Evaluation of Anti –diabetic activity of Asteracantha longifolia in Long Evans Rats

A research paper is submitted to the Department of Pharmacy, East West University in conformity with the requirements for the degree of Bachelor of Pharmacy.

Submitted by

Jannatul Ferdous Setu

ID: 2013-3-70-018

Supervised by

Dr. JMA Hannan
professor
Department of Pharmacy

East West University

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Abstract

Asteracantha longifolia (L.) Nees, Acanthaceae, is a source of the ayurvedic drug, 'Kokilaaksha' and the Unani drug, Talimakhana. The seeds are acrid, bitter, aphrodisiac, tonic, sedative, used for diseases of the blood. The plant is known to possess antitumor, ant diabetic , aphrodisiac, antibacterial, free radical scavenging and lipid peroxidation, hepatoprotective and haematopoietic activity. It contains lupeol, stigmasterol, butelin, fatty acids, and alkaloids. The present review article is focused on phytochemical, pharmacological and other important aspects of Talimakhana.In the current study , the ethanolic extract of Asteracantha longifolia is in vestigated to con firm its properties and activities mentioned in the traditional medicine .This research includes study on anti diabetic activity by Disaccharidase test and six segment investigations . Six Segment method, the amount of sucrose unabsorbed in different GIT segments were evaluated in control rats vs. rats fed with 100mg/kg extract at 30 minutes, 1hour, and 2hour. In assessing the effect of the plant materials on intestinal disaccharidase activity, the amount of unabsorbed sucrose in Pancreatic Enzymes are evaluated in control rats vs rats fed with 100mg/kg extract. The extract caused a significant ($p<0.05$), dose dependent inhibition of glucose absorption and showed hypoglycemic effects in Long-Evans rats weighing about 100-200 gm.The objective of the study was to evaluate the antti diabetic activity of ethanolic fraction of Asteracantha longifolia and to probe into its mechanism of action. Asteracantha longifolia ethanolic extract showed significant antidiabetic activity .This study suggest that ethanolic extract of Asteracantha longifolia has significant antidiabettic effect in a dose dependant manner and these may be effective in the treatment of diabetes .

Keywords: Anti-Diabetic, Asteracantha longifolia, , Hypoglycemic, Glucose, Sucrose.

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Declaration by the candidate

I, Jannatul ferdous setu hereby declare that the dissertation entitled Evaluation of Anti – diabetic activity of **Asteracantha longifolia** in Long Evans Rats submitted by me to the Department of Pharmacy, East West University and in the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, work carried out by us during the period 2017 of our research in the Department of Pharmacy, East West University, under the supervision and guidance of Dr. JMA Hannan , Professor, Department of Pharmacy, East West University. The thesis paper has not formed the basis for the award of any other degree/diploma/fellowship or other similar title to any candidate of any university.

_____

Jannatul Ferdous Setu
ID:2013-3-70-018
Department of Pharmacy
East West University

Certificate by the Supervisor

This is to certify that the thesis entitled Evaluation of Anti –diabetic activity of **Asteracantha longifolia** in Long Evans Rats submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, was carried out by Jannatul Ferdous Setu (student ID:2013-3-70-018) During the period 2016-2017 of their research in the Department of Pharmacy, East West University, under the supervision and guidance of me. The thesis has not formed the basis for the award of any other degree/diploma/fellowship or other similar title to any candidate of any university.

_____

Dr. JMA Hannan
Professor & Supervisor
Department of Pharmacy
East West University, Dhaka.

Certificate by the Chairperson

This is to certify that the thesis entitled Evaluation of Anti –diabetic activity of **Asteracantha longifolia** in Long Evans Rats submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, was carried out by Jannatul Ferdous Setu(ID 2013-3-70-018)During the period 2016-2017 of their research in the Department of Pharmacy, East West University.

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Dr. Chowdhury Faiz Hossain
Chairperson & Professor
Department of Pharmacy
East West University, Dhaka

Introduction

1.1 Rationale of the work

Plants have been used for mankind as remedies from the very beginning of civilization and an impressive number of modern drugs have been isolated from natural sources, many based on their use in traditional medicine. It has been noted that the original source of many important Pharmaceuticals in current use have been plants used by indigenous people. This is because plant sources provide the most diverse range of medicinal substances. Well known examples of medicinal products derived from plant sources include atropine, .morphine (narcotic analgesic derived from opium poppy) and cinchona bark (anti-malarial agent). Though synthetic sources had become the most popular source of medicinal products for a certain period of time, the importance of plant sources has highly increased due to the reduced effectiveness and increased toxicities of the former.

With onset of scientific research in herbals, it is becoming clearer that the medicinal herbs have a potential in today's synthetic era, as numbers of medicines are becoming resistant. According to one estimate only 20% of the plant flora has been studied and 60%of syntheticmedicines owe their origin to plants. Ancient knowledge coupled with scientific principles can come to the forefront and provide us with powerful remedies to eradicate the diseases.

The practice of traditional medicine is widespread in China, India, Japan, Pakistan, Sri Lanka and Thailand. In China about 40% of the total medicinal consumption is attributed to traditional tribal medicines. In Thailand, herbal medicines make use of legumes encountered in the *Caesalpiniaceae,* the *Fabaceae,* and the *Mimosaceae.* In the mid-90s, it is estimated that receipts of more than US$2.5 billion have resulted from the sales of herbal medicines. And, in Japan, herbal medicinal preparations are more in demand than mainstream pharmaceutical products .

The medicinal plants are rich in secondary metabolites (which are potential sources of drugs) and essential oils of therapeutic importance. The important advantages claimed for therapeutic uses of medicinal plants in various ailments are their safety besides being economical, effective and their C. roseus availability Because of these advantages the medicinal plants have been widely used by the traditional medical

practitioners in their day to day practice. According to a survey (1993) of World Health

Organization (WHO), the practitioners of traditional system of medicine treat about 80% of patients in India, 85% in Burma and 90% in Bangladesh.

1.2 Objective of the work

Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been isolated from natural sources, many based on their use in traditional medicine. It has been noted that the original source of many important Pharmaceuticals in current use have been plants used by indigenous people. It has been reported that about 64% of the total global population remains dependent on traditional medicine and medicinal plants for provision of their health-care needs. Apart from the use in the treatment of illness through self-medication, these medicinal plants are valuable for modern medicine in other ways. The use of traditional medicine and medicinal plants in most developing countries, as a normative basis for the maintenance of good health, has been widely observed.

Bangladesh imports a large quantity of pharmaceutical raw materials including medicinal plants and semi processed plant products to produce drugs and medicines. This huge foreign exchange can be saved if the indigenous medicinal plants or their semi-processed products are utilized by the manufacturers to satisfy their needs.

Bangladesh is a good repository of medicinal plants belonging to various families, including Acanthaceae. *Asteracantha longifolia* a plant belonging to this family. Although *Asteracantha longifolia* has not been evaluated in depth for its pharmacological properties, but it has its traditional use in numerous medical conditions.

The aims of the present investigation were (1) Anti-diabetic effects of ethanol extract by six segment method. (2) Anti-diabetic effects of ethanol extract by gut perfusion method. (3) Anti-diabetic effects of ethanol extract by Fasting blood glucose level test. (4) Anti-diabetic effects of ethanol extract by Glucose Tolerance test

1.3Plants as Therapeutic tools

With the development of human civilization, the implementation of phototherapy exhibits a stepwise development, which can be enumerated as-

1.3.1 First stage: Crude drugs were employed, prepared in the roughest manner, such as powdered willow bark in the management of pain.

1.3.2 Second stage: These were converted into more active and manageable forms, such as ' extracts or solution, watery or alcoholic.

1.3.3 Third stage: The pure active principles separated from the crude drugs were employed, e.g. salicylic acid.

1.3.4 Fourth stage : Attempt to synthesize the active drug in the laboratory and indeed structural modification e.g. aspirin ,the wonder drug .

1.4 Approaches to Drug Discovery from Plants

There are many approaches to the search for new biologically active principles in higher

plants one can simply look for new chemical constituents and hope to find a biologist who is willing to test each substance with whatever pharmacological test is available. This is not considered to be a very valid approach. A second approach is simply to collect every readily available plant, prepare extracts, and test each extract for one or more types of pharmacological activity. This random collection, broad screening method is a *Asteracantha longifolia* onable approach that eventually should produce useful drugs, but it is contingent on the availability of adequate funding and appropriate predictable bioassay systems . Modern drug development from plant source is carried out according to a synthetic investigation as ascribed .Selection and correct identification of the proper medicinal plant.

2. Collection of plant at suitable time.
3. Drying the plant or plant parts by cutting into suitable size.
4. Grinding and sieving to obtain powdered drug.
5. Extraction with suitable solvent(s).
6. Detection of biological activity crude extract and establishment of a bioassay system to permit the identification of the active fractions and rejection of the inactive ones.

1.5 Medicinal Plants: Indirect Contribution to Modern Synthetic Drugs

Plants have contributed and are still contributing to the development of modern synthetic drugs and medicine in a number of ways as stated below:

- Novel structures of biologically active chemical compound, isolated from plant sources, often prompt the chemist to synthesize similar or better semi-synthetic compounds.
- Synthetic drugs with similar or more potent therapeutic activity often prepared by structural modification of the plant-derived compounds with known biological activity.Various analogues and derivatives of plant constituents with similar or better pharmacological actions and therapeutic properties are often prepared by chemists for use as potent drugs.

1.6 Medicinal plants of Bangladesh

Homatropine (a synthetic tropane alkaloid similar to atropine), syrosingopine (a synthetic derivative of reserpine), chloroquine (a synthetic derivative of quinine) dihydro- morphinone, methyldihydromorphinone, oxymorphine, ethymorlhine and N-alkylnormorphine (synthetic derivatives of morphine) are some example of such synthetic drugs, which plants have contributed indirectly. Even in age of synthetic drugs, there are some naturally occurring drugs, such as the Digitalis glycosides used in cardiac complications and the Catharanthus alkaloids used in cancers. Those have no synthetic alternatives, in such cases, plants continue to remain as their principal and only sources .There are approximately 5000 plant species in Bangladesh of which about 1000 are thought to possess medicinal properties .More than 250 of these plants are used in the traditional systems of medicine that serves as the primary healthcare for most of the people of Bangladesh. The most commonly used plants are *Rauwolfia Serpentian*(treating high blood pressure, insanityand insomnia), *Terminalia arjuna*(treating heart diseases), *Allium Sativum*(reducing blood cholesterol level), *Coccinea Indica*(management of diabetes). So, research in medicinal plants is a vital sector for the discovery of promising drugs in Bangladesh.

1.7 Research in medicinal plants

In the perspective of developing countries like Bangladesh, research on indigenous plants has additional significance. The economic condition of the people of this country is not bright. They can hardly afford to spend much money for the prevention and cure of their disease. As a result, about 70-80 percent of the populations of this country still have to depend on the indigenous systems for the maintenance of their health. So, continued research on indigenous medicinal plants is essential in order to:

- Establish scientific evidence of their pharmacological use.
- Isolate the active constituent. This may offer a local natural source of a commonly used drug or a novel therapeutic agent.
- Modernize the indigenous systems.
- Provide cheap health care services for the general people.
- Earn substantial foreign exchange by exporting medicinal plants to other countries.

1.8 Important medicinal plants and their uses

Plant Common name	Botanical Name &Family	Parts Used	Medicinal Use
Amla	EmblicaofficinalisFam-euphorbiaceac	Fruit	Vitamin - C, Cough, Diabetes, cold, Laxativ, hyper acidity.
Ashok	SaracaAsocaFam : Caesalpinanceac	Bark Flower	Menstrual Pain, uterine, disorder, Deiabetes.
Aswagandha.	WithaniaSomniferaFam: Solanaccac	Root, Leafs	Restorative Tonic, stress, nerves disorder, aphrodiasiac.
BhumiAmla	PhyllanthousamarusFam : euphorbiaccac	Whole Plant	Aenimic, jaundice, Dropsy.
Guluchi / Giloe	TinosporaCordifoliaFam	Stem	Gout, Pile, general debility, fever, Jaundice.
Kalmegh/ Bhuineem	AndrographisPaniculataFam : scanthaccac	Whole Plant	Fever, weekness, releaseof gas.
Long peeper /	Peeper longumFam :	Fruit, Root	Appetizer, enlarged spleen

Pippali	Piperaccac		,Bronchities, Cold, antidote.
Makoi	SolanumnigrumFam: Solanaccac	Fruit/whole plant	Dropsy, General debility, Diuretic, anti dysenteric.
Sandal Wood	Santalum Album Fam: santalinaccac	Heart wood , oil	Skin disorder, Burning, sensation, Jaundice, Cough.
SarpaGandha	RanwolfiaSerpentina Fam: apocynaccac	Root	Hyper tension, insomnia.

PLANT INFORMATION

Asteracantha longifolia

flower

seeds

Plant profile :

Scientific classification –

Kingdom: Plantae

Division: Angiospermae

Class: Equisetopsida C. Agardh

Order: Personales

Family: Acanthaceae

Genus: *Asteracantha*

Species: *Asteracanthalongifolia*

Synonyms

The plant Astercantha is known in Latin as Hygrophila auriculata (Schum).Hygrophila spinosa Anders and Astercantha longifolia (Linn.) Nees, belonging to family Acanthaceae.Its synonyms are - Hygrophila auriculata (Schumach); Heine; Hygrophila spinosa T. Andes. In Sanskrit it is known as Ikura, Atichhatra and Vajra; in Bengali it is known as Kuliakhara; in Guajarati it is known as Ekharo; in Hindi it is known as Gokhulakanta, Kailaya and Talmakhana; in Malayalam it is known as Nermulli; in Marathi it is known as Talimakhana; in Tamil it is known as Golmidi, and in Urdu it is known as Talmakhana. In Kannan it is known as Kalavankabija and in Telugu it is known as Gobbi, and Neerugobbi. In Malayalam it is called as Culi, Nirchuli, and Vayalkuli.In Bengali it is called as Kuliakhara, and Kulekhade.

INTRODUCTION

A number of aquatic weeds and wetland-herbs have been found to have immense medicinal values, and Tal- makhana is one of them. It is taxonomically known as *Astercantha longifolia* Linn. Nees. Traditional - medicinal applications and pharmacological studies of the plant revealed by ancient literature and modern researches show that *Astercantha longifolia* is a plant of immense medicinal and ethno -botanical importance. It is robust and erect, annual herb with sub-quadrangular thickened nodes; oblanceolate leaves with yellow spines in axils, flowers pale to purple blue, densely clustered in axils, and fruits oblong, glabrous capsules 4 to 8 seeded.

Figure : *Astercantha longifoli*a growing in the wild.

Morphological Features

It is a spiny, stout, annual herb, common in water logged areas. The plant has a number of fasciculated, usually unbranched sub glandular stems, each 60 to 120 cm tall. The stems have nodules hispid with long hairs. Leaves are sessile, oblong-lanceolate or linear lanceolate, spines yellowish brown and 2 to 3 cm (sometimes more) long. These are found in whorls of 6 at each node. The two outer leaves of the whorl remain much larger than the four inner ones. Each leaf is greenish brown in colour. These are acute, entire and hairy.

Flowers are yellowish brown to blue in colour. These usually occur in apparent whorls of eight in four pairs at each node. Bracts occur on nodes. These are usually 2.5 cm long with long and white hairs. Corolla is about 3 cm long, widely two lipped,

tube about 1.6 cm long, abruptly swollen at top. Stamens are four in number, didynamous with the second pair larger. Calyxes are four- partite with upper sepal 1.6 to 2 cm long, broader than the upper three. Calyxes are linear, lanceolate, and coarsely hairy on the back and with hyline ciliated margins. Fruits are two celled, linear, and oblong, compressed about 8cm long, and pointed 4 to 8 seeded capsules. These have single layer of epidermis covered with striated cuticle, followed by 5 to 10 layered, thick walled, oval to hexagonal, lignified sclerenchymatous cells. Seeds are ovate, flat or compressed, 0.2 to 0.25 cm long and 0.1 to 0.1 to 0.15 cm wide, hairy, appearing smooth when soaked in water immediately get coated with mucilage, light brown, taste slightly bitter and odour not distinct.

Figure: Showing thorns, sepals and petals

Distribution

This plant is widely distributed throughout tropical and sub-tropical regions of India and other parts of the world including Phillippines, Srilanka, Burma, and Malaya, Nepal and in many other parts of the world. It is usually found in stagnant streams, freshwater swamps and ponds and alongside river beds. In India it is seen luxuriously growing in wet low lands near roads, buildings, and Tals (swallow water filled low lands).However, with the activities of habitat destruction, and fast reclamation of low lands the herb is disappearing fast.

Ayurvedic and Ethno-herbological considerations

The plant Astercantha longifolia is a source of Kokilaksha, the Ayurvedic drug and Talimakhana, the Unani drug. The plant has been described in the Ayurvedic treatise like Sushruta Samhita and Charak Samhita as Rasayana or rejuvenator. What is a Rasayana? Well, it is a specific category of drugs of Indian Ayurvedic System. The word Rasayana is composed of Rasa meaning elixir and Ayana meanng House. Thus the word Rsayana signifies the property of plant that helps to rejuvenate the system.

Rasayana have been being used for the management of neurodegenerative diseases, as rejuvenators, immunomodulators, aphrodisiac and tonic (Thakur et al., 2007). This plant has been described as Iksura, Ikshugandha, and Kokilaksha in Ayurvedic literature. The Sanskrit word Kokilaksha literally means an eye of the cuckoo. The flowers of this plant resemble in the color of cuckoo's eyes, hence the name. According to Vaidya, 1970, its parts form constituents of Ayurvedic preparation Striativallabhpug pak and Rativardhan yog. These medicines are recommended to improve sexual behavior of women. It also acts as a general tonic.

According to Ayurveda, the extract of the plant or of its parts can be administered for following actions –

- In breaking and expulsion of kidney stones .To nourish genital system so as to enable even an old person to enjoy his sexual life like a young person .

- To enhance the strength of body .It can nourish each and every cell of the body and it is due to this property that it is useful in emaciation and malnutrition conditions .In a nut shell the plant can be used for –
- Nourishing the genital system
- Enhancing body strength
- Nourishing each and every cell of the body
- Breaking and expulsing kidney stones
- Protecting liver actions

Phytochemicals contained in different parts of the plant

The extract of leaves has been reported to contain phenolics and flavonoide. Thus it shows promising antioxidant activity. Swadogo et al., 2006 have reported that methanolic extract of leaves of this plant contain phenolic and flavonoide showing promising antioxidant activity. Dasgupta and De 2007 have reported that the aqueous extract of leaves of A. longifolia showed potent antioxidant activity in various in vitro models.

Nadkarni, 1978 and Chopra et al. 1986 have reported that the whole plant of A. longifolia has great Ayurvedic and ethno-medicinal properties. The whole plant including ashes is extensively used in traditional systems of medicine for treating various types of ailments like rheumatism, inflammation, jaundice, hepatic obstruction, pain, urinary infections, oedema and gout.

In Ayurvedic system the plant has been classified as Seethviryam, Madhuravipaka and is used for the treatment of Premeham (diabetes), arthisaram (dysentery) etc.

Vijay Kumar et al. 2006 who studied the impact of Ethanol extract of aerial parts of A. longifolia on rats, found that when administered at the rate 100 and 200mg/kg of body weight for three weeks it showed significant reduction in blood glucose level. Decrease in thiobarbituric acid reactive substances (TBARS) and Hydro peroxide in both liver and kidney was also observed. The treatment with ethanol extract has also

been reported to increase the glutathione s- transferase (GST) and catalase (CAT) in drug treated group comparable to the control group. These rats also showed decrease in Lipid peroxidation which is associated with increased activity of superoxide dismutase and catalase.

The effect of hot water extract of A. longifolia on glucose tolerance of normal human beings and maturity onset diabetic patients has been investigated by Fernando et al. (1991).Hewawasam et al., 2003 and Usha et al., 2007 have found that aqueous extract of Panchang (all the five parts of the plant root, stem, leaves, flowers, fruits) of A. longifolia possesses hepatoprotective and antioxidative properties against CCL4 – and paracetamol induced hepatotoxicities.

Singh and Handa, 1999 have reported that methanolic extracts of the seeds of the plant show hepatoprotective activity against paracetamol and thioacetamide intoxication in rats. Shalajan et al., 2005 have showed that the slurry of the whole plant was hepatoprotective against CCl4 induced liver dysfunction in rats. Later in 2007 they also showed that the slurry, aqueous extract and ethanol extract of the whole plant powder were hepatoprotective against galactosamine induced hepatotoxicity. Thus it can be inferred that the extract of the whole plant of A. longifolia is hepatoprotective and can further be examined for synthesizing hepatoprotective and anti- diabetic medications.

Patra et al.009a; 2009b have reported that chloroform and alcoholic extracts of A. longifolia have anti-inflammatory, analgesic and anti-pyretic activities. Earlier, Patra et al., 2008 have reported that petroleum ether, chloroform, alcohol, and aqueous extract of leaves of the plant produced significant anthelmintic activity and both the alcoholic and chloroform extracts of the plant showed significant anti-bacterial activity. Thus, it is inferred that the extract of A. longifolia can be used as anti-inflammatory and analgesic agent.

Mazumdar et al., 1996 have reported that petroleum ether extract of root of A. longifolia caused significant increase in WBC count. Pawar et al.2006a;2006b have reported that petroleum ether and chloroform extract of leaves showed hematopoietic

activity by increasing the erythrocyte count, leucocyte count, and hemoglobin level significantly. Thus, it can be concluded that the extract of the plant A. longifolia can be administered for hematopoietic activities and further researches are needed to synthesize medications for such activities from the extract of the plant.

Mazumdar et al., 1997 found that administration of extract of the plant repressed the rapid increase of body wight of tumor bearing mice. Ahmad et al., 2001 studied the effect of application of methanol extract of seeds of A. longifolia and found that it inhibits hematocarcinogenesis in Wistar rats. The petroleum ether extract of A. longifolia roots exhibited antitumor activity in Ehrlich ascites carcinoma and sarcoma- 180 bearing rats. It has been reported that the administration of extract of this plant suppresses the tumor fluid volume significantly.

Chauhan et al., 2009, 2010 studied the impact of administration of seed extract of A. longifolia on sexual behavior of rats in dose dependent manner. It was found to improve the histo-architecture of testes and increase the concentration of sperm count in epididymis and also increase the testosterone level. These findings confirm that the extract of seeds of A. longifolia can be administered for enhancing the sexual power and activity in humans.

Phytochemicals found in different parts of *A. longifolia*

A number of studies confirm the phytochemical content of A. longifolia. It contains various phytochemicals in varying amounts in its different parts. The entire plant has been reported to contain lupeol, stigmasterol, an isoflavon glycoside, an alkaloid and small quantities of uncharacterized bases. The oil extracted out from its seeds contains about 23 % of linoleic acid, 10% of oleic acid, 12% of stearic acid, 6% of palmitic acid and small quantity of myristic acid.Sondhi and Agarwal,1995 isolated a number of minerals from the plant using Flame photometer, Atomic Absorption Spectrometer and Inductively coupled plasma. They found that the plant contained Mn, Mg, Zn, Ca, Fe, Ni, Cr, Na, K, Al, and Sr. Chowdhary and Bandhyopadhyay, 1998 confirmed the presence of Fe, Cu, and CO in the plant extract.Quasim and Dutta, and 1967 studied the root contents of the plant and found that it contained stigmasterol. The aerial parts of the plant contain lupeol, stigmasterol, and butelin. Seeds of the plant are reported to

contain fatty acids as principal constituents. Mishra et al.2001, isolated two aliphatic easters from the aerial part of the plant.

Thus, from various researches done so far it has been confirmed that the plant A. longifolia contains Apignin-7-0-glucoside, 7-0- glucoside, histidine, lysine, phenylalanine, linoleic acid, palmitic acid, stearic acid, xylos, uronic acid, polysaccharides, xylan, protease, lupeol, betulin, phytosterol, ascorbic acid, nicotinic acid etc. Longifolia, A. (2017)

PHARMACOLOGICAL ACTIVITIES

Anti-diabetic (hypoglycemic) effects

Muthulingam investigated the effect of leaf extract of *Asteracantha longifolia* on diabetic rats. It appears that *Asteracantha longifolia* increased insulin secretion which brought glucose back to normal levels. The antidiabetic effect of leaf extracts of *Asteracantha longifolia* may be due to increased release of insulin from the existing beta-cells of pancreas similar to that observed after glibenclamide (antidiabetic drug) administration.

Liver Damage Protection

Many animal studies are suggesting that seed as well as root of *Asteracantha longifolia* extract may possess liver damage protection effects.

Hematopoietic activity

Petroleum ether extract of root from A. longifolia increases WBC count significantly. Ethanolic extract (100 and 200 mg/kg) of the aerial parts of H. spinosa significantly increased the hemoglobin, hematocrit, RBC and total WBC, as compared with vehicle treated control rat. In anemic male albino rats, the extract significantly increased hemoglobin, hematocrit and RBC count. Petroleum ether and chloroform extract of leaves show hematopoietic activity as it significantly increases erythrocyte count, leukocyte count, and hemoglobin count

(Pawar et al, 2006)

Antioxidant Activity

Aqueous extract of leaves of A. longifolia shows potent antioxidant activity in various in vitro model

(Sathya A, 2012)

Aphrodisiac Activity

The ethanolic extract of seeds shows androgenic as well as improvement of sexual behavior of rat in dose dependent manner, it also improve the histoarchitecture of testis and increase the concentration of sperm count in epididymis and also increase testosterone level.

(Chauhan et al, 2017)

Miscellaneous activity

Petroleum ether extract of root potentiated the sedative-hypnotic action of chlorpromazine, diazepam, pentobarbitone, chlordiazepoxide and protected against strychine-induced convulsions. Preliminary study shows it possess diuretic activity. Aqueous extract of root and leaves cure patient suffering from dropsy .Ethanolic extract of whole plant showed diuretic effects in rats.

Non medicinal use

Talmakhana is used in the preparation of fuchka in Bangladesh. It is a popular snack in Bangladesh.

Mechanism of Action

Scientific findings on the action mechanisms of the plant compounds have proposed many means in which they act to provide the anti-hyperglycemic and anti-hyperlipidemic effects. Some of them relate to their effects on the activity of pancreatic ß cells (synthesis, release, cell regeneration/revitalization) or the increase in the protective/inhibitory effect against insulinase and the increase of the insulin sensitivity or the insulin-like activity of the plant extracts. Other mechanisms involve improved glucose homeostasis including an increase of peripheral utilization of glucose, an increase of synthesis of hepatic glycogen and/or decrease of glycogenolysis acting on enzymes, inhibition of intestinal glucose absorption, reduction of glycogenic index of carbohydrates, reduction of the effect of glutathione.

1.9 Diabetes mellitus (DM):

Introduction:

Diabetes mellitus (DM) is now one of the most common non-communicable diseaseglobally. Conventional medical treatments are available to control diabetes and its complications. However, some people also try complementary and alternative medicine (CAM) therapies, including dietary supplements. The seeds of *Asteracantha longifolia* commonly known as talmakhna, have been traditionally consumed in various forms for treatment of diabetes. Moreover, the crushed seeds of the tree are used to treat most effective cold , jaundice ,cough . Roots are sweet, sour, bitter, refrigerant, diuretic, anti-inflammatory, analgesic, haemopoictic, hepatoprotective and tonic. It is useful in inflammations, hyperdipsia, strangury, jaundice and vesical calculi. It is also used in flatulence and dysentery. Leaves are haemopoictic, hepatoprotective, anti-inflammatory, antioxidant, analgesic, antidiabetic, stomachic, ophthalmic, diuretic and liver tonic. It is used in hepatic obstruction, jaundice, arthritis, rheumatism and diseases of urinogenital tract. It is useful in flatulence and other stomach related diseases. It is useful in anemia and for treating blood diseases. It is used to lower the blood sugar level. Seeds are gelatinous, febrifuge, rejuvenating and nervine tonic. It is used in burning sensation, fever and headaches. It is also used in diarrhoea and dysentery. A paste of the seeds mixed with buttermilk or whey, is given for diarrhoea. A decoction of the roots is used as a diuretic and to treat rheumatism, gonorrhoea, and other diseases of the genito-urinary tract, jaundice and anasarca.

Diabetes is undoubtedly one of the most challenging health problems in the 21st century. Complications from diabetes, such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society. Amongst ethnic minorities, cultural beliefs about diabetes mellitus often differ and may compromise adherence to therapy. Complementary and alternative medicine involves the use of herbs and other dietary supplements as alternatives to mainstream Western medical treatment. Diabetes mellitus is a condition in which a person has a high blood sugar (glucose) level as a result of the

body either not producing enough insulin, or because body cells do not properly respond to the insulin that is produced. Insulin is a hormone produced in the pancreas which enables body cells to absorb glucose, to turn into energy. If the body cells do not absorb the glucose, the glucose accumulates in the blood (hyperglycemia), leading to various potential medical complications.

In traditional practice medicinal plants are used in many countries to control diabetes mellitus. The hypoglycemic action of these medicinal plants is being studied (Alarcon-Aguilara et al., 1993). Plant drugs are frequently considered to be less toxic and more free from side effects than synthetic ones (Pari and Umamaheswari, 2000). In the traditional system of Indian medicine plant formulation and in several cases, combined extracts of plants are used as the drug of choice rather than individual. Many of these have shown promising effects (Kumari and Devi, 1993). Various herbal formulations like D-400 (Mitra et al., 1996), Trasina (Bhattacharya et al., 1997S.K. Bhattacharya, K.S. Satyan and A. Chakrabrati, Effect of Trasina, an Ayurvedic herbal formulation, on pancreatic islet superoxide dismutase activity in hyperglycaemic rats. Ind. J. Exp. Biol. 35 (1997), pp. 297-299. View Record Scopus Cited By in Scopus are well known for their antidiabetic effects. Cogent db, a novel and unique herbal drug produced by Cybele Herbal Laboratories, Kerala, India for diabetes mellitus.Some of these are known to possess antidiabetic effects and have been used in indigenous systems of medicine to treat diabetes mellitus (Chattopadhyay; Prince and Sharma).

A recent study has estimated that up to 30% of patients with diabetes mellitus use complementary and alternative medicine. *Asteracantha longifolia* also known astalmakhna is a popular plant used for the treating of diabetes-related conditions.

Diabetes mellitus is a life-long disease affecting more than 150 million people all over the world and WHO has predicted the number will be doubled by the year 2025 (WHO 2002). Type 1 diabetes accounts for 5-10% of the diabetic population. Type 2 diabetes accounts for 90 - 95% of the people with diabetes and is more prevalent in adults (WHO 2002).

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (American Diabetes Association 2001). A consequence of the disease is adverse affects on both the macrovascular and microvascular system. Diabetic complications associated with macrovascular disease are atherosclerotic macrovascular disease and

ischemic coronary heart disease. Diabetic complications related to microvascular disease include retinopathy, nephropathy, neuropathy, and peripheral vascular disease

1.1.1 History

The term diabetes (Greek: 8iapfiTr|<;, diabetes) was coined by Aretaeus of Cappadocia. It was derived from the Greek verb Siapaivsiv, diabainein, itself formed from the prefix dia-, "across, apart," and the verb bainein, "to walk, stand." The verb diabeinein meant "to stride, walk, or stand with legs asunder"; hence, its derivative diabetes meant "one that straddles," or specifically "a compass, siphon." The sense "siphon" gave rise to the use of diabetes as the name for a disease involving the discharge of excessive amounts of urine. Diabetes is first recorded in English, in the form diabete, in a medical text written around 1425. In 1675, Thomas Willis added the word mellitus, from the Latin meaning "honey", a reference to the sweet taste of the urine. This sweet taste had been noticed in urine by the ancient Greeks, Chinese, Egyptians, Indians, and Persians. In 1776, Matthew Dobson confirmed that the sweet taste was because of an excess of a kind of sugar in the urine and blood of people with diabetes.

Diabetes mellitus appears to have been a death sentence in the ancient era. Hippocrates makes no mention of it, which may indicate that he felt the disease was incurable. Aretaeus did attempt to treat it but could not give a good prognosis; he commented that "life (with diabetes) is short, disgusting and painful."

Sushruta (6th century BCE) identified diabetes and classified it as Medhumeha. He further identified it with obesity and sedentary lifestyle, advising exercises to help "cure" it. The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine, and called the ailment "sweet urine disease" (Madhumeha). The Chinese, Japanese and Korean words for diabetes are based on the same ideographs ($tJP;;lp!) which mean "sugar urine disease".

In medieval Persia, Avicenna (980-1037) provided a detailed account on diabetes mellitus in The Canon of Medicine, "describing the abnormal appetite and the collapse of sexual functions," and he documented the sweet taste of diabetic urine. Like Aretaeus before him, Avicenna recognized a primary and secondary diabetes. He also described diabetic gangrene, and treated diabetes using a mixture of lupine, trigonella (fenugreek), and zedoary seed, which produces a considerable reduction in

the excretion of sugar, a treatment which is still prescribed in modern times. Avicenna also "described diabetes insipidus very precisely for the first time", though it was later Johann Peter Frank (1745-1821) who first differentiated between diabetes mellitus and diabetes insipidus.

The discovery of a role for the pancreas in diabetes is generally ascribed to Joseph von Mering and Oskar Minkowski, who in 1889 found that dogs whose pancreas was removed developed all the signs and symptoms of diabetes and died shortly afterwards. In 1910, Sir Edward Albert Sharpey-Schafer suggested that people with diabetes were deficient in a single chemical that was normally produced by the pancreas—he proposed calling this substance insulin, from the Latin insula, meaning island, in reference to the insulin-producing islets of Langerhans in the pancreas.

The endocrine role of the pancreasin metabolism, and indeed the existence of insulin, was not further clarified until 1921, when Sir Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski, and went further to demonstrate they could reverse induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs. Banting, Best, and colleagues (especially the chemist Collip) went on to purify the hormone insulin from bovine pancreas at the University of Toronto. This led to the availability of an effective treatment—insulin injections—and the first patient was treated in 1922. Insulin production and therapy rapidly spread around the world, largely as a result of this decision. Banting is honored by World Diabetes Day which is held on his birthday, November 14.

Despite the availability of treatment, diabetes has remained a major cause of death. For instance, statistics reveal that the cause-specific mortality rate during 1927 amounted to about 47.7 per 100,000 populations in Malta. Other landmark discoveries include:

- Identification of the first of the sulfonylurea in 1942
- Reintroduction of the use of biguanides for Type 2 diabetes in the late 1950s. The initial phenformin was withdrawn worldwide (in the U.S. in 1977) due to its potential for sometimes fatal lactic acidosis and metformin was first marketed in France in 1979, but not until 1994 in the US.
- The determination of the amino acid sequence of insulin (by Sir Frederick Sanger, for which he received a Nobel Prize)

- The radioimmunoassay for insulin, as discovered by Rosalyn Yalow and Solomon Berson (gaining Yalow the 1977 Nobel Prize in Physiology or Medicine)
- The three-dimensional structure of insulin (PDB 2INS)
- Dr Gerald Reaven's identification of the constellation of symptoms now called metabolic syndrome in 1988
- Demonstration that intensive glycemic control in type 1 diabetes reduces chronic side effects more as glucose levels approach 'normal' in a large longitudinal study, and also in type 2 diabetics in other large studies
- Identification of the first thiazolidinedione as an effective insulin sensitizer during the 1990s

In 1980, U.S. biotech company Genentech developed human insulin. The insulin is isolated from genetically altered bacteria (the bacteria contain the human gene for synthesizing human insulin), which produce large quantities of insulin. Scientists then purify the insulin and distribute it to pharmacies for use by diabetes patients.

1.1.2 Epidemiology

In 2000, according to the World Health Organization, at 171 million people worldwide suffer from diabetes, or 2.8% of the population. Its incidence is inrease rapidly, and it is estimated that by 2030, this number will almost double. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. The greatest icrease in prevalence is, however, expected to occur in Asia and Africa, where most patients will probably be found by 2030. The inrease in incidence of diabetes in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-Style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism (s) at present, though there is much speculation, some of it most compellingly presented.

According to the American Diabetes Association, approximately 18.3% (8.6 million) of Americans age 60 and older have diabetes. Diabetes mellitus prevalence increase with age, and the numbers of older persons with diabetes are expected to grow as the elderly population increase in number. The National Health and Nutrition Examination Survey (NHANES III) demonstrated that, in the population over 65

years old, 18% to 20% have diabetes, with 40% having either diabetes or its precursor form of impaired glucose tolerance.

Indigenous populations in first world countries have a higher prevalence and icreaseing incidence of diabetes than their corresponding non-indigenous populations. In Australia the age-standardised prevalence of self-reported diabetes in Indigenous Australians is almost 4 times that of non-indigenous Australians .

Preventative community health programs such as Sugar Man (diabetes education) are showing some success in tackling this problem.

1.1.3 Common Diagnosis

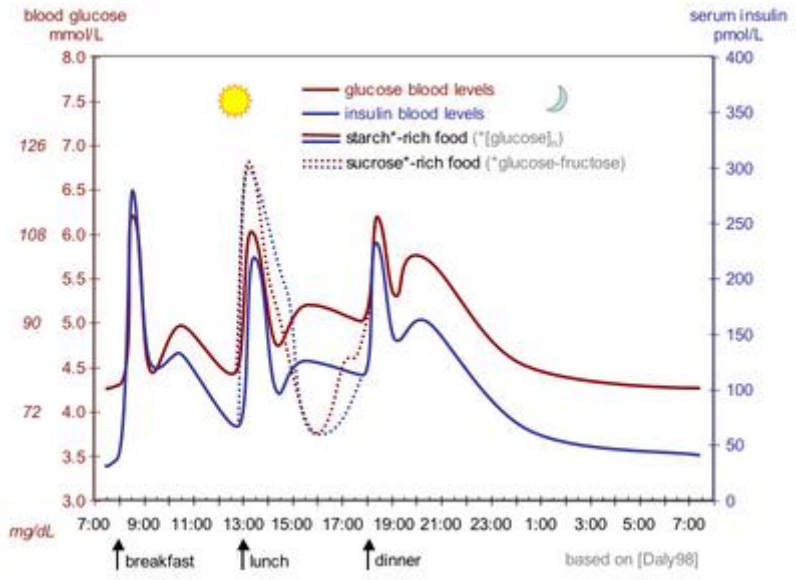
Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level at or above 7.0 mmol/L (126 mg/dL).
- Plasma glucose at or above 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test.
- Symptoms of hyperglycemia and casual plasma glucose at or above 11.1 mmol/L (200 mg/dL).
- Glycated hemoglobin (hemoglobin A1C) at or above 6.5. (This criterion was recommended by the American Diabetes Association in 2010; it has yet to be adopted by the WHO.)

About a quarter of people with new type 1 diabetes have developed some degree of diabetic ketoacidosis (a type of metabolic acidosis which is caused by high concentrations of ketone bodies, formed by the breakdown of fatty acids and the deamination of amino acids) by the time the diabetes is recognized. Diagnosis also includes ordinary health screening; detection of hyperglycemia during other medical investigations; and secondary symptoms such as vision changes or unexplainable fatigue. Diabetes is often detected when a person suffers a problem that is frequently caused by diabetes, such as a heart attack, stroke, neuropathy, poor wound healing or a foot ulcer, certain eye problems, certain fungal infections, or delivering a baby with macrosomia or hypoglycemia.

Glucose tolerance tests are also a valuable indicator and according to the current definition , two fasting glucose considered above 126 mg/dL (7.0 mmol/dL) is considered diagnostic for diabetes mellitus .

Condition	2 hour glucose	Fasting glucose
	mmol/l(mg/ dl)	mmol / l (mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Impaired fasting glycaemia	< 7.8 (<140)	≥6.1 (≥110) & <7.0(<126)
Impaired glucose tolerance	≥7.8 (≥ 140)	<7.0(<126)
Diabetes mellitus	≥11.1 (≥200)	≥ 7.0(≥126)



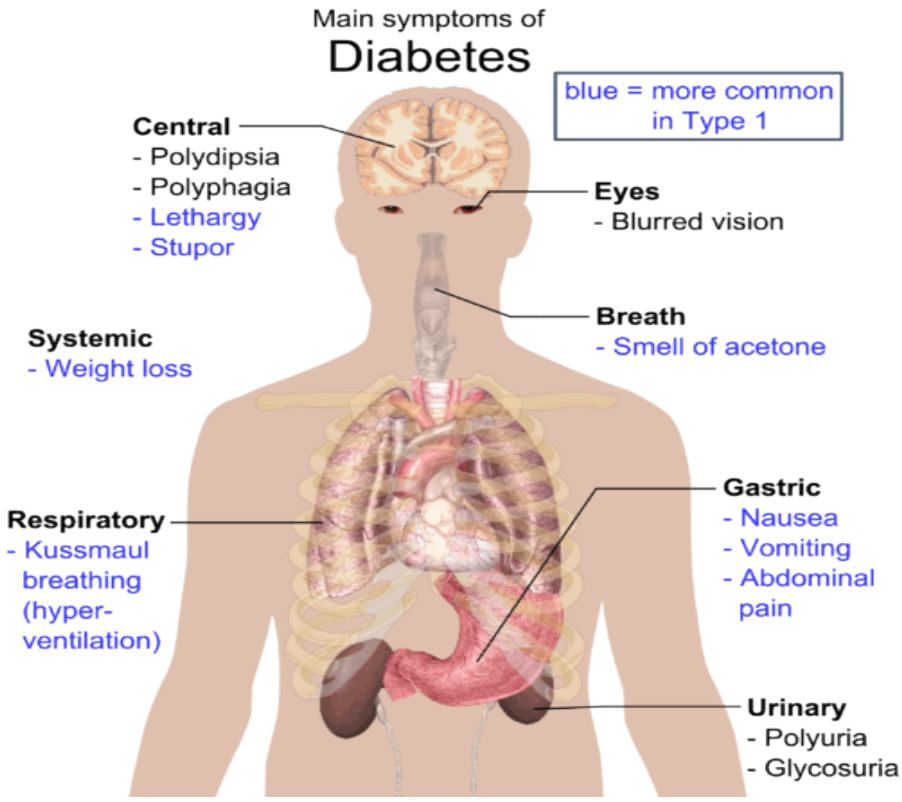
1.1.4 Screening

The screening test varies according to circumstances and local policy, and may be a random blood glucose test, a fasting blood glucose test, a blood glucose test two hours after 75 g of glucose, or an even more formal glucose tolerance test at various stages of life. Earlier screening is typically recommended for those with risk factors such as obesity, family history of diabetes, high-risk ethnicity (Hispanic, Native American, Afro-Caribbean, Pacific Islander, or Maori). People with a confirmed diagnosis of diabetes are tested routinely for complications. This includes yearly urine testing for microalbuminuria and examination of the retina of the eye for retinopathy.

1.1.5 Possible Complications

After many years, diabetes can lead to serious problems with your eyes, kidneys, nerves, heart, blood vessels, and other area in your body. In general, complications include: High blood pressure, damage to the blood vessels that supply the legs and feet (peripheral vascular disease) stroke, high cholesterol, nerve damage, other problems with the stomach and intestines, heart, and other body organs. It also includes: Foot sores or ulcers, which can result in amputation, worsening of eyesight or blindness due to diabetic retinopathy, macular edema, cataracts, glaucoma, kidney

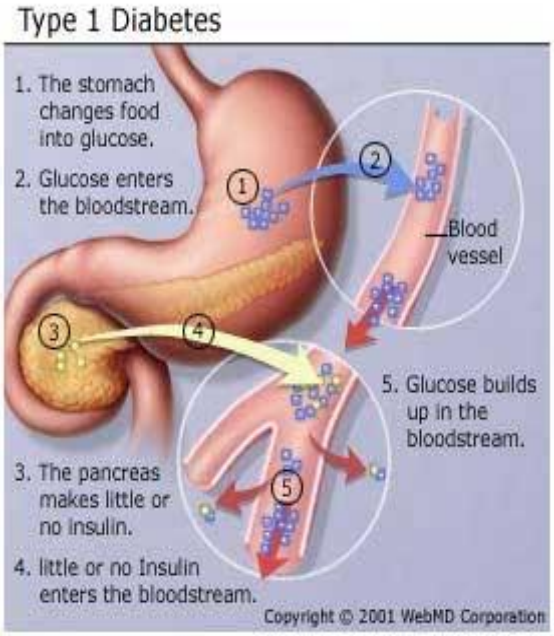
disease and kidney failure (diabetic nephropathy), erection problems, and infections of the skin, female genital tract, and urinary tract.



1.2 Classification of Diabetes Mellitus

The World Health Organization (WHO) classifies diabetes into main groups: type 1 diabetes also called insulin-dependent diabetes mellitus or IDDM and type 2 diabetes also called non-insulin dependent diabetes mellitus or NIDDM (WHO 2002). Maturity-Onset Diabetes of the Young (MODY) and gestinational diabetes are less frequently occurring forms of diabetes. It is also worth noting that the current classification of diabetes on the basis of age is becoming problematic because the age of individuals presenting type 1 diabetes is increasing getting older and there is increase of type 2 diabetes in the young. In addition increasing numbers of non-insulin dependent diabetic patients are becoming dependent on exogenous insulin administration.

1.2.1 Type 1 Diabetes



Type 1 diabetes, defined by an absolute requirement for administration of exogenous insulin, results from the autoimmune destruction of the insulin-secreting pancreatic beta cells. Type 1 diabetes is a severe form associated with ketosis in the untreated state. It arises most commonly in juveniles but occasionally in non-obese adults and elderly. It is a catabolic disorder hi which circulating insulin is virtually absent with elevated level of plasma glucagon. Exogenous insulin is therefore required to reverse the catabolic state, prevent ketosis and reduce the elevated blood glucose level. It is thought to result from an infectious or toxic environmental-induced autoimmune disorder (Karam 1998). Autoimmunity has beenproposed to be the main reasonon for (3 cell destruction associated with type 1 diabetes (Eisenbarth 1986, Rossini et al 1993).The pathogenesis of type 1 diabetes is initiated by activation of monocytes by unidentified factors from islet tissues. With the production of IL-1 by macrophages, nitric oxide and free radicals can be induced resulting in the abolishment of glucose-induced insulin secretion in pancreatic β-cells and ultimately β -cell death (Sandier et al 1989, Dunger et al 1996, Hoorens et al 2001, Suk et al 2001). The reason of auto-antigens due to destruction of β cells could further trigger the activation of T lymphocytes and the production of islet cell antibodies leading to a self-perpetuating and self-limiting circuit of cytokine production (Nerup et al 1988). The secretion of

tumor necrosis factor (TNF) by macrophages can also further enhance the effects of IL-1 on pancreatic (3 cells which is controlled by a gene in HLA regions (Nerup et al 1988). On the other hand, HLA-DR3, DR4, DR9, and HLA-DQ have been associated with susceptibility towards type 1 diabetes in various ethnic groups (Aparicio 1991, Baisch et al 1992, Ikegami et al 1992, Chuang et al 1995, Israel et al 1998). In addition, if one of a pair of identical twins has type 1 diabetes, the probability for the other to develop the condition is 20 - 30% (Abbas et al 1994, American Diabetes Association 2002). Therefore, genetic factors are considered to be quite important in type 1 diabtes .

Although the role of viral infections in inducing type 1 diabetes remains controversial, toxic chemicals with structural similarities to alloxan or streptozotocin, may contribute to pancreatic P cell demise and destruction in animal model of type 1 diabetes. This environmentally mediated cell destruction could result in accidental of self-antigens to the immune system leading to the triggering of islet-specific autoimmunity . The moderate to long-term symptomless phase of the disorder could readily be identified through circulating cytoplasmic auto-antibodies, such as islet cell cytoplasmic antibodies (ICA), including insulin autoantibodies (IAA) and glutamic acid decarboxylase .

1.2.1.1 Signs and Symptoms

Type 1 diabetes signs and symptoms can come on quickly and may include: Polyuria and polydipsia, incresed thirst and frequent urination, polyphagia Extreme hunger, weight loss,feeling tired or Fatigued, blurred vision.Other symptoms include: Losing the feeling or feeling tingling in your feet, deep, rapid breathing, dry skin and mouth, flushed face, fruity breath odor, nausea or , vomiting, unableto keep down fluids, stomach pain.Low blood sugar (hypoglycemia) can develop quickly in people with diabetes who are taking insulin. Symptoms typically appear when the blood sugar level falls below 70. Common symptoms and signs include: Headache, hunger, nervousness, rapid heartbeat, shaking, sweating, and weakness.

1.2.1.2 Signs and tests

The following tests can be used to diagnose diabetes:

- urinalysis shows glucose and ketone bodies in the urine, but a blood test is required for diagnosis
- fasting blood glucose is 126 mg/dL or higher
- random (nonfasting) blood glucose exceeds 200 mg/dL (this must be confimed with a fasting test)
- insulin test (low or undetectable level of insulin)
- C-peptide test (low or undetectable level of the protein C-peptide, a by-product of insulin production)

1.2.1.3 Causes:

Environment: Environmental factors can strongly influence expression of type 1. Despite having the exact same genome, one twin had the disease, where the other did not; this suggests that environmental factors, in addition to genetic factors, can influence disease prevalence.

Genetics: Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its expression. Depending on locus or combination of loci, it can be dominant, recessive, or somewhere in between.

1.2.1.4 Pathophysiology:

The cause of type 1 diabetes is not fully understood. Some theorize that type 1 diabetes is a virally triggered autoimmune response in which the immune system attacks virus infected cells along with the beta cells in the pancreas. The Coxsackie virus family or German is implicated, although the evidence is inconclusive. In type 1, pancreatic beta cells in the Islets of Langerhans are destroyed decreasig endogenous insulin production. This distinguishes type 1's origin from type 2 DM. The type of diabetes a patient has is determined only by the cause—fundamentally by whether the patient is insulin resistant (type 2) or insulin deficient without insulin resistance (type 1). Studies suggest presence of a

genetic vulnerability and there is indeed an observed inherited tendency to develop type 1. It has been traced to particular HLA genotypes, though the connection between them and the triggering of an auto-immune reaction is still poorly understood. A subtype of type 1 (identifiable by the presence of antibodies against beta cells) typically develops slowly and so is often confused with type 2. In addition, a small proportion of type 2 cases manifest a genetic form of the disease called maturity onset diabetes of the young (MODY).

Type 1 diabetes was previously known as juvenile diabetes because it is one of the most frequent chronic disease in children; however, the majority of new-onset type 1 diabetes is seen in adults. Scientific studies that use antibody testing (glutamic acid decarboxylase antibodies (GADA), islet cell antibodies (ICA), and insulinoma-associated (IA-2) autoantibodies) to distinguish between type 1 and type 2 diabetes demonstrate that most new-onset type 1 diabetes is seen in adults. Some chemicals and drugs preferentially destroy pancreatic cells. The exact cause(s) of type 1 diabetes are not yet fully understood, and research on those mentioned, and others, continues.

1.2.1.5 Management and treatment

Type 1 is treated with insulin replacement therapy-usually by insulin injection or insulin pump, along with attention to dietary management, typically including carbohydrate tracking, and careful monitoring of blood glucose levels using glucose meters. Today the most common insulin are biosynthetic products produced using genetic recombination techniques; formerly, cattle or pig insulins were used, and even sometimes insulin from fish. Major global suppliers include Eli Lilly and Company, Novo Nordisk, and Sanofi-Aventis. The immediate goals of treatment are to treat diabetic ketoacidosis and high blood glucose levels. Because type 1 diabetes can come on suddenly and the symptoms can be severe, newly diagnosed people may need to stay in the hospital. The long-term goals of treatment are to reeduce symptoms and prevent diabetes-related complications such as blindness, kidney failure, nerve damage, amputation of limbs, and heart disease. The treatment and management can be summarized as:

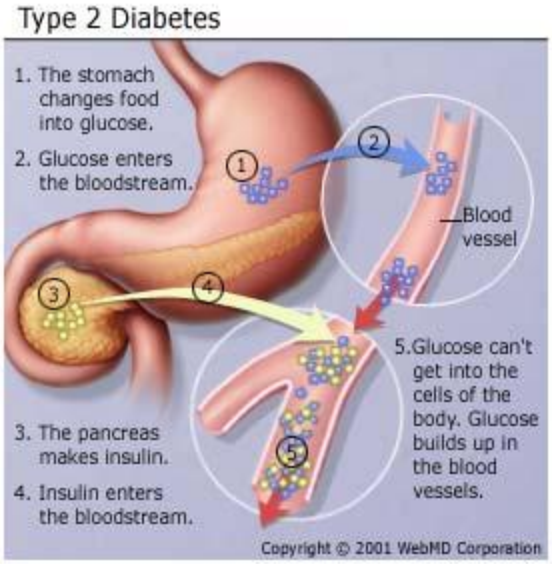
- Insulin: Insulin lowers blood sugar by allowing it to leave the bloodstream and enter cells. People with type 1 diabetes can't make their own insulin. They must take insulin every day. Insulin is usually injected under the skin. In some cases, a pump delivers the insulin continuously. Insulin does not come in pill form. More than one type of insulin may be mixed together in an injection to achieve the best blood glucose control.
- Diet: People with type 1 diabetes should eat at about the same times each day and try to be consistent with the types of food they choose. This helps to prevent blood sugar from becoming extremely high or low.

- Physical Activity: Regular exercise helps control the amount of sugar in the blood. It also helps burn excess calories and fat to achieve a healthy weight.
- Foot Care: Diabetes causes damage to the blood vessels and nerves. This can reduce your ability to feel injury to or pressure on the foot. The injury may go unnoticed and amputation of the affected limb may be needed when these skin ulcers do not improve or become larger or deeper. So special care must be taken with the foot.
- Treating low blood sugar: Hypoglycemia can develop quickly in people with diabetes. Symptoms typically appear when the blood sugar level falls below 70. If a hypoglycemic attack occurs eating something with sugar: 4 ounces of fruit juice, 3-4 Lifesavers candies, or 4 ounces of regular soda. Symptoms should go away within 15 minutes. If the symptoms don't go away, repeating the sugar-containing food as above, and testing the sugar level again until safe range is achieved.
- For extreme cases: Untreated type 1 diabetes commonly leads to coma, often from diabetic ketoacidosis, which is fatal if untreated.
  - Pancreas transplantation: Pancreas transplants are generally performed together with or sometime after a kidney transplant.
  - Islet cell transplantation: Islet cell transplantation is expected to be less invasive than a pancreas transplant which is currently the most commonly used approach in humans.

1.2.1.6 Prevention

Currently, there is no way to prevent type 1 diabetes. There is no effective screening test for type 1 diabetes in people with no symptoms. But possible approaches which are underway in the near future are: "Immunization" approach, DiaPep277 injection, inntra-nasal insulin, BCG research, diamyd vaccines.

1.2.2 Diabetes mellitus type 2:



Diabetes mellitus type 2 or type 2 diabetes (formerly called non -insulin-dependent diabetes mellitus (NIDDM), or adult-onset diabetes) is a disorder that is characterized (American Diabetes Association, 2001) by high blood glucose in the context of insulin resistance and relative insulin deficiency. Diabetes is often initially managed by increasing exercise and dietary modification. As the condition progresses, medications are typically needed. There are an estimated 23.6 million people in the U.S. (7.8% of the population) with diabetes with 17.9 million being diagnosed, 90% of whom are type 2. With prevalence rates doubling between 1990 and 2005, CDC has characterized the increase as an epidemic. Traditionally considered a disease of adults, type 2 diabetes is diagnosed in children in parallel to rising obesity rates due to alterations in dietary patterns as well as in life styles during childhood. Unlike type 1 diabetes, there is very little tendency toward ketoacidosis in type 2 diabetes, though it is not unknown. One effect that can occur is nonketonic hyperglycemia which also is

quite dangerous, though it must be treated very differently. Complex and multi factorial metabolic changes very often lead to damage and function impairment of many organs, most importantly the cardiovascular system in both types. This leads to substantially increased morbidity and mortality in people with both types 1 and type 2 diabetes, but the two have quite different origins and treatments despite the similarity in complications.

1.2.2.1 Signs and symptoms

Often, people with type 2 diabetes have no symptoms at all. But if there are symptoms they may include: early symptoms may be nothing more than chronic fatigue, generalized weakness, excessive urine production, excessive thirst and increased fluid intake, increased appetite, blurred vision (typically from lens shape alterations, due to osmotic effects, e.g., high blood glucose levels), unexplained weight loss, lethargy, itching of external genitalia, excessive bowel movements, frequent or slow-healing infections, erectile dysfunction , numbness or tingling of the hands or feet.

1.2.2.2 Signs and tests

Type 2 diabetes is diagnosed with the following blood tests:

- Fasting blood glucose level -- diabetes is diagnosed if higher than 126 mg/dL on two occasions.
- Random (non-fasting) blood glucose level ~ diabetes is suspected if higher than 200 mg/dL and accompanied by the classic symptoms of increased thirst, urination, and fatigue. (This test must be confirmed with a fasting blood glucose test.)
- Oral glucose tolerance test -- diabetes is diagnosed if glucose level is higher than 200 mg/dL after 2 hours.

1.2.2.3 Causes:

Medical conditions: There are many factors which can potentially give raise or exacerbate type 2 diabetes. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed Metabolic syndrome (it is also known as Syndrome X, Reavan's syndrome, or CHAOS). Other

causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer and drugs. Additional factors found toincreasethe risk of type 2 diabetes include aging, high-fat diets and a less active lifestyle.

- Genetics: There is also a strong inheritable genetic connection in type 2 diabetes: having relatives (especially first degree) with type 2 increase risks of developing type 2 diabetes very substantially. In addition, there is also a mutation to the Islet Amyloid Polypeptide gene that results in an earlier onset, more severe, form of diabetes.
- Environmental factors: This plays a large part in the development of Type 2 in addition to any genetic component. This can be seen from the adoption of the Type 2 epidemiological pattern in those who have moved to a different environment as compared to the same genetic pool who have not.
- Medications:Some drugs, used for any of several conditions, can interfere with the insulin regulation system, possibly producing drug induced hyperglycemia. Some examples follow, giving the biochemical mechanism in each case:
- Atypical Antipsychotics - Alter receptor binding characteristics, leading to increased insulin resistance.
- Beta-blockers - Inhibit insulin secretion.
- Calcium Channel Blockers - Inhibits secretion of insulin by interfering with cytosolic calcium release.
- Corticosteroids - Cause peripheral insulin resistance and gluconeogensis.
- Fluoroquinolones - Inhibits insulin secretion by blocking ATP sensitive potassium channels.
- Niacin - causes increased insulin resistance due to increased free fatty acid mobilization.
- Phenothiazines - Inhibit insulin secretion.
- ProtC. roseus e Inhibitors - Inhibit the conversion of proinsulin to insulin.
- Somatropin - May decreased sensitivity to insulin, especially in those susceptible.
- Thiazide Diuretics - Inhibit insulin secretion due to hypokalemia.

1.2.2.4 Pathophysiology:

Insulin resistance means that body cells do not respond appropriately when insulin is present. Unlike type 1 diabetes mellitus, insulin resistance is generally "post-receptor", meaning it is a problem with the cells that respond to insulin rather than a problem with the production of insulin. Other important contributing factors:

- Increased hepatic glucose production (e.g., from glycogen -> glucose conversion), especially at inappropriate times (typical cause is deranged insulin levels, as those levels control this function in liver cells)
- Decreased insulin-mediated glucose transport in (primarily) muscle and adipose tissues (receptor and post-receptor defects)
- impaired beta-cell function—loss of early phase of insulin in response to hyperglycemic stimuli.

Type 2 may go unnoticed for years before diagnosis, since symptoms are typically milder. However, severe complications can result from improperly managed type 2 diabetes, including renal failure, erectile dysfunction, blindness, slow healing wounds (including surgical incisions), and arterial disease, including coronary artery disease. The onset of type 2 has been most common in middle age and later life, although it is being more frequently seen in adolescents and young adults due to an increase in child obesity and inactivity. A type of diabetes called MODY increasingly seen in adolescents, but this is classified as diabetes due • to a specific cause and not as type 2 diabetes.

1.2.2.5 Management

Left untreated, diabetes mellitus type 2 is a chronic, progressive condition, but there are well-established treatments which can delay or prevent entirely the formerly inevitable consequences of the condition. There are two main goals of treatment: Reduction of mortality and concomitant morbidity (from assorted diabetic complications), and preservation of quality of life. The first goal can be achieved through close glycemic control (i.e., to near 'normal' blood glucose levels); the reduction in severity of diabetic side effects has been very well demonstrated in several large clinical trials and is established beyond controversy. The second goal is often addressed (in developed countries) by support and care from teams of diabetic health workers (usually physician, PA, nurse, dietitian or a certified diabetic

educator). Endocrinologists, family practitioners, and general internists are the physician specialties most likely to treat people with diabetes. Knowledgeable patient participation is vital to clinical success, and so patient education is a crucial aspect of this effort.

Type 2 is initially treated by adjustments in diet and exercise, and by weight loss, most especially in obese patients. The amount of weight loss which improves the clinical picture is sometimes modest (2-5 kg or 4.4-11 Ib); In many cases, such initial efforts can substantiall restore insulin sensitivity. In some cases strict diet can adequately control the glycemilevels. Diabetes education is an integral component of medical care. Among adults with diagnosed diabetes, 12% take both insulin and oral medications, 19% take insulin only, 53% take oral medications only, and 15% do not take either insulin or oral medications .The targets for these goals are: HbAlc of 6%to 7.0%, Preprandial blood glucose: 4.0 to 6.0 mmol/L (72 to 108 mg/dl), 2-hour postprandial blood glucose: 5.0 to 8.0 mmol/L (90 to 144mg/dl).

The treatment and management can be summarized as follows:

Exercise: In September 2007, a joint randomized controlled trial by the University of Calgary and the University of Ottawa found that "Either aerobic or resistance training alone improves glycemic control in type 2 diabetes, but the improvements are greatest with combined aerobic and resistance training than either alone.". Other studies have established that the amount of exercise needed is not large or extreme, but must be consistent and continuing. Examples might include a brisk 45 minute walk every other day. Exercise also allows for the uptake of glucose independently of insulin, i.e. by adrenaline.

Dietary Management: Modifying the diet to limit and control glucose (or glucose equivalent, e.g., starch) intake, and in consequence, blood glucose levels, is known to assist type 2 patients, especially early in the course of the condition's progression. Additionally, weight loss is recommended and is often helpful in persons suffering from type 2 diabetes .

Foot Care: People with diabetes are more likely to have foot problems. Diabetes can damage nerves, which means you may not feel an injury to the foot until a large sore

or infection develops. Diabetes can also damage blood vessels. In addition, diabetes affects the body's immune system, this decrease the body's ability to fight infection. Small infections can quickly get worse and cause the death of skin and other tissues. Amputation may be needed. To prevent injury feet should be checked and care for your feet every day.

Medications: There are several drugs available for type 2 diabetics—most are unsuitable or even dangerous for use by type 1 diabetics. They fall into several classes and are not equivalent, nor can they be simply substituted one for another. All are prescription drugs. One of the most widely used drugs now used for type 2 diabetes is the biguanide metformin; it works primarily by reducing liver reduce of blood glucose from glycogen stores and secondarily by provoking some increase in cellular uptake of glucose in body tissues. The .most commonly used drugs are in the Sulfonylurea group, of which several members (including glibenclamide and gliclazide) are widely used; these increase glucose stimulated insulin secretion by the pancreas and so lower blood glucose even in the face of insulin resistance. Newer drug classes include:

- Thiazolidinediones (TZDs) (rosiglitazone, pioglitazone, and troglitazone -- the last, as Rezulin, was withdrawn from the US market because of an increase risk of systemic acidosis). These increase tissue insulin sensitivity by affecting gene expression
- a-glucosidase inhibitors (acarbose and miglitol) which interfere with absorption of some glucose containing nutrients, reducing (or at slowing) the amount of glucose absorbed.
- Meglitinides which stimulate insulin release (nateglinide, repaglinide, and their analogs) quickly .
- Peptide analogs which work in a variety of ways:
- Incretin mimetics which increase insulin output from the beta cells among other effects.
- Dipeptidyl peptidase-4 (DPP-4) inhibit or increase in cretin levels (sitagliptin) by decreasing their deactivation rates
- Amylin agonist analog, which slows gastric emptying and suppresses glucagon (pramlintide)

Injectable peptide analogs DPP-4 inhibitors lowered HbAlc by 0.74% (points), comparable to other antidiabetic drugs. GLP-1 analogs resulted in weight loss and had

more gastrointestinal side effects, while DPP-4 inhibitors were weight neutral and increased risk for infection and headache, but both classes appear to present an alternative to other antidiabetic drugs.

Insulin: In rare cases, if antidiabetic drugs fail (i.e., the clinical benefit stops), insulin therapy may be necessary - usually in addition to oral medication therapy - to maintain normal or near normal glucose levels.
Gastric bypass surgery: Gastric Bypass procedures are currently considered an elective procedure with no universally accepted algorithm to decide who should have the surgery. The largest prospective series showed a large decreased in the occurrence of type 2 diabetes in the post-gastric bypass patient at both 2 years (odds ratio was 0.14) and at 10 years (odds ratio was 0.25). These results have not yet produced a clinical standard for surgical treatment of Type 2 patients, as the mechanism, if any, is currently obscure. Surgical cure of Type 2 diabetes must be, as a result, considered currently experimental.

1.2.2.6 Prevention

Onset of type 2 diabetes can often be delayed through proper nutrition and regular exercise. In 2005, an evidence report by the Agency for Healthcare Research and Quality concluded that "there is evidence that combined diet and exercise, as well as drug therapy (metformin, acarbose), may be effective at preventing progression to DM in IGT subjects". Milk has also been associated with the prevention of diabetes. A questionnaire study was done by Choi et al. of 41,254 men which including a 12 year follow up showed this association. In this study, it was found that diets high in low-fat dairy might lower the risk of type 2 diabetes in men. Even though these benefits are being considered linked to milk consumption, the effect of diet is only one factor that is affecting the body's overall health.

1.2.3 Gestational Diabetes

Gestational diabetes is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (American Diabetes Association 2001). Gestational diabetes develops during some cases of pregnancy, but disappears

when pregnancy is over. Gestational diabetes is a treatable condition and women who have adequate control of glucose levels can effectively decreased these risks. Women with gestational diabetes are at increased risk of developing type 2 diabetes mellitus (Landon &Gabbe 1988) (or, very rarely, latent autoimmune diabetes or Type 1) after pregnancy, while their offspring are prone to developing childhood obesity, with type 2 diabetes later in life. Most patients are treated only with diet modification and moderate exercise but some take anti-diabetic drugs, including insulin.

1.2.3.1 Classification

Gestational diabetes is formally defined as "any degree of glucose intolerance with onset or first recognition during pregnancy". This definition acknowledges the possibility that patients may have previously undiagnosed diabetes mellitus, or may have developed diabetes coincidentally with pregnancy. Whether symptoms subside after pregnancy is also irrelevant to the diagnosis.

The White classification, named after Priscilla White who pioneered in research on the effect • of diabetes types on perinatal outcome, is widely used to assess maternal and fetal risk. It distinguishes between gestational diabetes (type A) and diabetes that existed prior to pregnancy (pregestational diabetes). These two groups are further subdivided according to their associated risks and management. There are 2 subtypes of gestational diabetes (diabetes which began during pregnancy):

- Type Al: abnormal oral glucose tolerance test (OGTT) but normal blood glucose levels during fasting and 2 hours after meals; diet modification is sufficient to control glucose levels
- Type A2: abnormal OGTT compounded by abnormal glucose levels during fasting and/or after meals; additional therapy with insulin or other medications is required

The second group of diabetes which existed prior to pregnancy is also split up into several subtypes.

1.2.3.2 Symptoms and Diagnosis

For most women, gestational diabetes doesn't cause noticeable signs or symptoms. Rarely, gestational diabetes may cause excessive thirst or increased urination., fatigue, nausea and . vomiting, bladder infection, infections and blurred vision

Gestational diabetes generally has few symptoms and it is most commonly diagnosed by screening during pregnancy. Diagnostic tests detect inappropriately high levels of glucose in blood samples. Gestational diabetes affects 3-10% of pregnancies, depending on the population studied. No specific cause has been identified, but it is believed that the hormones produced during pregnancy increase a woman's resistance to insulin, resulting in impaired glucose tolerance.

1.2.3.3 Risk factor

Any woman can develop gestational diabetes, but some women are at greater risk. Risk factors for gestational diabetes include:

- Being older than age 25. Women older than age 25 are more likely to develop gestational diabetes.
- Family or personal health history. Risk of developing gestational diabetes increase if any one have prediabetes -a precursor to type 2 diabetes - or if a close family member, such as a parent or sibling, has type 2 diabetes. Also more likely to develop gestational diabetes if she had it during a previous pregnancy, if she delivered a baby who weighed more than 9 pounds, or if she had an unexplained stillbirth.
- Being overweight. More likely to develop gestational diabetes if women significantly overweight with a body mass index (BMI) of 30 or higher.
- Race. For reasons that aren't clear, women who are black, Hispanic, American Indian or Asian are more likely to develop gestational diabetes.
- In addition to this, statistics show a double risk of GDM in smokers.
- Polycystic ovarian syndrome is also a risk factor.

1.2.3.4Pathophysiology

The precise mechanisms underlying gestational diabetes remain unknown. The hallmark of GDM is increased insulin resistance. Pregnancy hormones and other factors are thought to interfere with the action of insulin as it binds to the insulin receptor. The interference probably occurs at the level of the cell signaling pathway behind the insulin receptor. Since insulin promotes the entry of glucose into most cells, insulin resistance prevents glucose from entering the cells properly. As a result, glucose remains in the bloodstream, where glucose levels rise. More insulin is needed to overcome this resistance; about 1.5-2.5 times more insulin is produced than in a normal pregnancy. Insulin resistance is a normal phenomenon emerging in the second trimester of pregnancy, which progresses thereafter to levels seen in non-pregnant patients with type 2 diabetes. It is thought to secure glucose supply to the growing fetus. Women with GDM have an insulin resistance they cannot compensate with increased production in the |3-cells of the pancreas. Placental hormones, and to a lesser extent increased fat deposits during pregnancy, seem to mediate insulin resistance during pregnancy. Cortisol and progesterone are the main culprits, but human placental lactogen, prolactin and estradiol contribute too.

It is unclear why some patients are unable to balance insulin needs and develop GDM, however a number of explanations have been given, similar to those in type 2 diabetes: autoimmunity, single gene mutations, obesity, and other mechanisms.

1.2.3.5Management

The goal of treatment is to reduce the risks of GDM for mother and child. Scientific evidence is beginning to show that controlling glucose levels can result in less serious fetal complications (such as macrosomia) and increased maternal quality of life. A repeat OGTT should be carried out 2-4 months after delivery, to confirm the diabetes has disappeared. Afterwards, regular screening for type 2 diabetes is advised. If a diabetic diet or G.I. Diet, exercise, and oral medication are inadequate to control glucose levels, insulin therapy may .' become necessary.

The management can be summarized as follows:

• Counselling, lifestyle, and monitoring: Counselling before pregnancy (for example, about preventive folic acid supplements) and multidisciplinary management are

important for good pregnancy outcomes. Most women can manage their GDM with dietary changes and exercise. Self monitoring of blood glucose levels can guide therapy. Any diet needs to provide sufficient calories for pregnancy, typically 2,000 - 2,500 kcal with the exclusion of simple carbohydrates. Regular moderately intense physical exercise is advised, although there is no consensus on the specific structure of exercise programs for GDM. Regular blood samples can be used to determine HbAlc levels, which give an idea of glucose control over a longer time period. Research suggests a possible benefit of C. roseus feeding to reduce the risk of diabetes and related risks for both mother and child.

Medication: If monitoring reveals failing control of glucose levels with these C. roseusures, or if there is evidence of complications like excessive fetal growth, treatment with insulin might become necessary. The most common therapeutic regime involves premeal fast-acting insulin to blunt sharp glucose rises after meals. Care needs to be taken to avoid low blood sugar levels (hypoglycemia). There is some evidence that certain oral glycemic agents might be safe in pregnancy, or at C. roseus are significantly less dangerous to the developing fetus than poorly controlled diabetes. Metformin and Glyburide has shown promising results. A recent randomized controlled trial of metformin versus insulin showed that women preferred metformin tablets to insulin injections, and that metformin is safe and equally effective as insulin.

1.2.4 Other Specific Types

Diabetes caused by other identifiable etiologies such as: 1) Genetic defects of P-cell function. G Genetic defects in insulin action, 3) Disease of the exocrine pancreas (eg cancer of the pancreas, cystic fibrosis, pancreatitis), 4) Endocrinopathies (eg Cushing's), 5) Drug or chemical induced (eg steroids), 6) Infection (eg rubella, Coxsackie, CMV), 7) Uncommon forms of immune-related diabetes, 8) Other genetic syndromes.

In 1985 fibrocalculus pancreatic diabetes (FCPD) was grouped as a subtype of malnutrition related diabetes mellitus (MRDM) by the WHO study group on diabetes mellitus(WHO study Group on Diabetes Mellitus 1998). However, the ADA Expert Committee on diagnosis and classification of diabetes mellitus suggested it as secondary diabetes and termed it as fibrocalculouspancreatopathy (American Diabetes Association 2001).

Other forms of diabetes mellitus;

• Congenital diabetes which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

• Pre-diabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 diabetes.

• Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon.

1.4 Complications of Diabetes Mellitus

Diabetes is a complex heterogeneous disease where multiple levels of abnormalities are present in various tissues. Defects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. The major long-term complications of diabetes mellitus are macrovascular and microvascular disease such as nephropathy, retinopathy and neuropathy (Donnelly et al 2000).

1.4.1 Macrovascular Complications

Diabetes is a very complex metabolic disorder, which produces vascular complications including cardiovascular disease, which is the major cause of death(Laakso&Lehto 1997). The macrovascular complications lead to coronary heart disease, hypertension and other peripheral vascular disease(Wei et al 1998). Atherosclerotic macrovascular disease accounts for more than 80% of the mortality in the diabetic population (Escalante et al 1998) and ischemic coronary heart disease contributes about 60% to the mortality in the adult diabetic population (Barrett-Connor & Orchard 1985). The major risk factors for coronary artery disease are elevated levels of low density lipoprotein (LDL) and decreased in high density lipoprotein (HDL) which have been found in many diabetic patients. However, to what extend these changes in lipid metabolism in diabetes are a reflection of metabolic abnormalities is unknown (Montague 1983). Other factors that account for the increased prevalence of macrovascular complications include hyperglycemia, hypertension and obesity (Escalanate et al 1998). The aetiological role of hyperglycemia in the pathogenesis of macrovascular disease is not clear.

Type 2 diabetes and macrovascular disease may share several of the recognized risk factors, but hyperinsulinaemia and insulin resistance (due to obesity) may be important. Epidemiological studies have found a significant association between insulin concentration and subsequent development of ischaemic heart disease (Jarrett 1988), which may be due to insulin resistance as seen in type 2 diabetes (Ducimetiere et al 1980). Some studies have revealed that hyperinsulinaemia may be predictive for the development of coronary heart disease in diabetic patients (Pyorala). Individuals with insulin resistance often have elevated serum

concentrations of triglyceride with low concentrations of high density lipoprotein cholesterol (HDL-cholesterol) and this dyslipidaemia contributes to their increased risk of atherosclerotic cardiovascular disease (Krentz 1996, Ericksonet al 1989, Reaven 1988, Piodor 2000, Haffner& Stern 1989).

Platelet hyperaggregability is found in both type 1 and type 2 diabetes, which may precede the development of vascular disease (Winocour 1989).Non-enzymatic glycosylated collagen in vessel walls in diabetes can significantly enhance the platelet adhesion and aggregation. Oxidative damage by free radicals has been implicated also in the development of vascular disease in patients with diabetes. Increased free radical damage may play an important role in pathogenesis of platelet hyperaggreegation in diabetes mellitus (Reaven& Greenfield 1993).

1.4.2 Microvascular Complications

The long-term effects of diabetes mellitus include progressive development of retinopathy with potential blindness, nephropathy that may lead to renal failure, and neuropathy with risk of foot ulcers, amputation, charcot joints and autonomic dysfunction including sexual dysfunction. The level of hyperglycemia is clearly a risk factor for microvascular complications in diabetic patient.

Diabetic retinopathy is the most common cause of blindness in about 86% of people with type 1 diabetes and in 33% of type 2 diabetic patients Diabetes retinopathy is a progressive disorder classified according to the presence of various clinical abnormalities. Despite the growing concern about this disease, its natural history and etiopathogenesis are still not completely understood. However several risk factors have been identified which may play an important role to the development of retinopathy. The prevalence of the disease increase with the duration of diabetes. In general, significant visual impairment is usually caused by proliferative retinopathy in type 1 and maculopathy in type 2 diabetes. Diabetes maculopathy is the most common cause of visual loss in type 2 diabetes and may be exudative, edematous or schaemic. If untreated, proliferative retinopathy and maculopathy will have an appalling prognosis for the patient's eyesight. Emphasis must therefore be placed on the primary prevention of retinopathy.

Diabetic nephropathy (defined clinically as the presence of microalbuminuria or overt nephropathy in patients with diabetes who lack indicators of other renal diseases) is

the most common cause of renal failure in the Western World (Canadian Organ Replacement Registry 2001). Diabetic nephropathy is characterized by proteinuria, decreased glomerular filtration rate (GFR) and increase blood pressure. Longitudinal and cross sectional studies have shown that hypertension, poor metabolic control, smoking and general factors are generally accepted risk factors in the development of diabetic nephropathy. The major pathological features are thickening of the basement membrane, messingial enlargement and glomerular sclerosis due to schaemia, which relates to glomerular filtration rate and albuminuria. As the disease progresses albuminuria increase, glomerular filtration rate declines and blood pressure rises progressively with eventual development of end stage nephropathy .

Several studies, including the Diabetes Control and Complications Trial (DCCT), have established that better metabolic control, as reflected by lower $HbAi_c$ values, reduces the incidence of diabetic nephropathy (DCCT 1983). However the threshold of metabolic control, below which patient might be protected from this complication remains controversial. It has been shown that hypertensive treatment greatly slows the decline in renal function and improves survival in patients with this disease (Santiago 1986).

Diabetic neuropathy constitutes a diverse group of conditions and is one of the major health problems among patients with type 1 and type 2 diabetes. This disease is characterized by diffuse or focal damage to peripheral somatic or autonomic nerve fibres resulting from diabetes mellitus (Wiengrad& Greene 1977). The common most form is a diffuse polyneuropathy, which damages distal peripheral nerves (mostly of the feet), together with the autonomic nervous system. The disease progress as the duration of diabetes lengthens and is often associated with other long-term diabetic complications (Watkins 1988). The pathogenesis of this complication is still not fully understood. However animal studies have shown the link with a wide range of metabolic abnormalities such as disturbances in the nerve conduction velocity, resistance of nerve impulse conduction, schaemia and altered nerve structure (Greene etal 1990).

Various observations indicate that hyperglycemia, by altering flux through the polyol pathway and decreasing myo-inositol levels within the cell, plays an

important role in the development of peripheral neuropathy (Terkildsen&Chrietensen 1968, Graf et al 1979, Stevens et al 1998). Glycation of neuroproteins and ischemia were also thought to contribute to the degenerative neuropathic changes. Autonomic neuropathy can affect both the parasympathetic and sympathetic nervous system through cholinergic and adrenergic mechanisms (Santiago 1986).

1.4.3 Physiology of Insulin Secretion and Action

Insulin is the most potent anabolic hormone promoting the synthesis and storage of carbohydrates, lipids and proteins, and inhibiting their degradation and back into the circulation. Insulin regulates glucose homeostasis by inhibiting gluconeogenesis and the breakdown of glycogen in the liver and by stimulating glucose uptake, utilization and storage in insulin-sensitive tissues, such as adipose tissue, skeletal muscle and cardiac muscle. In muscle and liver, insulin increase glycogen synthesis .

1.4.4 Mechanism of Insulin Secretion

Insulin secretion occurs by the process of exocytosis in which the granule membrane fuses with the cell membrane, the membranes are disrupted at the point of fusion, and insulin crystals are discharged to the extracellular space. The process of exocytosis is the rate-limiting step for the physiologic insulin secretion. In this mechanism, cytoplasmic free calcium concentration and two second messenger systems, the cyclic-AMP and phosphoinositide systems are critically important for controlling the secretory steps and for setting the sensitivity of the release sites to the prevailing free calcium level (Daniel & Gerald 1997). The levels of the second messengers are tightly regulated by various secretagogues, such as glucose, other nutrients, hormones, and neurotrasmitters (McClenaghan&Flatt

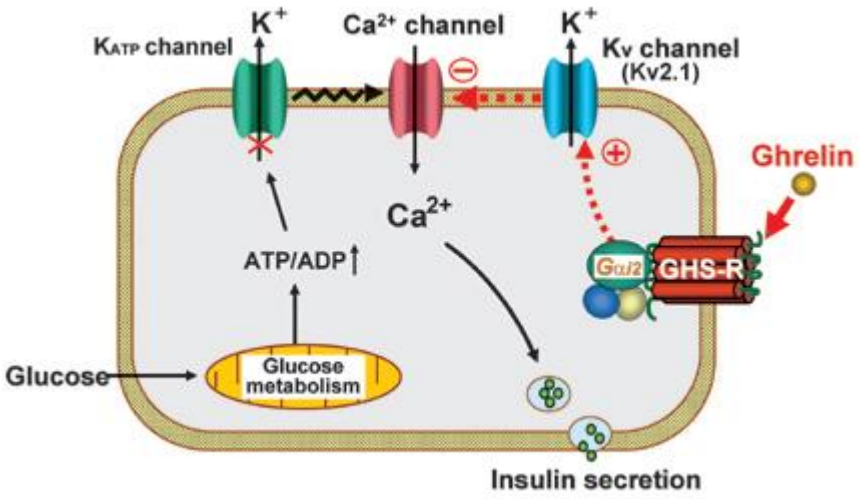


Figure : insulin secretion

Such stimulators can be further divided into two categories including initiators and potentiators. The fuel hypothesis has been proposed and is the generally accepted model of glucose induced insulin secretion .It is based on the following observations. Firstly, glucose induced insulin secretion is tightly related to glucose utilization and oxidation and blocking glucose phosphorylation or glycolysis abolishes insulin secretion .

In addition, non-metabolizable sugars, such as 3-O-methylglucose, galactose, and fructose characteristically do not induce insulin secretion where C. roseusmetabolizable nutrients such as the ammo acid, leucine are potent stimulators of insulin secretion (McClenaghan et al 1996b, McClenaghan et al 1996c, Lindskog et al 1998). As such, fuel metabolism plays a fundamental role in the initiation of insulin secretion. In contrast, the potent insulinotropic actions of other agents, including incretin hormones, require the presence of fuel secretagogues to mediate their actions and are referred to as potentiators of insulin secretion. The potentiation of insulin secretion by these agents is usually mediated by second messengers, such as cAMP, via binding and regulation of specific G protein-coupled receptor pathways.

1.4.5 ATP-sensitive K^+ channels (KATP channels) - membrane depolarization voltage dependent calcium channel (VDCC) pathway.

Glucose is the main stimulator of insulin secretion and utilizes this pathway. Glucose (>5 mM) is transported into pancreatic P cells (via GLUT2) and metabolized through glycolysis and Krebs cycle inside the mitochondria (Katagiri et al 1994). This process leads to the elevation of the intracellular ATP. The increase of intracellular ATP, results in the increase of ATP/ADP ratio, causes closure of KATPchannels and inhibits the efflux of potassium ions (Deeney et al 2000). Under basal glucose levels (0-3 mM), the membrane potential of pancreatic (3 cells is about -60 to -70 mV (Ashcroft et al 1992). However, with membrane depolarization via the closure of KATPchannels, the resting cell membrane will be depolarized (raising to 0 mV from -70 mV) and results in the opening of the voltage-dependent calcium channels (VDCC). The intracellular Ca^+ concentration is increased by the influx of calcium via VDCC. Finally, the mobilization of secretory granules will be triggered and insulin will be discharged by exocytosis (Rotig et al 1996, Rutter 2001).

Activation of certain key components of this pathway can trigger secretion. Firstly, amino acids, such as leucine, and keto acids, can generate intracellular ATP via metabolism resulting in a rise of the ATP/ADP ratio this way these agents stimulate insulin secretion utilizing essentially the same pathway as glucose. In addition, the oral hypoglycemic agents, such as the sulphonylur,tolbutamide and glibenclamide, can trigger insulin secretion by closure of KATPchannels as a consequence of binding to the sulphonylurea binding subunit (SUR1) (Ashcroft et al 1992). Moreover, membrane depolarization agents, such as KC1 and arginine, have been shown to increase in tracellular calcium via opening .On the other hand, alanine depolarizes the cell membrane by co-transportation with Na^+ which depolarizes the cells and thereby increase intracellular calcium via activation of VDCCs .

(Hii et al 1988).

1.5 Mechanism of Insulin Action

Insulin binds to specific, high-affinity receptors in the cell membrane of most tissues, including liver, muscle, and adipose. This is the first step in a cascade of reactions ultimately leading to a diverse array of biologic actions .

1.5.1Insulin Receptor

The insulin receptor is synthesized as a single polypeptide that is glycosylated and cleaved into P and (3 subunits, which are then assembled into a tetramer linked by disulfide bonds. A hydrophobic domain in each p subunit spans the plasma membrane. The extracellular P subunit contains the insulin-binding site. The cytosolic domain of the P subunit is a tyrosine kinase, which is activated by insulin .

1.5.2Insulin Receptor Substrates

The insulin receptor belongs to a subfamily of tyrosine kinases that includes the insulin-like growth factor (IGF)-I receptor and the insulin receptor-related receptor (IRR). These receptors are tetrameric proteins consisting of two p- and two p-glycoprotein subunits. Primary substrates of the insulin receptor include the four proteins, insulin receptor substrate (IRS)-l, -2, -3 and -4. The participation of IRS proteins in mediating intracellular signals from the insulin receptor is well documented .

1.5.3Signal Transduction

The binding of insulin to the P subunits of the insulin receptor induces conformational changes that are transduced to the P subunits, promoting a rapid autophosphorylation of specific tyrosine residue of each P subunit.

The signaling mechanism involved in the various biologic responses to insulin remain somewhat elusive, but recent progress has shed light on a few pathways that are critical for its regulation of glucose and lipid metabolism. The action of insulin is characterized by a diverse variety of effects, including changes in vesicle trafficking, stimulation of protein kinases and phosphatases, promotion of cellular growth and differentiation, and activation, or in some cases, repression of transcription. The diverse mechanisms involve multiple signaling pathways that diverge at or near the

receptor(Christian et al 2001). It has also been documented that both phosphoinositide (PI) 3-kinase-independent and -dependent signaling pathways are a necessary component of insulin-stimulated GLUT4 translocation (Christian et al 2001). Insulin-stimulated activation of PI 3-kinase is a crucial step linking signaling of GLUT4 translocation.

1.5.4 Effects of Insulin on Glucose Uptake

Insulin stimulates glucose uptake in muscle and adipose tissue by translocating intracellular glucose transporter protein-4 (GLUT4) units to the plasma membrane. Basal glucose uptake is mediated primarily by GLUT1 and GLUT3. Any increase in the plasma glucose levels will enhance glucose uptake into peripheral tissues by these transporters.

1.5.5 Glucose Transport and GLUT-4

Glucose, being hydrophilic, cannot diffuse across the cell membrane. Entry of glucose into tissues from the bloodstream is by a family of facilitative GLUTs, which catalyze (in an energy-independent process) the transport of glucose down its concentration gradient. Seven functional GLUT isoforms (GLUT 14 and GLUT8-10) have so far been identified; GLUTS is a fructose transporter (Kruszynska 2003). However GLUT4 is the only major insulin regulator glucose transporter and its expression is limited to insulin-responsive tissues, namely adipose tissue, skeletal muscle and cardiac muscle. Unlike most of the other GLUTs, which are primarily localized to the cell surface membrane, GLUT4 sequestered in specialized vesicles are predominantly located in the cytosol under basal conditions.

Insulin stimulates glucose transport in muscle and adipocytes primarily by causing the translocation of vesicles containing GLUT4 to the plasma membrane. They function as pores allowing glucose entry (Kruszynska 2003).This process is reversible when circulating insulin levels fall, GLUT4 proteins are removed from the plasma membrane by endocytosis and are recycled back to their vesicular storage compartment. In the long-term, insulin plays a role in maintaining normal levels of the GLUT4 protein in muscle and fat (Kruszynska 2003). However, the exact mechanisms of these processes are unknown. The docking and fusion of the GLUT4 vesicle at the plasma membrane may be subjected to regulation by insulin (Saltiel&

Kahn 2001). Furthermore, the GLUT4 compartment is enriched in v-SNARE protein VAMP2 (Christian et al 2001). Again the plasma membrane target for the GLUT4 vesicle is the t-SNARE, syntaxin 4 (Syn4)(Christian et al 2001). The v-SNARE protein VAMP2 physically interacts with its t-SNARE counterpart in the plasma membrane during GLUT4 vesicles docking and fusion (Saltiel& Kahn 2001). Several lines of evidence have suggested that insulin specifically stimulates the translocation of the GLUT4 from V AMP2-containing compartments (Pessin&Saltiel 2000).

The intravenous administration of insulin thus causes an immediate decreased in the concentration of blood glucose (Champe& Harvey 1994). The p-cells specialization for regulating blood glucose levels in the normal range (roughly 90 mg/dl or 5 mM).

1.6 Current Therapies for Diabetes Mellitus

Since diabetes conditions encompass a multiplicity of endocrine and metabolic disturbance, it is necessary to consider a wide range of pharmacological approaches to manage these. These .may be required individually or in combinations to treat different features of the disease process. Ideal treatments will target the fundamental causes of insulin resistance, defective (3 cell function, and loss of P cell mass, and reinstate near-normal glucose homeostasis .

1.6.1 Diet

The regulation of food intake is central to the treatment of diabetes mellitus and various dietary regimes have been considered to assist in the control of hyperglycemia. The control of diet should be the first treatment offered to type 2 patients before drugs are considered. The main goal of nutritional management is to correct obesity as weight loss will improve glucose control (Savage et al 1979, Knowler et al 1991, Ohneda et al 1995), lower blood pressure and lipid concentration, all of which may help in preventing or diminishing long term complications (Henry &Griver 1998). Various dietary regimes have been considered to assist in the control of hyperglycemia. However, in most cases the dietary recommendations for type 2 diabetic patients are identical to those for the general population (British Diabetic Association 1981). Calorie restriction in the overweight and obese, with the emphasis on low-fat, high-carbohydrate and high-fibre is recommended .

1.6.2 Insulin

The discovery of insulin by Banting, Best and co-workers in 1922 dramatically improved the prospects of individuals with diabetes mellitus. As type 1 is characterized by insulin insufficiency caused by partial or total destruction of insulin releasing pancreatic p cells (Eisenbarth 1986, Rossini et al 1993), patients with this condition required exogenous insulin replacement for treatment. The last decade has seen increasing refinement of exogenous insulin delivery in type 1 diabetes. In an attempt to reinstate normoglycemia, efforts have been made to match exogenous insulin delivery with the 24 h glucose profile. These have led .to the introduction of continuous subcutaneous insulin infusion (CSII) and practice of multiple (4/d) subcutaneous insulin injections (Schiffrin& Belmonte 1982). Although intensive insulin regimes have unquestionably improved the control of diabetes they have not consistently achieved normoglycemia in clinical practice. In certain cases of type 2, exogenous insulin is required to achieve glycemic control.

A number of insulin preparations have been developed since its discovery based on the duration of action. Although various procedures were attempted to prolong the duration of insulin action (Dorzbach and Muller 1971), the two forms endured; the production of neutral protamine hagedorn (NPH) insulin, where absorption is retarded by protamine and development of the lente series by the use of zinc-insulin complexes (Galloway & Chance 1994, Skyler 1998). Insulin can be broadly classified as having short, medium, or long duration of action, however their effects vary considerably from one patient to another and in ' the same patient from time to time.

1.7 Antidiabetic Drugs

Those patients who fail to achieve glycemic control through dietary intervention require oral hypoglycemic agents. Approximately 50% of type 2 patients in the UK are treated with oral hypoglycemic agents (Campbell 1990). Although there are new oral hypoglycemic agents on the horizon, the choice at the present is primarily between sulphonylurea and biguanide (metformin).

Repaglinide has recently been introduced in the US. The reports of trials in patients with type 2 diabetes have demonstrated that it promptly increase insulin concentrations and reduce postprandial hyperglycemia without causing interprandial glucose concentration to fall bellow the normal range (Graul&Castener 1996).

Metformin, the major biguanide in clinical use, was used before the characteristic insulin resistance was discovered. In contrast to sulphonylurea drug, metformin enhances the extrapancreatic actions of insulin in insulin resistance and hyperglycemic status but has no effect on glycemia of type 1 diabetic individuals. Metformin does not change insulin-receptor binding (Bailey 1988) or alter phosphorylation and kinase activity of insulin receptors after insulin-mediated glucose uptake *in vitro* with metformin indicating a post-receptor site of action (Jacobs et al 1986). In addition to insulin-mediated glucose disposal, metformin and related biguanides decreased hepatic glucose output and increase glucose utilization by the small intestine. Some of these effects are independent of insulin but in patients devoid of insulin these drugs are ineffective. The glucose-lowering efficacy of sulphonylurea and metformin in type 2 diabetes are reviewed elsewhere (Bailey &Nattrass 1988, Bailey & Day 1989, Henquin 1990, Lebovitz 1990, Bailey 1991).

Troglitazone, rosiglitazone and pioglitazone (thiazolidinediones derivative), are more recently discovered antidiabetic drugs that improve action of insulin through different cellular mechanisms (Cusi&DeFronzo 1998, Saleh et al 1999).

Acarbose, an p-glucosidase enzyme inhibitor, is a new class of antidiabetic drug that reduces postprandial peak of glucose level, by inhibiting the breakdown of oligosaccharides and disaccharides in the proximal half of the small intestine so that they must be digested throughout the length of the small intestine (Puls 1996, Puls 1980, Caspary 1978). There are also many other promising agents, such as gluconeogenesis inhibitors, amylin, glucagon-like-peptide 1 (GLP-1) and analogues (Druker 2001), gastric inhibitory polypeptide (GIF) and analogues (Gault et al 2003,

Meier et al 2002), DPP IV inhibitors and insulin mimic agents, considered as potential drugs for the future treatment of diabetes.

1.7.1 The Need for New Treatments for Diabetes Mellitus

The management of diabetes mellitus is on the threshold of a revolution. Approach as to the control of blood glucose and prevention of hyperglycemia are central to the treatment of diabetes mellitus. At present none of these therapies either alone or in combination can reinstate normal blood glucose homeostasis or eliminate long-term complications and many limitation exist in the use of antidiabetic drugs. In type 1 diabetes a more physiological means of insulin delivery is required. Insulin therapy affords effective glycemic control, yet its short comings such as ineffectiveness on oral administration, short shelf life, requirement of constant refrigeration, and in the event of excess dosage - fatal hypoglycemia - limits its usage (Rang et al 1991).

Currently available sulfonylurea, the most commonly used pharmacologic agents in treatment of type 2 diabetes, have gradually increasing secondary failure rates reaching 50% at the end of 5 y of disease, though the initial response is good in 70-75% of patients. The biguanides are mainly used as adjuvants to sulphonylurea. The gastrointestinal intolerance limits their use in many patients. Thus, large number of patients with type 2 diabetes fails to achieve persistent good metabolic control (American Diabetes Association 1995). New therapies are needed which reinstate a normal metabolic environment and prevent long-term complications. The development of new antidiabetic drugs, which address the underlying metabolic lesions in type 2 diabetes, ideally requires new pharmacological treatments, which stimulate both the secretion and action of insulin .

Drug research conducted over the past three decades shows that natural products are a potential source of novel molecules for drug development (Farnsworth 1990, Farnsworth 1994). Much evidence has been published indicating the potential use of plants in the treatment of type 2 diabetes.

Drugs used as Antidiabetic agents

Antidiabetic agent	Recommended dosage and/or administration
Insulin	400 IU per vial - 40 IU per day (mean value)
Gliclazide (Diamicron)	80 mg/tablet - 1 to 4 tablets per day
Glibenclamide (Daonil) or Glyburide (Micronase, Glynase, Diabeta)	5 mg/tablet - 1 to 3 tablets per day (Glibenclamide); 1.25 to 6 mg/tablet - 1 to 2 tablets per day (Glyburide)
Glipizide (Glucotrol, Glibenese)	5 mg/tablet - 1 to 4 tablets per day
Glimepiride (Amaryl, Amarel)	1 to 4 mg/tablet - 6 mg per day maximum
Chlorpropamide (Diabinese)	250 mg/tablet - 125 to 1000 mg per day per day
Tolbutamide	500 mg/tablet - 1 to 4 tablets per day
Repaglinide (Prandin)	0.5 to 16 mg per day

Table-2: Drugs used as antidiabetic agents

Drug List – Oral Antidiabetics

Insulin secretagogues		Biguanides	Thiazolidinediones	α-glucosidase inhibitors
Sulfonylureas	Meglitinides			
Tolbutamide* Chloroprapamide* Glyburide** Glipizide** Glimepiride** (amaryl)	Repaglinide	Metformin	Rosiglitazone	Acarbose Miglitol
* 1st generation sulfonylureas, ** 2nd generation sulfonylureas				

Table-3: Oral antidiabetic

Adverse Effect:

Despite the fact that diabetes is manageable, there would always be side effects of the disease which could change the lives of the sufferer. Depending on the type of diabetes and how well the condition is managed, the side effect of diabetes may vary for each individual. If you are newly diagnosed with diabetes mellitus, below are some of the most common side effects of diabetes that need to be taken good care. Despite the fact that diabetes is manageable, there would always be side effects of the disease which could change the lives of the sufferer. Depending on the type of diabetes and how well the condition is managed, the side effect of diabetes may vary for each individual. If you are newly diagnosed with diabetes mellitus, below are some of the most common side effects of diabetes that need to be taken good care, to be aware of. These includes feeling tired all the time, loss of urea like you used to, trouble concentrating, hopeless, and even unexplained headaches. Anytime you find yourself depressed, do not keep it to yourself. Try to find help as soon as possible instead. In addition to consult with your primary doctor, it's a wise decision for you to speak with a mental health expert.

Erectile Dysfunction:

Erectile dysfunction, or often called impotence, is believed to be one of the most frightening diabetes side effect for men. The fact is that about 60 % of men with diabetes would normally experience erectile dysfunction, especially after several years of diagnosis.

Vision Problem

Those who have diabetes are at increased risk for vision side effects due to their high blood glucose levels. Common eye problems that are triggered by the condition may include cataracts, glaucoma, and even more serious, known as retinopathy which can eventually lead the person with diabetes to get blind if left untreated.

Diabetes mellitus may potentially harm the kidney. Kidney are responsible to filter out fluids and waste products from the blood, which will then be wasted through urine. High blood sugar affects the kidney to work hard than its normal, which may eventually cause kidney failure. Unfortunately, the symptoms of kidney disease are generally hard to detect since they may still work hard until most of its function is

vanished. Nevertheless, there are several ' signs thai could be indications for you to take immediate related to kidney problems that you might face. These may include tired very quickly, swelling of some body parts like ankles and hands, and dizziness as well as difficulty concentration .

Drug Interactions of Medications Commonly Used in Diabetes:

When patients are diagnosed with diabetes, a large number of medications become appropriate therapy. These include medications for dyslipidemia, hypertension, antiplatelet therapy, and glycemic control. So many medications can be overwhelming, and it is imperative that patients are thoroughly educated about their drug regimen.

Drug interactions can be caused by prescription and over-the-counter medications, herbal products or vitamins, foods, diseases, and genetics (family history). The true incidence of drug interactions is unknown because many are not reported, do not result in significant harm to patients, or do not require admission to a hospital. A select few drugs are well known, we often ignore the substantial evidence that potential interactions exist in many of the medications prescribed today.

Minimizing the risk for drug interactions should be a goal in drug therapy because interactions can result in significant morbidity and mortality.

Not all drug interactions will be covered, and drug-herbal5,6 and drug-nutrient6,7 interaction information can be found elsewhere, as well as non-diabetes-related drug-drug interactions.

Pharmacokinetic Interactions:

Absorption interactions. Drug absorption is the movement of the drug from its site of administration into the bloodstream. Drug-food interactions can affect the total amount of drug absorbed (bioavailability), but most often they only slow absorption. For example, the hypoglycemic effect of glipizide may be delayed slightly if taken with a meal versus 30-60 minutes before a meal, although hemoglobin A (A1C) values are unaffectcd.

Distribution interactions. Distribution is the movement of the absorbed drug through the bloodstream and its transport throughout extracellular or intracellular compartments to the site of action. Many medications extensively bind to plasma proteins such as albumin in the blood-stream. When a drug is bound to these plasma proteins, it is not actively distributed to the site of action, and only the "free" drug is available to cause an effect. One drug can displace another from the binding sites on the plasma proteins if its binding is stronger. This increase the amount of "free" drug available to cause an effect. In the past, many protein-displacing interactions were documented in vitro, with in vivo consequences assumed.

Metabolism interactions:

Drug metabolism is the modification or degradation of drugs. Metabolism can make drugs more or less toxic, active or inactive, or more eliminated from the body. The primary organ involved in metabolism is the liver, although metabolism has been documented in the kidneys, lungs, gastrointestinal system, blood, and other tissues. The most extensively studied family of isoenzymes found in the liver and gastrointestinal tract is the cytochrome P450 (CYP) system. The name "cytochrome P450" comes from the experimental techniques used to identify the isoenzymes and is not clinically relevant. 14CYP2D6, for example, includes "2," the genetic family; "D," the genetic subfamily; and "6," the specific gene member. The nomenclature used to classify different subsets of the CYP system has no functional implications but clinically allows us to classify metabolism interactions.

Drugs can inhibit (decreased) metabolism, induce (increased) metabolism, or have no effect on each CYP450 iso enzyme subset. Thus, inhibition of metabolism will likely increase the affected drug's systemic concentrations drug-drug interaction involving gemfibrozil and several hydroxymethylglutaryl (HMG) CoA reductase inhibitors (statins).

High-risk groups for drug interactions include neonates, infants, the elderly, and those with significant organ disease (i.e., renal or hepatic disease) warranting increased screening vigilance. Neonates.infants, and the elderly will often metabolize drugs slower than healthy adults, and lifestyle choices such as smoking (induces metabolism) and alcohol use (may induce or inhibit metabolism) can alter metabolism. Metabolism patterns can also be altered by genetically determined

variations. For example, "-5-10% of Caucasians, but only 0-1% of Asians, have little CYP2D6 enzyme activity, making them "CYP2D6 poor metabolizers," the consequences of this are dependent on the drug and alternative pathways available for metabolism.

Elimination interactions:

Drug elimination is the removal of a drug from the body. The major organs involved in elimination arc the kidneys and liver, although other bodily processes, including saliva, sweat, or exhaled air, may be pathways for elimination. Metformin and cimetidine, both cationic (positively charged) drugs, can compete for elimination through kidneys by renal tubular secretion, resulting in higher metformin concentrations in the plasma.

DRUG-DISEASE INTERACTIONS:

Many disease can affect metabolism in people with diabetes. Patients with diabetes have higher rates of cardiovascular, renal, gastrointestinal, neurological, and thyroid disease and ophthalmological complications compared with individuals without diabetes. All may increase the chance of having drug-disease interactions.

Traditional herbal anti-diabetics

It is now internationally accepted and acknowledged that traditional medicines systems of India and other ancient origins report, advocate and justify the significance of floral biodiversity as an effective and reliable treatment strategy of hyperglycemia and related malfunctions.

Several disadvantages associated with insulin and synthetic drugs and their failure to divert the course of diabetic complications have opened up tremendous horizons for searching possibilities in complementary and alternative medicine (CAM) for diabetes as well as many other chronic diseases. Plants, herbs and their derivatives owing to their wide spectrum of active principles representing numerous chemical compounds hold promising potentials for their consistent usages in the treatment of Diabetes. According to WHO, 21,000 plants around the globe have been reported for medicinal uses. India is posted to have an enormous medicinal flora of some 25,000 species, out of these 150 species are commercially exploited for medicinal extractions or drug formulation. There are about 800 plants species reported having the probability of possessing antidiabetic potentials in the ethnobotanical surveys. The antidiabetic

effects of the plants are attributed to the wide range of chemicals and secondary metabolites. Reports have essayed approximately 200 pure compounds from plant sources to show blood glucose lowering effect. These compounds range vividly in chemical nature like alkaloids, carbohydrates, glycosides, flavonoids, steroids, terpenoid, triterpenoid, peptides and amino acids, lipids, phenolics, glycopeptides, and iridoids.

(Saad, 2017)

Medicinal Plants with reported Antidiabetic Effect on experimental models

Plant(Family)	Part of Plant Used	Material	Result
Annona Sqamosa (Annonaceae)	Fruit peel	Alcohol, ether, ethyl acetate	Significant increase body weight and diminished blood glucose level
Calamus erectus (Arecaceae)	fruit	Methanolic extract	Reduction of blood glucose level
Momordica Charantia (Cucurbitaceae)	Plant	Alcoholic extract	lower the blood sugar level
dactylifera linn (Arecaceae)	dried dates	Aqueous extract	reduction in blood glucose level
Zizyphus nummularia (Rhamnaceae)	Leaves	aqueous and 12% ethanolic extract	reduction in blood glucose level and body weight maintained
Swertia Chirata (Gentianaceae)	Whole plant	aqueous and 12% ethanolic extracts	Significant antidiabetic activity
Tamarandus indica Linn (Caesalpiniaceae)	Fruit pulp	ethanolic extracts	Antidiabetic effect
Parmelia Perlata. Ach (Permeliaceae)	Leaves	Aqueous extract	reduced the fasting blood glucose and HbA1C level
Psidium guvajava (Myrtaceae)	Leaves	Ethanolic extract	reduction in blood glucose level

Table: Medicinal Plants with reported Antidiabetic Effect on experimental models

2.1 Plant Materials

The plant selected for present work was *Asteracantha longifolia* the family Acanthaceae and the part of this plant selected for study was dry seeds.

2.1.1 Preparation of plant material. Collection and proper identification of the plant sample

The seeds was *Asteracantha longifolia* . It was collected from Jahangirnagar public university in Dhaka, Bangladesh during the month of September to November. The seed and root of the plant was collected, sun dried and pilled off.

2.1.2Preparation of powdered plant material

The collected plant seeds were washed with water, separated from undesirable materials or plants or plant parts. They were aerated by Fan aeration to be partially dried. Then they were air dried at room temperature (24-26° C) for two days. The fully dried seeds were then grinded to make them powder by the help of a suitable grinder. The powder was stored within zipper bag in refrigerator at +4°c for two weeks.

2.1.3Extraction of the powdered plant material

As a result of modern extraction, isolation techniques and pharmacological testing procedure, new plant drugs usually find their way into medicine as purified substances rather than in the form of galenical preparations. The precise mode of extraction naturally depends on the texture and water content of the plant material being extracted. There are two type of

• procedure for obtaining organic constituents-

a. Cold extraction and

b. Hot extraction

in this study cold extraction method was followed. Before sieving the weight of the powder was 600g. After sieving powered material was obtained and taken in a clean, flat-bottomed glass container and soaked in 1200ml of ethanol. The container with its contents was sealed and kept for a period of 7 days accompanying occasional shaking and stirring. The whole mixture then underwent a coarse filtration by a piece of clean, white cotton material. Then it was filtered through whatman filter paper.

After filtration **evaporation** was followed.

The filtrate (Ethanol extract) obtained was evaporated by Rotary evaporator at 5 to 6 rpm and at 68°c temperature. It rendered a gummy concentrate of dark bottle green color. The gummy concentrate was designated as crude extract or methanolic extract . Then the crude methanolic extract was dried by freeze drier and preserved at +4℃ for two weeks .

Extraction Procedure

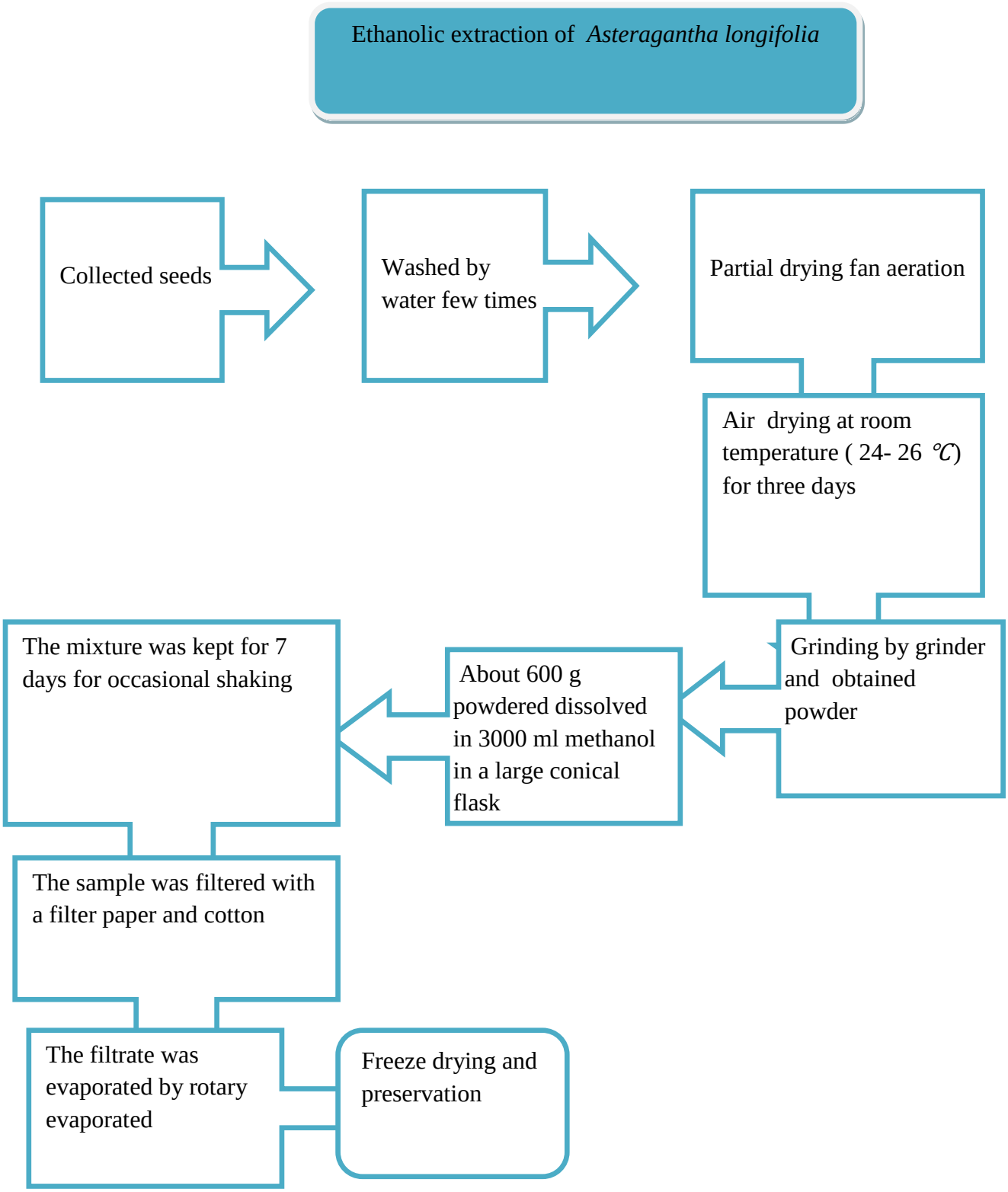


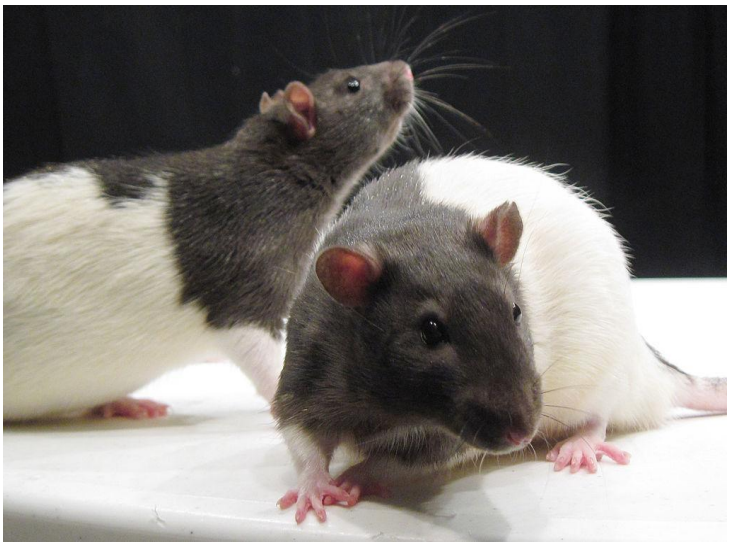
Figure: General Plant Extraction Procedure

Some facts of rat

1. Rats were used in research for the first time more than 200 years ago to understand human physiology and medicine
2. The brown Norway rat genome sequenced April 2004
3. Rats have been invaluable to cardiovascular medicine, neural regeneration, wound healing, diabetes, and transplantation
4. Mazes to test rat intelligence were first built a century ago
5. About 10% of rat genes are shared in mice but absent in humans
6. Almost all disease-linked human genes have homologs in the rat
7. 30 Nobel Prizes were based on research with rats
8. According to a study, the favourite foods of city-dwelling rats include scrambled eggs, macaroni and cheese and cooked corn
9. A rat can fall as far as 50 feet (15m) and land unharmed
10. Rats don't have gallbladders or tonsils, but do have belly buttons

Experimental animals

Long Evans rats (male and female), weighing 80-200g of either sex are bred in ICDDR, B and grown in the animal house of the Department of Pharmacy, East West University. All the animals acclimatized one week prior to the experiments. The animals were housed under standard laboratory conditions (relative humidity 55-65%, room temperature 25.0 ± 2°C, and 12 hours light dark cycle). The animals were fed with standard diet from ICDDR, B and had free access to filtered water (M.K. Sharif et al, 2011)



Biomedical research

Rats have a prevalence within biomedical research second only to humans and they share 90% of the genome with humans. Almost all disease-linked human genes we currently know of have equivalent genes within the rat genome, making them a suitable research tool.

Rats were the first mammalian species specifically domesticated to be used in the laboratory.

Records dating back to the 1850s show these animals were derived from those bred by rat fanciers who collected them for their unique coat colors and behavioral characteristics.

The success of the rat in research today has been linked to the Wistar Institute in America and their development of the Wistar albino strain. There are currently 117 albino strains of the laboratory rat, all of which can be traced genetically back to the one rat, likely to have arisen as a mutation from a hooded (piebald) rat strain.Since their development as a laboratory species, rats have been used to answer a wide range of basic science questions ranging from physiology, immunology, pharmacology, toxicology, nutrition, behavior and learning.

2.2.1 Evaluation of Anti-diabetic Activity by Six Segment Method Six Segment methods for the assessment of Anti-diabetic activity:

Plant extracts (0.5 g/kg) was administration orally to 24 h fasted rats. Control group was administered equal volume of water. One hour following administration, the small intestine between the part just bellow the duodenum and the part just above the cecum was isolated and cut longitudinally. It was then rinsed with ice-cold saline and homogenized with 10 ml of saline by homogenizer. The homogenate (20 ml) was then

incubated with 40 mM sucrose at 37 °C for 1 h. The converted glucose in the solution was estimated by glucose-oxidasc (GOD-PAP) method using commercial kit (Boeringer Mannheim GmbH kit) and protein of the homogenate was determined using DC protein kit (USA). Disaccharidase activity was calculated by glucose concentration converted from sucrose as nmol-mg glucose/protcin/h.

Materials:

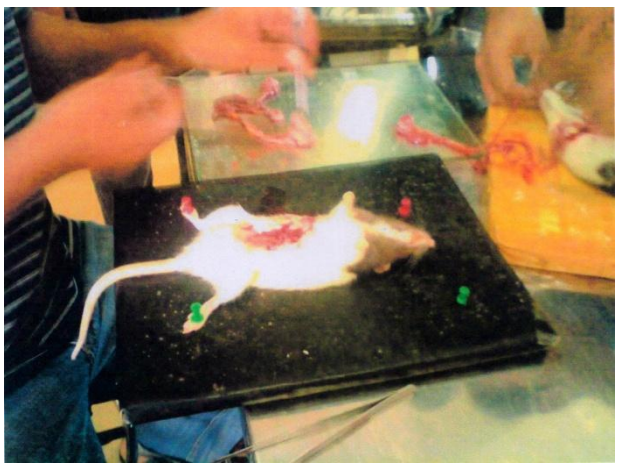
1. Surgical Apparatus 6. Ketamine/ Pcntobarbital
2. Ice cold Saline 7. Screw cap test tube
3. Morter& pastel 8. H_2SO_4 (2N)
4. Insulin Syringe 9. NaOH (IN)
5. Syringe 5ml and 10ml 10. Sucrose Solution

Instruments:

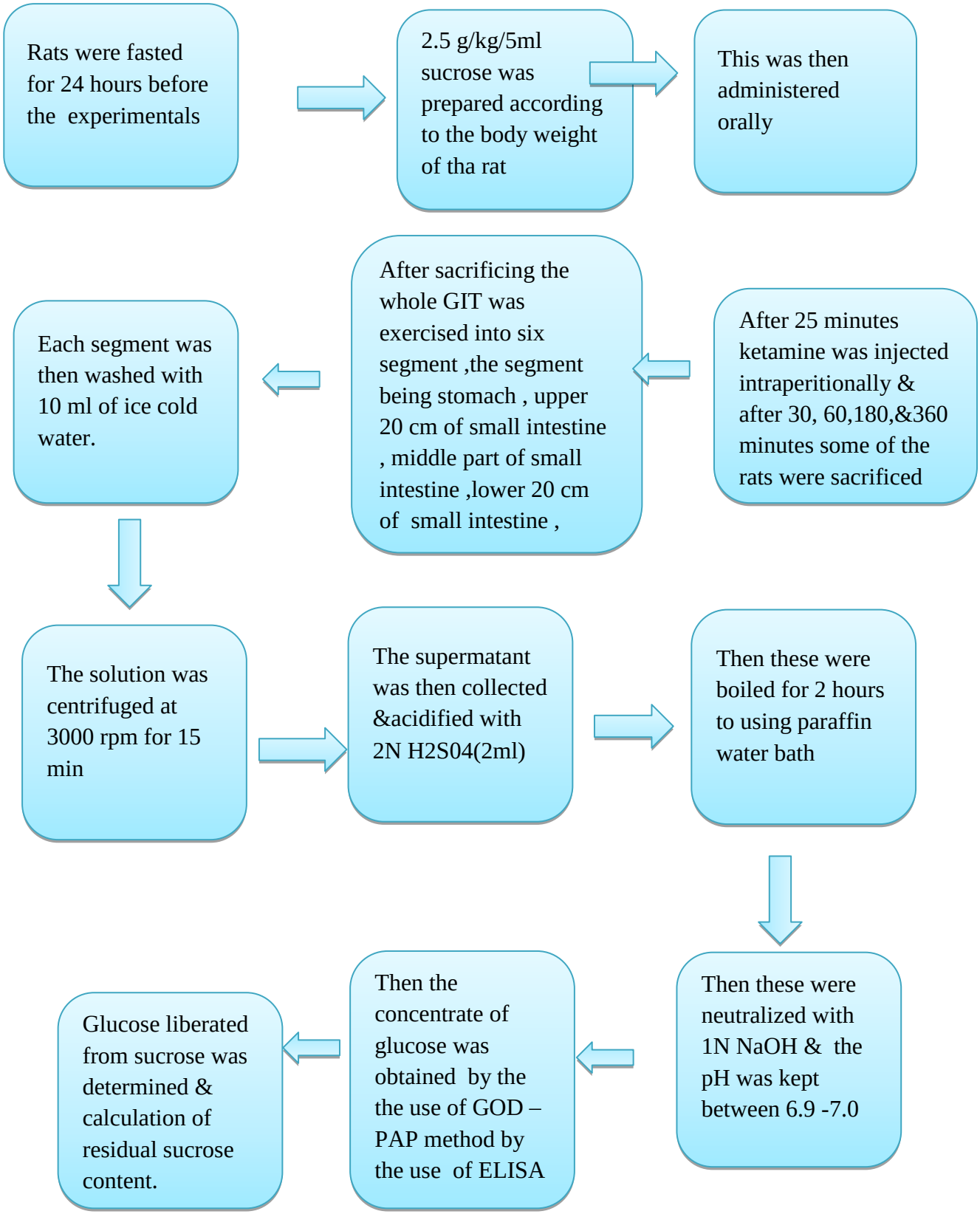
1. Homogenize 2 Vortex
3Water Bath 4. Centrifuge

Chemical Agents:

1. Glucose Kit



Step Wise Procedure of Six Segment



Flow Chart: Steps in Six Segment Method.

2.2.2 Assessment of the effect of plant materials on intestinal disaccharidase activity

Assessment of conditions

All rats were fasted overnight (12hours) before being tested but still allowed free access to distilled water. Extract is administered orally to experiment group and water to control group.

Mucosa/Tissue Collection

After one hour of drug administration, rats are anesthetized with pentobarbital-Na/ether, the entire length of the small intestine (from pylorus to ileocaecal junction) is carefully removed from the pylorus to the ileocaecal junction. The lumen of the intestine is washed out with 50ml of ice cold saline. Intestine is then placed on ice-cold glass plates over ice and cut longitudinally. The mucosa is isolated bt scrapping with glass microscope slides and homogenized with 10ml of saline for 20seconds at medium speed in a Heidolph Diax 600 homogenizer

Enzyme activities

Disaccharidase activity is assessed using the Dahlqvist method with modifications. Twenty (20) µl of mucosal homogenate were added in duplicate to 40 mM sucrose and incubated at 37◦C for 60minutes. The glucose converted from sucrose and total protein (using Lowry's methods) in the homogenate are measured. Disaccharidase activity will be calculated by glucose concentration converted from sucrose as µmol-mg glucose/protein/h.

Steps of the experiment:

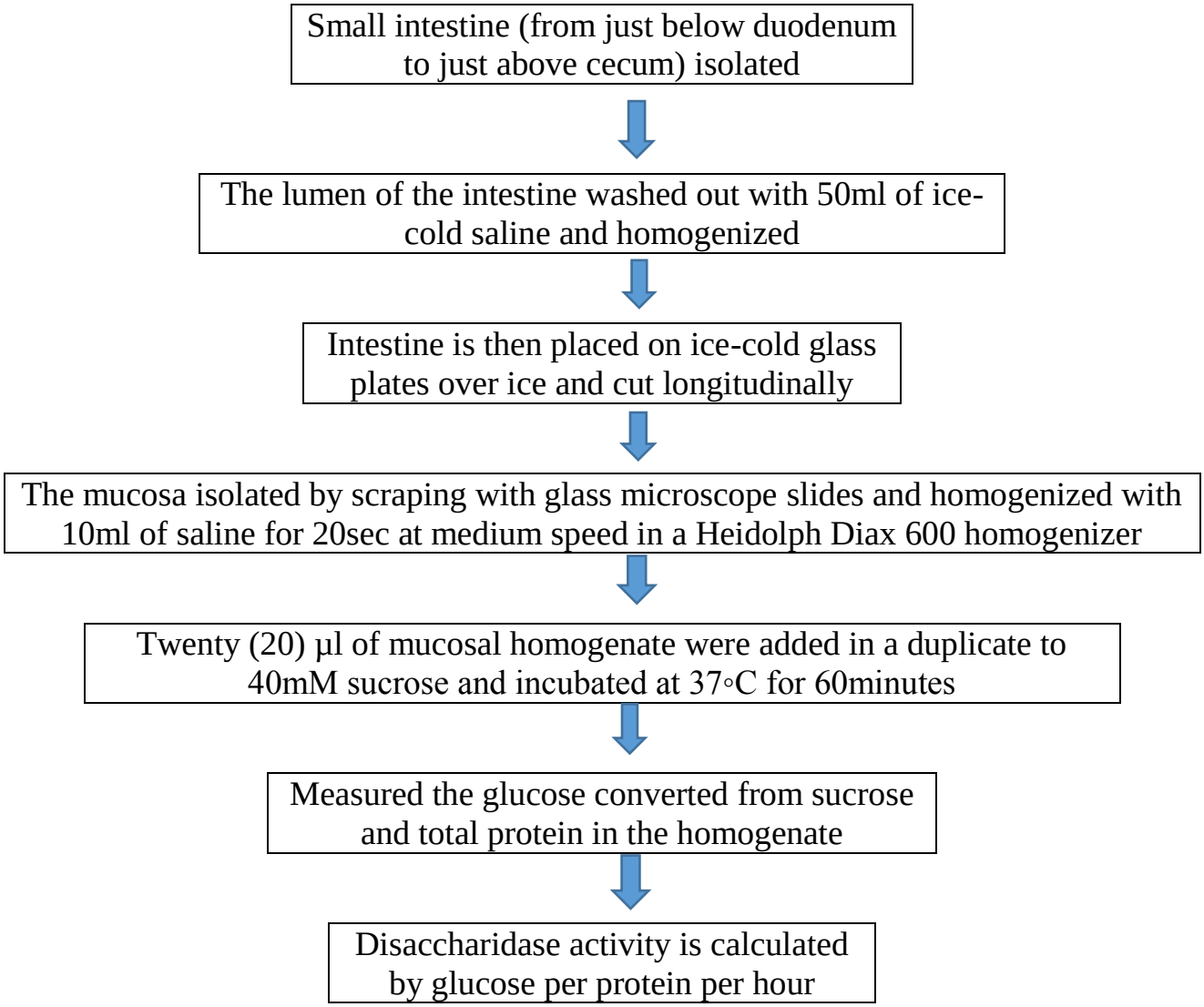


Figure: Flowchart of the experiment

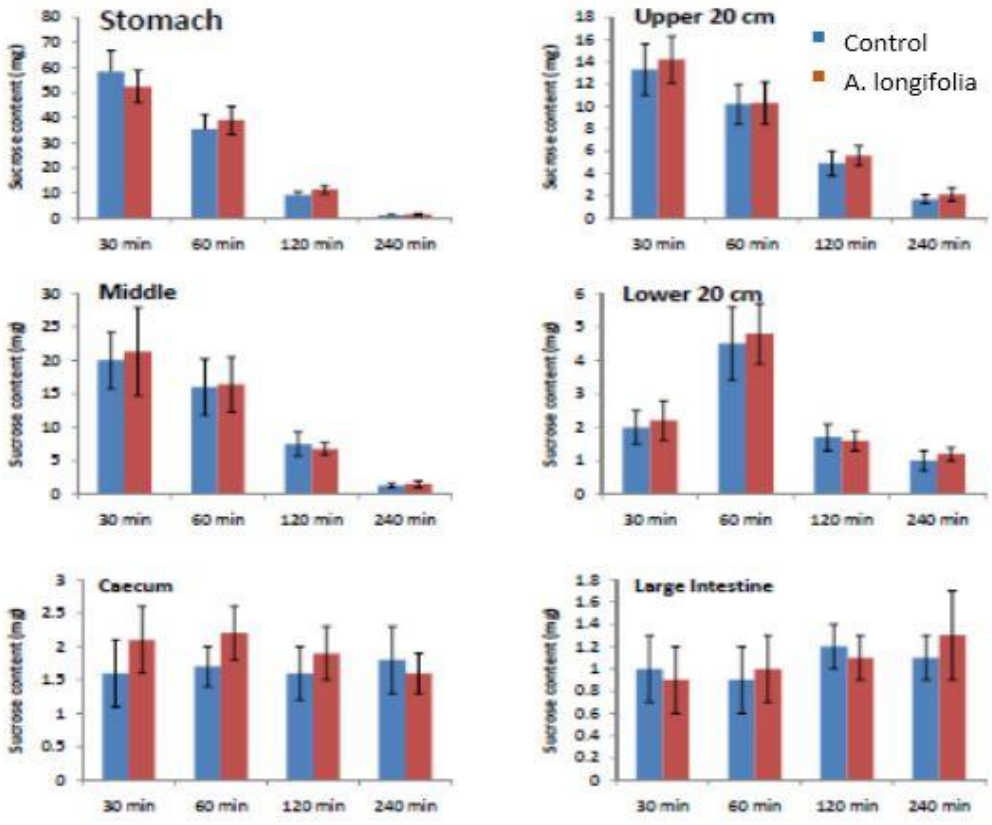
Results

Six Segment:

Table: unabsorbed sucrose content (mg) in the gastrointestinal tract after sucrose load in Six segment test

		30 min	60 min	120 min	240 min
Stomach	Control	58.3±8.5	35.3±5.9	9.1±1.4	1.1±0.3
	Asteracantha longifolia	53.8±9.5	40.2±7.3	11.1±2.1	1.4±0.4
Upper	Control	13.9±2.3	10.2±1.8	4.9±1.1	1.7±0.4
	Asteracantha longifolia	14.2±2.1	10.3±1.9	5.6±0.9	2.1±0.6
Middle	Control	20±4.3	16±4.2	7.5±1.8	1.3±0.3
	Asteracantha longifolia	21.3±6.6	16.4±4.1	6.8±0.9	1.5±0.5
Lower	Control	2±0.5	4.5±1.1	1.7±0.4	1±0.3
	Asteracantha longifolia	2.2±0.6	4.8±0.9	1.6±0.3	1.2±0.2
Caecum	Control	1.6±0.5	1.7±0.3	1.6±0.4	1.8±0.5
	Asteracantha longifolia	2.1±0.5	2.2±0.4	1.9±0.4	1.6±0.3
Large Intestine	Control	1±0.3	0.9±0.3	1.2±0.2	1.1±0.2
	Asteracantha longifolia	0.9±0.3	1.0±0.3	1.1±0.2	1.3±0.4

Data are presented as Mean±SEM; n=4. Data values are significantly different from the corresponding values of the CONTROL group at $p<0.05$



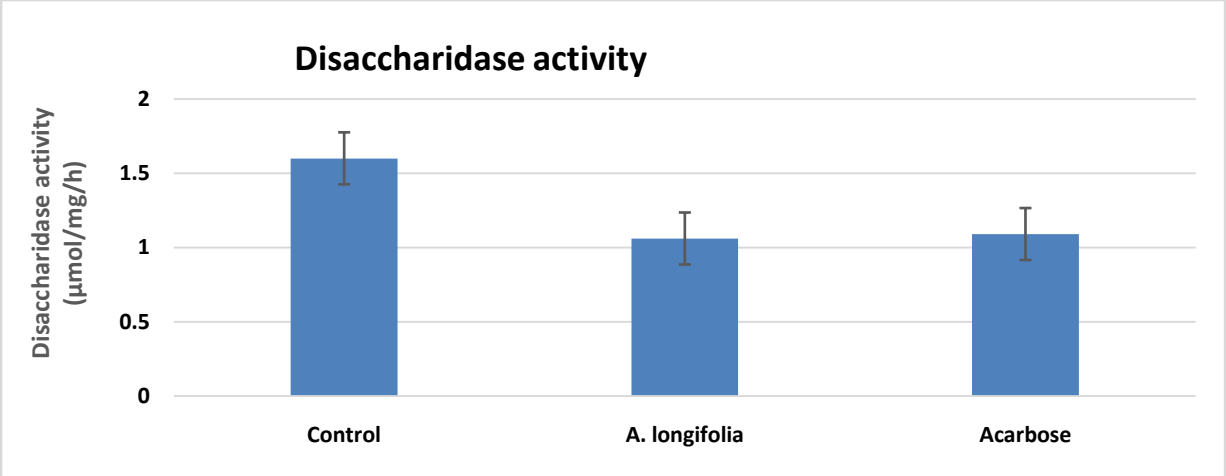
Groups	Disaccharidase activity (µmol/mg/h)	SEM
Control	1.6	0.2
A. longifolia	1.06	0.1
Acarbose	1.09	0.1

Effect of *A. longifolia* on Intestinal Disaccharidase Enzyme Activity

Asteracantha longifolia extract showed significant inhibition ($p<0.05$) of disaccharidase enzyme activity.

Figure : Effects of ethanol extract of ***A. longifolia*** on intestinal disaccharidase activity in normal rats: Rats were fasted for 20 h before the oral administration of ethanol extract of ***A. longifolia*** (100mg/kg body weight) or water (control). Enzyme activity was determined at 60min. Acarbose(200 mg/Kg) was used as reference control for disaccharidase activity test. Values are means and standard deviations represented by vertical bars (n=12). It significantly decreased ($p<0.05$) disaccharidase enzyme activity (derived from repeated-measures ANOVA and adjusted using Bonferroni correction).

Discussion



The prevalence of diabetes is rising relentlessly around the world. Current estimates suggest that, globally, the number of persons with diabetes will rise from 151 million in the year 2000, to 221 million by the year 2010, and to 300 million by 2025 (Amos et al 1997, King et al 1998).

This rise is predicted to occur in virtually every nation, with the greatest increases expected in developing countries.

Nature has been a source of medicinal treatments for thousands of years, and plants-based systems continue to play an essential role in the primary health care of 80% of the world's underdeveloped and developing countries (King et al 1998). Biguanides developed from a prototypic plant molecule is an excellent example of anti-diabetic drug development from plants. Thus, it is prudent in the current context to look for new and if possible more efficacious hits from the vast reserves of phytotherapy. Many herbal medicines have been recommended for the treatment of diabetes. On the other hand, as indicated by Marles & Farnsworth (1995), not all of the plants reported to be useful are entirely safe, and they emphasize the need for carefully planned scientific research to identify those hypoglycemic plants with true therapeutic efficacy and safety.

Renewed attention in alternative medicines and natural therapies has led to a revived interest in the use of traditional plants for the treatment of diabetes. In this regard the screening of plant materials for hypoglycemic properties is important as it might provide a new lead(s) as antidiabetic agent(s). *Asteracantha longifolia* has been using as an antidiabetic agent for a long time. Efficacy of this plant in the treatment of

diabetes has been studied in details. In the present study, this plant was selected to explore the mechanism of action in Long Evans rat.

In previous studies it has been found that *Annona squamosal* helped in total control of diabetes. In the present study we explored the extra pancreatic action of the plant in Long Evans rats.

In six segment method, the sucrose extract solution was administered to the model rat, water and sucrose was administered to the control. Then after 30 minutes, 60 minutes, 180 minutes and 360 minutes the rats were sacrificed to observe the amount of sucrose remaining in the gastrointestinal tract. From the result we can deduce that the extract of the leaf of *Asteracantha longifolia* was capable to cause a decrease in the amount of unabsorbed sucrose from the gastrointestinal tract.

The results obtained from both six-segment method and Intestinal Disaccharidase Enzyme Activity test significantly demonstrates, more conclusively, that the ethanol extract of *Asteracantha longifolia* can be effective in diabetic treatment.

Conclusion

The rapidly increasing prevalence of diabetes mellitus throughout the world will continue to challenge the existing therapies and encourage new approaches to counter DM.

The present study has evaluated potential antidiabetic activity of *Asteracantha longifolia*, traditionally used in the treatment of DM. The experiment carried out showedpositive hypoglycemic effects of the plant. Hopefully this will provide as a lead to carry out further investigation to assess whether or not *Asteracantha longifolia extracts* may be used commercially.

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