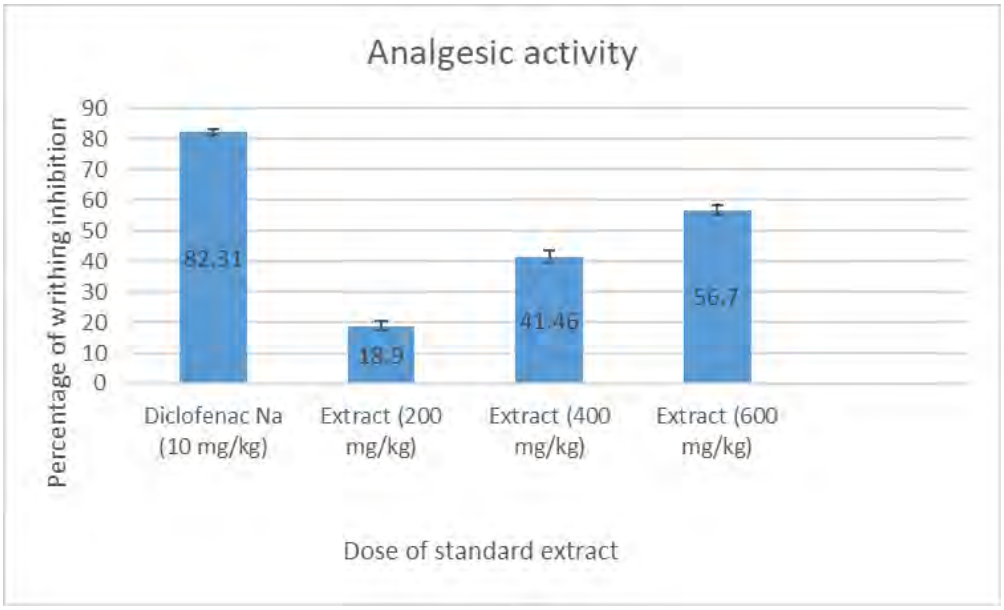


Figure 3.2: Analgesic activity of Pterocarpus indicus extract by percentage of inhibition

Interpretation:

Statistical analysis of the data showed that crude extract of leaves of the plant had significant suppression of writhing in a dose-dependent manner. At 200 mg/kg extract showed 18.90% writhing inhibition, at 400 mg/kg of body weight extract showed 41.46% writhing inhibition and at 600 mg/kg of body weight showed 56.70 %. These were compared to a standard group (Diclofenac Na) whose writhing inhibition was 82.31%. Although, in 200 mg/kg the number of writhing was low initially but it gradually increased at 600 mg/kg to 56.70%. Hence, the highest number of writhing inhibition and analgesic activity was evident compared to the standard group.

3.2 Antidiabetic effect on *Pterocarpus indicus* extract on alloxan-induced mice

Mice were administered a mixture of alloxan and normal saline (0.9%) intraperitoneally at 150 mg/kg for inducing diabetes. After 48 hours of administering the injection, rising glucose levels were determined from the tail of the mice. The alloxan induced mice were treated with different doses of *Pterocarpus indicus* leaf extract (200 mg/kg, 400 mg/kg and 600 mg/kg) body weight while selecting mice of the same characteristics in each 6 groups.

Table 3.2: Anti-diabetic activity of Pterocarpus indicus at different intervals

Groups	**Doses**	**Day 1 (mg/dl)**	**Day 3 (mg/dl)**	**Day7 (mg/dl)**	**Day14 (mg/dl)**
Normal control (Normal saline 0.9%)	10 ml/kg	102.33±2.58	97±4.24	95.83±3.25	94.16±4.49
Diabetic control (Normal saline 0.9% +Alloxan)	150 mg/kg	221±4	223.33±4.84	223±5.79	221.16±4.70
Standard (Glibenclamide)	5mg/kg	227.33±4.27	195.66±3.93*	177.66±5.98*	140±1.41*
Pterocarpus indicus I	200 mg/kg	218.16±9.74	202.66±7.58*	190.83±5.63*	176.33±2.58*

Pterocarpus indicus II	400 mg/kg	214.33±13.42	196.16±10.41*	179.16±8.84*	163.66±3.93*
Pterocarpus indicus III	600 mg/kg	210.16±6.91	182.33±4.80*	165.5±4.67*	153.33±3.61*

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

Interpretation:

The crude extract of *Pterocarpus indicus* showed a significant antihyperglycemic effect at dose-dependent manner when compared to diabetic control group. In case of *Pterocarpus indicus* I, when 200 mg/kg is administered a decrease in glucose level was observed from 218.16±9.74 mg/dl on day 1 to 176.33±2.58 mg/dl on day 14. Likewise, when 400 mg/kg is given glucose level decreases from 214.33±13.42 mg/dl on day 1 to 163.66±3.93 mg/dl on day 14. In the study, it was seen that diabetic mice had a significant increase in insulin level when treated with 600 mg/kg dose. As the concentration of extract increased gradually, notable antihyperglycemic activity was observed.

3.3: Evaluation of CNS depressant effect of *Pterocarpus indicus* extract on mice

To determine the sedative effect of crude extract hole cross test on mice model was conducted. Standard group of mice was given 1 mg/kg of diazepam while the treated group was given doses with different concentrations of *Pterocarpus indicus* leaf extract.

Table 3.3: CNS depressant effect of Pterocarpus indicus leaf extract

Groups	**Doses**	**0 Minutes**	**30 Minutes**	**60 Minutes**	**90 Minutes**	**120 Minutes**
Control	1% tween 80 in water (10 ml/kg)	27.6±1.14	24.8±0.83	23.2±1.09	20.8±0.83	18.8±0.83
Diazepam	1 mg/kg	19.6±1.14*	15.2±0.83*	9.2 ± 0.83*	4.8±0.83*	1.8 ±1.30*
Pterocarpus indicus I	200 mg/kg	24.4±0.89*	22.8 ±1.30	19.8±1.48*	18 ±1.41*	15.8±1.64
Pterocarpus indicus II	400 mg/kg	25 ± 1*	18±1*	13±1.22*	11±0.70*	8.8±0.83*

Pterocarpus indicus III	600 mg/kg	25.4±0.54*	17.8±0.83*	14±1.22*	11±0.70*	9.4±0.89*

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

Interpretation:

The table represents the effect of different concentrations of crude extract on the movement of animals. The animal administered with diazepam (1 mg/kg) and extracts of 200 mg/kg, 400 mg/kg, and 600 mg/kg showed diminished locomotion activity in a dose dependent manner when compared with the control group. At 200 mg/kg of the extract, the animal showed a decrease in movement from 24.4±0.89 in 0 minutes to 15.8±1.64 in 120 minutes. Notable, decline in motor activity of mice were observed with time being when 400 mg/kg of extract induced, from 25 ± 1 in 0 minutes to 8.8±0.83 in 120 minutes and 600 mg/kg dose was injected from 25.4±0.54 in 0 minutes to 9.4±0.89 in 120 minutes.

Chapter four:

Discussion

The world is changing faster than our imagination due to the advancement of technology. Similarly, our healthcare sector keeps switching its solution with the diseases. As people have become more health conscious, different types of drugs and lead compounds are preferably made from medicinal plants in comparison to chemically synthesized ones. In this study, the medicinal plant *Pterocarpus indicus* (Padauk) of the Fabaceae family was investigated. Till now there are 46 species found in genus *Pterocarpus*. One of the species, *Pterocarpus santalinus has* been reported with free radical scavengers, antidiabetic, anti-inflammatory, anticancer activity (Priya, D, & Senthilkumar*, 2022). Furthermore, antidiabetic, antibacterial, anti-inflammatory, antidiarrheal studies on *Pterocarpus marsupium* have been carried out. However, very few studies were carried out on identifying medicinal properties of *Pterocarpus indicus* leaf extract. In this study, analgesic, antidiabetic and CNS depressant activity of sample extract was carried out in animal models.

The analgesic activity of ethanol leaf extracts of *Pterocarpus indicus* was determined by acetic acid-induced writhing at different concentrations. Acetic acid stimulates arachidonic acid from tissue to produce pain. This nociception is produced by Prostaglandin E2, ASICs. Here, the ethanolic extract of *P. indicus* showed reduction in the number of writhing and produced analgesic effect at the dose of 200 mg/kg, 400 mg/kg and 600 mg/kg. In our study, at higher dose (600 mg/kg) ethanol leaf extract of *Pterocarpus indicus* showed 56.70% of writhing inhibition while alcohol leaf extract of the similar species showed 49.63% at higher dose of

500 mg/kg in previous studies (Rahman et al., 2021). So, the ethanol leaf extract of *Pterocarpus indicus* has significant analgesic effect.

By restoring β cells in the body, extracts exhibit antidiabetic effects. As compared to the negative control group, the standard group (Glibenclamide 5 mg/kg) exhibited reduction in glucose level. At 600 mg/kg leaf extract of *Pterocarpus indicus* decreased glucose level on alloxan induced mice to 153.33±3.61 mg/dl on day 14 from 210.16±6.91 mg/dl. Previously, using the same extraction on another species *Pterocarpus marsupium* heartwood at 100 mg/kg showed a diminished level of glucose in blood on STZ induced diabetic model by 287±6.91 mg/dl at day 14 was observed (Mishra et al., 2013). Although, same solvent was used for the extracts, *Pterocarpus* marsupium showed a relatively better antidiabetic effect.

For the evaluation of CNS depressant effects of *Pterocarpus indicus* plant extract, the hole cross method is a good indicator as the locomotion and nervousness of the test group was compared with the control group and standard group. This CNS depressant produces an effect by elevated production of GABA. Phytochemicals like alkaloids, flavonoids and glycosides have CNS depressant effects. Our study showed significant reduction in movement from the 0 minutes to the 120 minutes by 9.2 times on the other hand, at 500 mg/kg alcohol extract of similar doses showed 4.75 times reduction in locomotion (Rahman et al., 2021). Hence significant CNS depressant ability of leaf extract of *Pterocarpus indicus* was evident.

Chapter five

Conclusion and future perspectives

Pterocarpus indicus has great potential for pharmacological effects like, antihyperglycemic, antihypertensive, antiulcerant, antidepressant, analgesic, anticancer properties similar to other species of the genus *Pterocarpus*. In our study, the ethanol leaf extract of *Pterocarpus indicus* showed potent analgesic activity of the plant extract in mice at doses up to 600 mg/kg by decreasing the number of contractions in acetic acid writhing method. Similarly, in an alloxan induced diabetic test, significant reduction in blood sugar level was observed within the animal model and CNS depressant effect by hole cross method. Hence, the extract significant antidiabetic, potent analgesic and CNS depressant effects in preclinical trials for safety purposes. Further research can be done to investigate other properties of the sample extract.

Future perspectives

Although *Pterocarpus indicus* has a large market for introducing itself as a multidimensional medicinal plant, only few researches have been conducted. To develop a novel drug various aspect can be discussed in near future-

- To demonstrate the exact mechanism of action for the therapeutic action of this plant and identify individual compounds present in this crude extract using HPLC, GC-MS, and NMR techniques.
- Extraction and study of other extracts like stem, and bark of *Pterocarpus indicus* using ethanol, methanol as solvents.
- Formalin test can be done for further clarification of analgesic activity.

- Open field test for evaluating CNS depressant activity.
- Investigation of antidiarrheal, antipyretic, antihyperlipidemic and many more on leaf extract.
- Performing preformulation studies for drug design.
- Clinical trials for evaluating analgesic, antidiabetic, CNS depressant activity.

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