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A Review on Evaluation of Anti-Diabetic, Antipyretic and Anti-Cancer Activities of Ethyl Acetate Extract of *Jatropha curcas* Linn Fruits



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ABSTRACT

The present review justifies the potentials of *Jatropha curcas* Linn plant. *Jatropha curcas* l or physic nut is a drought resistant monoecious large shrub or small tree (5-8) m tall, belongs to the genus *Jatropha*, member of Euphorbiaceae family. The pharmacological studies revealed that *Jatropha curcas* Linn possess wound healing, antitumour, antimetastatic, antibacterial, larvicidal, anti-inflammatory, anti diabetic, anti-inflammatory and anti-arthritis activity. *Jatropha curcas* Linn possess a number of traditional as well as medicinal uses. Their traditional uses have attracted the attention of researchers, and as a result, reports on biological activity studies of the plant are increasing day by day. *Jatropha* is called by different names in different countries. In general, it is also called as Purging tree, Physic nut, curcas nut, Rathan jyot, Barbados nut, Curcas bean, Kukui haole, Purge nut, Katamanak, Kattamanakku, Pepalam, Kadaharalu, Jepal, Kanana Randa.



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INTRODUCTION

Medicinal plants have been used as a source of medicine to treat illness since ancient times, as the plant derived medicines have made huge contributions to human health. Their role is immersive in the development of new drugs. They may become the base for development of a medicine, a natural blueprint for the development of the new drugs or a phytomedicine to be used for the treatment. The chemical compounds present in the herbal products are a part of the physiological functions of living organisms and hence they are thought to have better compatibility with the human body^[1].

Diabetes

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and non-ketotic hyperosmolar coma. Serious long-term complications include cardiovascular diseases, stroke, chronic kidney failure, foot ulcers, and damage to the eyes^[2].

Complications responding to badly controlled diabetes^[5]:

Below is a list of possible complications that can be caused by badly controlled diabetes:

- **Eye complications** – glaucoma, diabetic retinopathy, cataracts and some others.
- **Foot complications** – neuropathy, gangrene, ulcers which may require that the foot be amputated
- **Heart problems** – such as ischemic heart disease, when the supply of blood to the heart muscle is reduced or diminished.
- **Skin complications** – people with diabetes are more susceptible to skin infections and skin disorders
- **Hypertension** – common in people with diabetes, which can raise the risk of kidney disease, eye problems, heart attack and stroke
- **Hearing loss** – hearing problems
- **Gum disease** – diabetes patients have higher prevalence of gum diseases
- **Mental health** – depression is more in patients with uncontrollable diabetes, anxiety and some other kind of mental disorders

- **Gastroparesis** – the muscles of the stomach stop working in proper.

MODELS FOR IDDM ^[3]

Chemically induced diabetes

Chemically induced Type-1 diabetes is the most commonly used animal model of diabetes. Chemical agent which produce diabetes can be classified into three categories, and include agent that

1. Specifically damage β -cell
2. Cause temporary inhibition of insulin production and / or secretion
3. Diminish the metabolic efficacy of insulin in the target tissues

Alloxan induced diabetes

Alloxan, a cyclic urea analog, was the first agent in this category, which was reported to produce permanent diabetes in animals

Mechanism of action

The mechanism by which it induces diabetes is not very clear. Alloxan is a highly reactive molecule that is readily reduced to diuretic acid, which is then auto-oxidized back to alloxan resulting in the production of free radicals. These free radicals damage the DNA of β cells and cause cell death. Second mechanism proposed for alloxan is its ability to react with protein SH groups, especially the membrane proteins like glucokinase on the β -cells, finally resulting in cell necrosis. However, there are major species differences in response to alloxan.

Streptozotocin-induced diabetes

STZ [2-deoxy-2-(3-methyl-3-nitrosourea)1-D-glucopyranose] is a broad-spectrum antibiotic, which is produced from *Streptomyces achromogenes*. Rakieta *et al* first described the diabetogenic property of STZ.

Mechanism of action

- *By process of methylation*
- *Free radical generation*
- *Nitric oxide production*

Hormone induced diabetes mellitus

Dexamethasone, a long-acting glucocorticoid, is used to produce NIDDM. An IDDM form of diabetes is produced when dexamethasone is administered at a dose of 2-5 mg/kg i.p twice daily over a number of days in rats.

Insulin antibodies-induced diabetes

Giving bovine insulin along with CFA to guinea pigs produces anti-insulin antibodies. Intravenous injection of 0.25-1.0 ml guinea pig anti-insulin serum to rats induces a dose dependent increase in blood glucose level up to 300 mg %. This unique effect to guinea pig anti-insulin serum is due to neutralization of endogenous insulin by the insulin antibodies. It persists as long as the antibodies are capable of reacting with insulin remaining in the circulation. Slow i.v infusion or i.p injection prolongs the effect for more than a few hours. However, large doses and prolonged administration are accompanied by ketonemia, ketonuria, glycosuria and acidosis and are fatal to the animals. After lower doses, the diabetes syndrome is reversible after a few hours.

Surgically induced diabetes

Induction of diabetes mellitus can be achieved through the surgical removal of all or part of the pancreas. In partial pancreatectomy, more than 90% of the organ must be removed to produce diabetes. Depending on the amounts of intact pancreatic cells, diabetes may range in duration from a few days to several months. Total removal of the pancreas results in an insulin- dependent form of diabetes and insulin therapy is required to maintain experimental animals. The portion of the pancreas usually left intact following a subtotal pancreatic resection is typically the anterior lobe or a portion thereof.

The third main form of diabetes is gestational diabetes which occurs when without a previous history of diabetes the pregnant women develop a high blood sugar level. Prevention and treatment involve a healthy diet, no tobacco use, physical exercise and attaining a normal body weight. People with this disease must also give immense care on blood pressure and proper food care. Type 1 diabetes is managed with insulin injections, with or without medication, type 2 diabetes may be treated. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in people with obesity is an effective measure in those with type 2 DM.

The following is the list of other causes of diabetes ^[4]

- **Genetic defects of β -cell function**
- Mature onset of diabetes
- Mitochondrial DNA mutations
- **Genetic defects in insulin processing or insulin action**
- Defects in proinsulin conversion
- Insulin gene mutations
- Insulin receptor mutations
- **Exocrine pancreatic defects**
- Chronic pancreatitis
- Pancreatectomy
- Pancreatic neoplasia
- Cystic fibrosis
- Hemochromatosis
- Fibrocalculous pancreatopathy
- **Endocrinopathies**
- Growth hormone excess (acromegaly)
- Cushing syndrome
- Hyperthyroidism
- Pheochromocytoma
- Glucagonoma
- **Infections**
- Cytomegalovirus infection
- Coxsackie B4 virus
- **Drugs**
- Glucocorticoids
- Thyroid hormone
- β -adrenergic agonists
- Statins

Pathophysiology

Insulin is the principal hormone that regulates uptake of glucose from the blood into cells of the body, especially liver, muscle and adipose tissue. Therefore, deficiency of insulin or the insensitivity and deficiency of the receptors play a central role in all forms of diabetes mellitus. Glucose is obtained in the body from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver, and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body. Insulin plays a critical role in balancing glucose level in body ^[4].

FEVER ^[5]

Fever refers to an elevation in body temperature. Technically, any body temperature above the normal oral measurement of 98.6 F (37 C) or the normal rectal temperature of 99 F (37.2 C) is considered to be elevated. Fever is the result of an immune response by the body to a foreign invader. These foreign invaders include viruses, bacteria, fungi, drugs, or other toxins. Fever, also known as pyrexia and febrile response, is defined as having a temperature above the normal range due to an increase in the body temperature set point. The increase in set point triggers increase muscle contraction and cause a feeling of cold.

Normal body temperature ^[6]

Normal body temperature shows certain variations over the period of a day which is controlled in the thermoregulatory centre located in the anterior hypothalamus. Fairly steady temperature is maintained by the body because of the hypothalamic thermoregulatory centre that balances the excess heat production, derived from metabolic activity in muscle and the liver, with dissipation of heat from the skin and lungs.

Hyperthermia ^[7]

When a body produces or absorbs more heat than it dissipates due to failed thermoregulation, hyperthermia occurs. To prevent disability or death, a medical emergency with immediate treatment is required. Extreme temperature elevation then becomes the most common causes include heat stroke and adverse reactions to drugs. The former is an acute temperature elevation caused by exposure to excessive heat, or combination of heat and humidity, that overwhelms the heat-regulating mechanism. The latter is a relatively rare side effect of many drugs, particularly those that affect the central nervous system. Malignant hyperthermia is a rare complication of some types of general anaesthesia. Hyperthermia differs from fever in

that the body's temperature set point remains unchanged. The opposite is hypothermia, which occurs when the temperature drops below that is required to maintain normal metabolism.

Pyrogens ^[7]

A pyrogen is a substance that induces fever. These can be either internal (endogenous) or external (exogenous) to the body. An example of exogenous pyrogen is the bacterial substance lipopolysaccharide present in the cell wall of some bacteria.

Pyrogenic cytokines ^[7]

Cytokines are pleiotropic molecules mediating several pathologic processes. The terms "granulocytic" or "endogenous pyrogen" were used to describe substance with the biologic property of fever induction.

Although fever is primarily associated with infectious diseases, a prominent component of many inflammatory and immunologically mediated diseases frequently accompanies certain malignancies. Increase in the total and relative numbers of circulating young neutrophils often occur. In addition, many febrile illnesses are accompanied by an increase in the synthesis of a variety of hepatic acute-phase proteins. These include antiproteases, haptoglobin, several complement components, fibrinogen, ceruloplasmin, and ferritin.

Fever, immunity and the inflammatory response ^[8]

Cytokine release is stimulated by exogenous pyrogen. IL-1, IL-6, TNF and INF reset the hypothalamic set point via the organum vasculosum of the lamina terminalis (OVLT). The body temperature is raised. Endogenous pyrogen also triggers immunologic, inflammatory and metabolic responses that in turn help control the exogenous pyrogen. Elevation in body temperature also improves the immunologic and inflammatory responses

WBC = white blood cell, IL-1= interleukin-1, IL-6 = interleukin-6, TNF = tumor necrosis factor, INF = interferon, NK = Natural Killer, Zn = zinc, Fe = iron, Cu = copper

Elevation of the hypothalamic set point by cytokines ^[9]

Levels of prostaglandin E₂ (PGE₂) are elevated in hypothalamic tissue and the third cerebral ventricle during fever. Near the circumventricular vascular organs networks of enlarged

capillaries surrounding the hypothalamic regulatory centres have the higher concentration of PGE₂.

The ability of pyrogens to produce fever is reduced by destruction of these organs. Both exogenous and endogenous pyrogens interact with the endothelium of these capillaries and that this interaction is the first step in initiating fever i.e., in raising the set point to febrile levels.

Production of cytokines in the CNS ^[5]

CNS production of these cytokines can raise the hypothalamic set point, by passing the circumventricular organs involved in fever caused by circulating cytokines. CNS cytokines may account for the hyperpyrexia of CNS haemorrhage, trauma, or infection.

Mechanism of antipyretic agents ^[5]

The reduction of fever by lowering of the elevated hypothalamic set point is a direct function of reducing the level of PGE₂ in the thermoregulatory centre. The enzyme cyclooxygenase accelerates the synthesis of PGE₂. The substrate for cyclooxygenase is arachidonic acid released from the cell membrane, and this release is the rate-limiting step in the synthesis of PGE₂. Major antipyretics act as inhibitors of cyclooxygenase. The inhibition of brain cyclooxygenase expresses the potency of antipyretics. Oral aspirin and acetaminophen are equally effective in reducing fever. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and specific inhibitors of COX-2 are also excellent antipyretics. Chronic, high-dose therapy with antipyretics such as aspirin or any NSAID does not reduce normal core body temperature. Thus, PGE₂ appears to play no role in normal thermoregulation.

Types ^[5]

- **Continuous fever:** Throughout the day, temperature remains above normal, and does not fluctuate more than 1 ° C in 24 hours, *e.g.* lobar pneumonia, typhoid, meningitis, urinary tract infection, brucellosis
- **Intermittent fever:** The temperature elevation is seen only for a certain period, later the temperature cycling back to normal, *e.g.* Malaria, kala-azar, pyrexia
- Following are the types of intermittent fever

- **Quotidian fever**, with a periodicity of 24 hours, typical of *Plasmodium falciparum* or *Plasmodium knowlesi* malaria
- **Quartan fever** (72 hours periodicity), typical of *Plasmodium malariae* malaria.
- **Remittent fever**: Temperature remains above normal throughout the day and fluctuates more than 1 °C in 24 hours, *e.g.*, infective endocarditis.
- **Pel-Ebstein fever**: A specific kind of fever associated with Hodgkin's lymphoma, being high for one week and low for the next week and so on.
- **Tertian fever** (48 hours periodicity), typical of *Plasmodium vivax* or *Plasmodium ovale* malaria

Pathophysiology ^[6]

Temperature is ultimately regulated in the hypothalamus. A trigger of the fever, called pyrogens, causes a release of prostaglandin E2 (PGE2). PGE2 then in turn acts on the hypothalamus, which generates a systemic response back to the rest of the body, causing heat-creating effects to match a new temperature level.

CANCER ^[10]

Cancer, known as a malignant tumour or malignant neoplasm, is a group of diseases involving abnormal cell growth which have the potential to invade or spread to other parts of the body. Not all tumours are cancerous; benign tumours do not spread to other parts of the body. The sign and symptoms include abnormal bleeding, a new lump, prolonged cough, and change in the bowel movements. While these symptoms may indicate cancer, they may also occur due to other issues.

Cancer is the name given to a collection of related diseases. In all types of cancer, some of the body's cells begin to divide without stopping and spread into surrounding tissue. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and divide to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.

On development this orderly process breaks down. As cells become more and more abnormal, old or damaged cells survive when they should die, and new cells form when they are not needed. The extra cells that are formed can particularly divide without stopping and

may form. Many cancers form solid tumours, which are masses of tissue in case of leukaemia, the cancer of blood, generally, do not form solid tumours.

Cancer at the cellular level

Cancer arises from the changes in genes that regulate cell growth. For a normal cell to transform into a cancer cell, genetic changes may occur in the genes that regulate cell growth and differentiation. The nature of the genetic change may be a single point change to a DNA nucleotide or the complete loss or gain of an entire chromosome. Most cancers require a series of genetic mutations in a cell before an invasive tumour results.

Tumour suppressor genes

These are genes which have a protective effect against oncogenes and are also known as anti-oncogenes. The tumour suppressor gene's normal function is usually to control the cell cycle or act as a checkpoint in division. When this function becomes lost due to mutations affecting both copies of the gene in a potentially malignant cell, other genetic mutations have a greater likelihood of progressing to cancer.

Tumour growth

A solid tumour represents a population of dividing and nondividing cells. In most solid tumours, the growth rate is very rapid initially and then slows as the tumour increases in size and age. The pattern of tumor growth kinetics has implications for chemotherapy is most successful when the number of tumour cells is low and the growth fraction is high, which is the situation in the very early stages of cancer.

Sign and symptoms

When cancer begins, it invariably produces no symptoms. Signs and symptoms only appear as the mass continues to grow or ulcerates. The findings that result depend on the type and location of cancer. Few symptoms are specific, with many of them also frequently occurring in individuals who have other conditions. Cancer is the new "great imitator". Thus, it is not uncommon for people diagnosed with cancer to have been treated for other diseases, which were assumed to be causing their symptoms

CHEMOTHERAPEUTIC AGENTS AND TREATMENT STRATEGIES ^[11]

There are a number of strategies in the administration of chemotherapeutic drugs used today. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms.

- **Combined modality chemotherapy** is the use of drugs with other cancer treatments, such as radiation therapy, surgery and/or hyperthermia therapy.
- **Induction chemotherapy** is the first line treatment of cancer with chemotherapeutic drug. This type of chemotherapy is used for curative intent.

Consolidation chemotherapy is given after remission in order to prolong the overall

- Disease-free time and improve overall survival. The drug that is administered is the same as the drug that achieved remission.
- **Intensification chemotherapy** is identical to consolidation chemotherapy but a different drug than the induction chemotherapy is used.
- **Combination chemotherapy** involves treating a patient with a number of different drugs simultaneously. The drugs differ in their mechanism and side-effects. The biggest advantage is minimizing the chances of resistance developing to any one agent. Also, the drugs can often be used at lower doses, reducing toxicity.
- **Neoadjuvant chemotherapy** is given prior to a local treatment such as surgery and is designed to shrink the primary tumor. It is also given to cancers with a high risk of micrometastatic disease.
- **Adjuvant chemotherapy** is given after a local treatment (radiotherapy or surgery). It can be used when there is a little evidence of cancer present, but there is risk of recurrence. It is also useful in killing any cancerous cells that have spread to other parts of the body.

PLANT PROFILE ^[12]

Classification

Kingdom	Plantae
Subkingdom	Tracheobionta

Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Malpighiales
Family	Euphorbiaceae
Genus	<i>Jatropha</i>
Species	<i>curcas</i>

Other names

Jatropha is called by different names in different countries. In general, it is also called as purging tree, physic nut, curcas nut, Rathan jyot, Barbados nut, curcas bean, kukui haole, purge nut, Katamanak, Kattamanakku, Pepalam, Kadaharalu, Jepal, Kanana randa.

Common names

Brazil	Pinhao manso
Nicaragua	Tempate
Philippines	Kasla/Tubatuba/Tubang
Indonesia	Jarak pagar
Tanzania	Mbono
Francophone Africa	Pourghere
Cambodia	Lahong Kwang
Vietnam	Dang iu ciu
Taiwan	Dang iu ciu
Nigeri	Lapalapa
Tamil Nadu	Aamanaku
Lao	Mak Nyao

Phytochemical constituents

- Curcacycline A (with anti-tumor activities)
- Phorbol esters
- Lysine
- Saponin
- Oleic acid
- β -sitosterol
- Jatropine Jatropham, Jatrophane and curcain with anti-cancerous properties
- **Bark:** β Amyrin, β -sitosterol and taraxerol.
- **Aerial parts:** o and p-coumaric acid, p-OH-benzoic acid, protocatechuic acid, resorsilic acid, saponins and tannins, β -Amyrin, β -sitosterol and taraxerol.
- **Seeds:** Curcin, lectin, phorbol esters, esterases and lipase.
- **Roots:** β sitosterol and its β -D-glucoside, marmesin, propacin, the Curculathyrans A and B and the curcusones A-D, diterpenoids, Jatrophol and jatropholone A and B, coumarin-tomentin, coumarino- Lignin-jatrophin, taraxerol.
- **Seed kernel:** phytates, saponins and trypsin inhibitor

REVIEW OF LITERATURE

Singhal Manmohan *et al* (2011) conducted a study on “Chemical and medicobiological applications of *Jatropha curcas*”, the main objective of the study was to discuss the taxonomy, botanical description of the plant, its distribution and ecological requirement, the presence of various chemicals constituents in different part of *Jatropha curcas* was also estimated, the potentiality of the plant and the pharmacological activities such as antioxidant, hepatoprotective, wound healing, anti-diabetic, anti-inflammatory, anti-ulcer activity using methanolic and hydroalcoholic extracts was carried out and found to have potential pharmacological activities^[13]

Muklesur Rahman et al. (2011) conducted a study on “Extraction of *Jatropha curcas* fruits for antifungal activity against anthracnose (*Colletotrichum gloeosporioides*) of papaya”. The antimicrobial activity of crude methanol extracts of *Jatropha curcas* fruits, pulp and seeds were investigated. Equivalent amounts of each ground sample of the *J. Curcas* fruits, pulp and seeds were soaked in methanol solvent and left to stand for 7 days before being filtered and evaporated. The extract was spread over potato dextrose agar (PDA) medium under an aseptic condition and incubated. The zone of inhibition of mycelia growth (mm) around the disc was measured. Both *Jatropha curcas* seed and pulp extracts had higher antifungal activity than whole fruit extract and concluded that Active microbial components in *Jatropha curcas* have the potential of an antifungal compound to control *Colletotrichum gloeosporioides* which causes anthracnose disease in papaya *in vitro*.^[17]

Ehsan Oskoueia et al. (2011) Conducted a study on Antioxidant, anti-inflammatory and anticancer activities of methanolic extracts from *Jatropha curcas* Linn, the main objective of the study was to estimate the phytochemical contents and biological activities of the methanolic extract from different parts of *Jatropha curcas* Linn and concluded that Cytotoxicity assay results indicated the anticancer therapeutic property of the root extract against human colon adenocarcinoma (HT-29) cell line but its cytotoxic effect on human hepatocyte was high.^[15]

Shanti Bhushan Mishra et al. (2010) Conducted a study on “antidiabetic effect of *Jatropha curcas* leaves extract in normal and alloxan-induced diabetic rats” aim was to investigate the antihyperglycemic effect of 50% ethanolic extract of leaves of *Jatropha curcas* (JCE) in alloxan induced diabetic rats and concluded that study demonstrated that the 50% ethanolic extract of *Jatropha curcas* had an antihyperglycemic effect in the alloxan induced diabetic rats when administered orally. It has been demonstrated that insulin deficiency in diabetes mellitus leads to a variety of derangements in metabolic and regulatory process, which in turns leads to accumulation of lipids such as cholesterol and triglyceride in diabetic patients. The abnormal high concentration of serum lipids in the diabetic subject is mainly due to increase in the mobilization of free fatty acids from the peripheral fat depots. In the present study, 50% ethanolic extract of leaves of *Jatropha curcas* decreases the cholesterol and triglyceride levels in the significant manner^[14]

FI Uche et al.(2010) Conducted a study on “The Phytochemical Constituents, Analgesic and Anti-inflammatory effects of methanol extract of *Jatropha curcas* leaves in Mice and Wister

albino rats “The analgesic and anti-inflammatory effects of the methanolic extract of the leaves of *Jatropha curcas* were investigated in mice and rats respectively. The phytochemical screening of the extract was also carried out and revealed the presence of flavonoids, steroids, triterpenoids, alkaloids, tannins and saponins in *Jatropha curcas* leaf extract. *Jatropha curcas* can be recommended for acute inflammatory disorders and diseases associated with pains ^[16].

CONCLUSION

However, still many drugs have to be investigated for their mode of their action and have not undergone through scientific investigations and accurate assessment of their effects. Hence it is time to consider all such natural herbs for determining their pharmacological activities isolating and finding out the real constituent responsible for the effect and developing suitable formulations. All the scientific data and observation leads to the conclusion that these support the traditional use of *Jatropha curcas* Linn fruits for treating the above stated diseases. Further research is required to isolate the bioactive constituents that are originally or accurately responsible for the reported biological activity. *Jatropha curcas* is a medicinal plant belongs to family Euphorbiaceae. It has several uses as a medicinal plant in various diseases like gout, jaundice, tumour, wound healing, toothache, blood coagulation from various ages. Plant extract is used in the treatment of allergies, burns, cuts, wound inflammation, leprosy, leucoderma and smallpox. Water extract of branches used to treat HIV and tumour. Plant extract is used to treat wound healing. Various parts of the plant are used in the treatment of various diseases.

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