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PHYTOCHEMISTRY AND THERAPEUATIC POTENTIAL OF EURYALE FEROX: A COMPREHENSIVE REVIEW

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Abstract
Euryale ferox recognized by various nomenclatures including Phool Makhana, Fox Nut, Black diamond and White balls is widely acknowledged due to its secondary metabolite composition and pharmacotherapeutic significance. It is a hydrophytes plant species, it consists of essential bioactive components comprising polysaccharide, polyphenols, flavonoids, dietary fiber, resistant starch, kaempferol, cystine, arginine and methionine. These components play significant developmental role and provide protection against certain lethal diseases. Evidenced based investigations have proved that Euryale ferox plays significant role in enhancing cardiovascular supply by increasing the number TRP32 and Trx-1 proteins. It also reduces the oxidative stress through its free radical scavenging activity. It is a nutrient dense food and it contains 84.9% carbohydrates, 9.5% protein, 4% moisture and 0.5% fat. Raw seeds and popped seeds both are implemented on substantial scale in both pharmaceutical and Agro-based industries. Special harvesting techniques and tools are employed during harvesting for preventing post-harvest deterioration. Fox nut has wide-ranging health attributes it is used as therapeutic agent for certain diseases including diarrhea, gonorrhea, spermatorrhea, ulcer, cancer, fatty liver and rheumatoid arthritis. It is rich in essential ammino acids which play crucial role in delaying aging.

INTRODUCTION

Euryale ferox is broadly acknowledge as foxnut or makhana. It is a plant specie that thrives only in aquatic habitat therefore referred as hydrophyte. It is affiliated with the Euryalaceae family which is taxonomically linked with more inclusive water lily family Nymphaeaceae which are rhizomatous perennials. Due to its commercial and nutraceutical importance it is globally cultivated as aquatic agronomic crop. Land in Mithila region in north Bihar India contains soil in which calcium carbonate commonly referred as lime is present in very negligible amount which yields conductive conditions for cultivation of makhana. As a consequence of this makhana crop is agronomically developed in this region. According to recent statistical analysis 10 districts located in this region have well entrenched makhana

cultivation system. The fields in which soil is saturated with water recognized as waterlogged fields, ponds and wetlands including swaps, marshes, flood buffers and coastal mangroves are the principal locations where farmers grow this crop. Makhana is processed through successive steps encompassing cultivation, harvesting of seeds, and processing in which raw makhana seeds are popped into edible makhana. The leading region of commercial makhana yield is Mithila where it boosts up the peasant sustenance and local economy (Jha and Kumar, 2022). An internationally acknowledge water dwelling flora *Euryale ferox* is identified by diverse nomenclature including Phool Makhana, Makhana, fox nut prickly water lily and gorgon nut but the most common name is Phool Makhana. In agriculture and local diets, it plays significant role in addition its processing and cultivation substantial for nutritional and economic purposes (Rathod et al., 2023).When the spherical seeds of *Euryale ferox* proliferate and become voluminous and soft textured edible enlarge kernel comes out from it. When seeds are in their raw form their outer most covering commonly referred as seed coat is dark pigmented and tough. Due to its jet black and lustrous looks it is dominated as "Black Diamond". During roasting on low flame, they swell and enlarge in size than usual they burst usually referred as popping and the dense jet-black integument explodes white and soft inner core appears. Due to spherical shape and pearl colored morphology, they are famous as "White Balls"(Journal W 2019).According to empirical investigation foxnut have high nutritional value because of the important nutrients inherent within it. It is abundant in carbohydrates which are the major source of energy. Carbohydrates give 4kcal of energy per gram. Proteins are obligatory for muscle development and repair. Proteins give same energy as carbohydrates. Fats are required for certain indispensable hormones synthesis and these all nutritionally significant nutrients are present in it. According to statistical analysis a single makhana seed contains 84.9% carbohydrates, 4% moisture, 9.5% protein and minimum fat content approximately 0.5% because excess of fat can leads to certain chronic diseases and makes it a healthy snack. Depending on processing techniques applied and diversity in makhana species nutritional content pertained in it may vary they can show higher protein content about 15.6% and fat content of 1.36%. During processing and harvesting important industrial raw material is separated from it which facilitates cotton industries. Comprehensively fox nut is considered as high energy, low fat and protein rich food. Some scientific investigations have revealed surprising facts about it like 100 grams of raw or popped makhana contains 362 kcal and 328 kcal means that during preparatory operations in makhana processing some calorie content is lost. Some nutritive dried fruits such as walnuts, coconuts, cashew nuts and almonds have same nutritional content as makhana has because they all have protein and healthy fats content in common. When the protein content of makhana is compared with that of a boiled egg it was evident that of an egg. In addition, it is abundant in certain conditionally essential ammino acids including arginine, alanine and tyrosine which play major role in regulating normal metabolic rate. As amino acids are the building block of proteins and proteins regulate important maturation and regeneration functions (Jannathulla et al.,2022). Phool makhana have pharmacodynamic effect on human body. It reduces elevated blood glucose level through its antidiabetic activity. Through several experiments it is concluded that it boosts up energy levels due to high carbohydrate content present in it and reduces tiredness through its antifatigue impact. Due to excess acid production in stomach, it starts do damage the mucosal lining of stomach leading to ulcer as *Euryale ferox* have the proficiency to repair mucosa so it is effective in the treatment of ulcer. Through the prevention of cell-to-cell inhibition phenomenon malignant (cancer) tumors appear it retards the proliferation of cancer tumors. Due to incomplete metabolism free radicals of nitrogen and oxygen starts to accumulate in body which later interact with cells and disrupt their activity Phool makhana fight against them and protects the body cells. As

diabetes is a chronic disease and it leads to kidney failure by interrupting the activity of nephrons which are the functional unit of kidney concerned with the filtration of blood and production of urine (Mittal R et al.,2020). Traditionally it is used to cure diverse pathological conditions like uncontrolled ejaculatory discharge referred as spermatorrhea. Pathogenic bacterial invasion (gonorrhea), menstrual cramping, loss of bladder control due to bladder muscle weakness are also treated through white balls. People suffering from diarrhea take it as a medicine (China Med. Sci 2020).

Structure of Euryale Ferox

Euryale ferox can propagate for one or many years depending on variety in an aquatic habitat like ponds, lakes and rivers therefore designated as annual or perennial amphibious herb. The main supportive stalk of plant (stem) is covered coated with sharp spikes. Prickly Waterlily have voluminous, buoyant and centrally petioled leaves that are not segmented. Leaves surface is broad ranging. Geometrical measurement of leaf is 30 ×25-110cm. Flowers are adhered to prolonged shoot above the water they are not floating like leaves because extended stem provides them support. At the base of flower 4 sepals are present they are obovate triangular and succulent clorophyllous prickles are surrounding them from outside and the inside is pink or violet. It has bi pigmented petals. Petals that are located inside towards the corolla are white in color and the petals located outside are usually purple red, deep violet or purple in shade. At the tip exserted petals are incurved, rectangular ovate and moderately bent. The male fertilizing part of a flower (stamen) consists anther and filament. In fox nut two types of stamens are observed outer stamen and inner stamen. Inner stamens are 4-6mm and outer stamens are 8-10mm long. Seeds of fox nut contain polysaccharide rich and light weight endosperm. Morphologically they are corrugated, dusky brown and ovoid spherical. They are 7-12mm in diameter. Each seed has a seed coat named as Testa that protects the underlying endospermic components in the periphery of seed coat snowy, delicate and juicy envelope is located named as aril. On aril interspersed markings are embedded (Jana, 2018). Euryale ferox is a genus that have only one specie therefore it is recognized as monotypic genus. Major requirement for its growth and propagation is water because it is a water loving plant specie. Flood plain marsh where water is static and marginal about 4-5 feet deep is best for its maturation because it satisfies all the optimum conditions required for it. When humidity, well aerated soil and high temperature were provided to Phool makhana seeds it was observed that they germinated under these optimum conditions. Hypogeal germination is a type of germination in which cotyledons hypocotyls stay inside the soil and grow up to a certain limit inside instead of coming outside. This germinative pattern is observed in *Euryale ferox* (Nehal N and Mann S 2015). Optimum conditions for the growth of this plant encompasses elevated temperature with abundant solar exposure. It cannot withstand with low thermal regime and drought prone conditions so these circumstances must be averted while its growth. Optimum temperature for its proliferation is 20-30 °C. Soil that is rich in micro and macro nutrients especially nitrogen and phosphorous and organic matter (dead or decade plants and animals residue) is most favorable for it (Yamada et, al 2001; Zhang et, al.2022).

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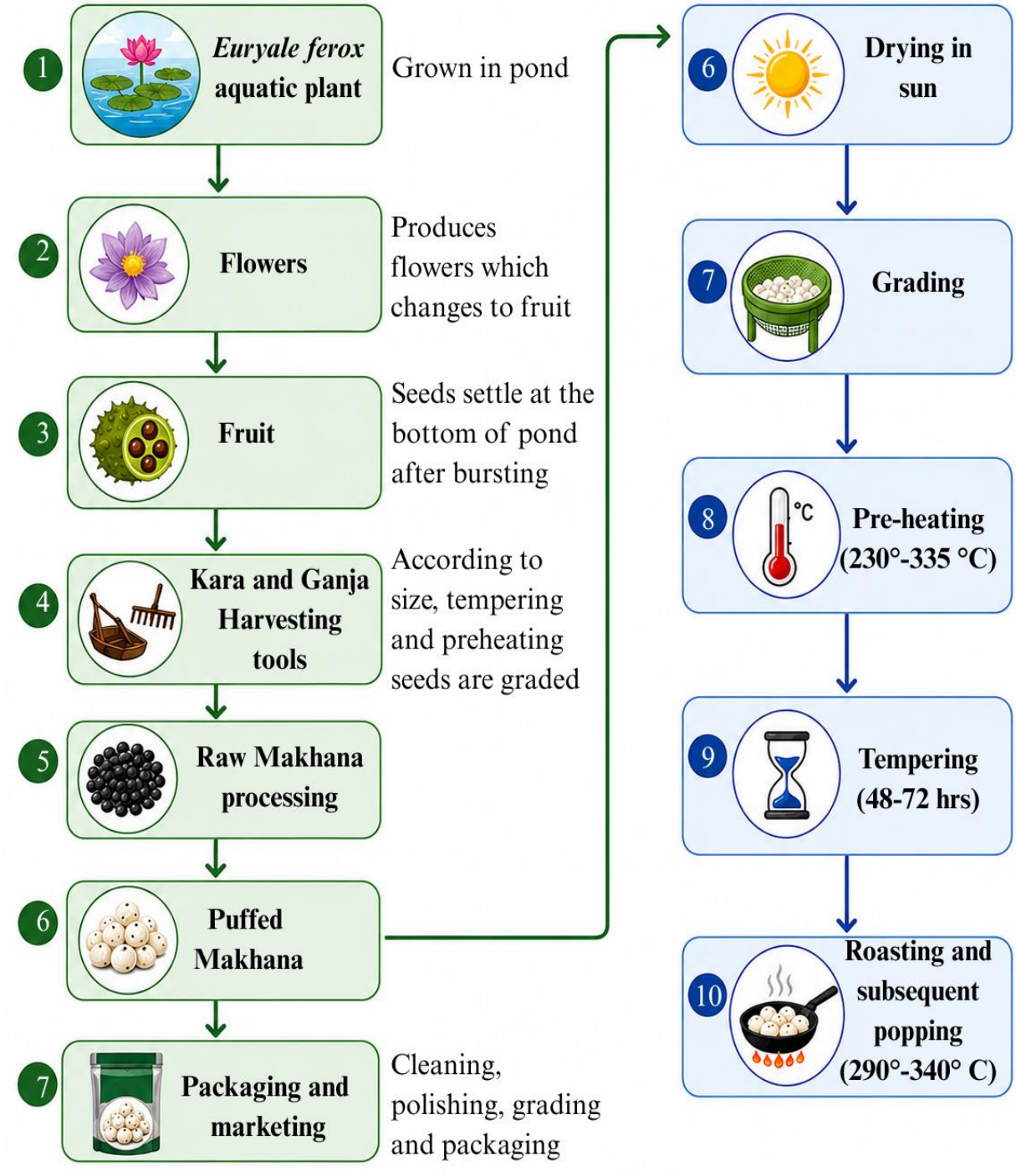


Figure Showing the processing of raw seeds of Fox nut

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BIOACTIVE COMPOUNDS PRESENT IN EURYALE FEROX

Polysaccharide

Polysaccharide is extended molecular frame work encompassing multiple monosaccharide units bridged through glycosidic bond. They are the important constituent of *Euryale ferox* because they have significant impact in the treatment of certain diseases and it is evident through multiple researches that *Euryale ferox* has been extensively used in medicinal drugs. In order to evaluate polysaccharide content contained within Phool makhana a range of investigative techniques including DEAE-52 cellulose chromatography and Sephadex G-100 column chromatography were applied. Through the application of these procedures a polysaccharide named as EPJ(1) was isolated. Predominantly these techniques are preferred to extract a particular compound from others that exist in plants. After comprehensive evaluation it was observed that EPJ is composed of two sugar units Glucose and rhamnose present in 5.46:1. Glucose is the main constituent of EPJ as proved by statistical analysis. 5.46 glucose molecules were recorded for a single rhamnose molecule. Molecular weight of this compound is 15.367 kDa which indicates that it is a intermediate molecular weight polysaccharide contained within fox nut (Chen et, al 2014).

Flavonoids

In order to prove the presence of flavonoid content in Fox nut seeds various experimental procedures were performed. Flavonoids are referred as secondary metabolites due to there essential pharmacological attributes in treatment of certain chronic diseases including cardiac arrest and inflammation etc. To prove the flavonoid content present in Phool makhana extract a sequential procedure was performed. 125 µL of phytochemical extract of *Euryale ferox* dissolved in methanol was taken. Plant extract was dissolved in methanol because it is highly polar and facilitates in extraction of bioactive compounds from the extract. After this 75 µl of 5% sodum nitrate was added in the above sample upon completion of 6 minute duration it started reacting with the total flavonoid content contained within it. After this $AlCl_3$ was added for the final detection of flavonoids because on reaction with aluminum chloride it forms a colored complex. After this 750µL of 1M NaOH is added. With optimal concentration add distilled water till the volume becomes 2.5mL this increases the pH of the solution above 7 which lies in the alkaline range due to which the color of the measurement is enhanced. After 15 minutes of incubation through the utilization of UV spectrophotometer measure absorbance at 510nm. Flavonoid content in the sample is measured by the absorbance of light of particular wavelength. Mg catechin equilent per gram of sample is the reference used to express the results. Standard compound catechin is compared with the flavonoid (Rebaya et al. 2015). *Euryale ferox* contains 129 different flavonoid compounds pertaining 11 flavanones, 16 flavanols, 8 dihydroflavanols, 29 flavanoids, 3 isoflavones, 29 flavanols, 12 anthocyanin, 3 isoflavones, 6 flavonoid glycosides which are the most eminent flavonoids (Wu et al., 2021).

Polyphenols

Polyphenols are endogenous metabolites enriched with trace elements in plants. They defend against ultraviolet irradiation activity which plays an important role in protection against certain crucial diseases. They are important phytochemicals in plant because they play role in protecting plants from environmental stress therefore referred as secondary metabolites. They are not essential for their existence. Systematic experimental investigation has elaborated that fruit, leaves, roots, seed shell and skin contain abundant presence of polyphenols. Ultrasonic assisted extraction technique is widely accepted and pervasively implemented world wide for extraction of polyphenols from *Euryale ferox.* When ultrasonic waves are bombarded on the plant it stimulates the release of more polyphenols from the fox nut it is the fastest technique of polyphenol extraction. As identification of polyphenol is a prolonged and exacting High Performance Liquid Chromatography commonly referred as HPLC is implicated. This technique accurately and

precisely explains the composition of each chemical component present in a particular plant specie. On HPLC of Phool Makhana 1 flavonoid and 3 polyphenols were obtained (Wu et al., 2021).

Dietary Fiber and Resistant Starch

Dietary Fiber is fermentable non digestible substrate. Human stomach is non endowed with specific enzymes required for its digestion because it is the food for beneficial intestinal bacteria and is also designated as intestinal fertilizer. It is a hydrogenous group encompassing gums, lignans , pectin, cellulose and hemicellulose. Staple crops including wheat and oats are the abundant source of fiber. Moreover cereal, millet bran, fruits and vegetables also contain dietary fiber. Recent scientific studies have evidenced that Phool makhana contain markedly elevated level of dietary fiber which is physiologically beneficial for the gut health. In order to study the total starch content present naturally in the *Euryale ferox* through milling operation raw Phool makhana seeds were converted in to refined flour and then it is treated with amylopullulanase which changes the structure of starch through its enzymatic activity. .As result of retro degradation starch becomes and behaves like fiber which is not easily digested and do not increase the glycemic index instantly therefore it is preferred for diabetic patients (Biswas et., al 2020).

Phytochemical content present in Foxnut

Phytochemicals present in Foxnut play very important role in strengthening the immune system. It pertains minute quantity of calcium about 0.02%. Calcium plays a significant role in muscle contraction and bone strengthening it also acts as a cofactor in certain enzymatic processes. Phosphorous is the main constituent of energy currency of cell commonly referred as Adenosine Tri Phosphate (ATP). It is the essential prerequisite for all the energy dependent metabolic processes running in the body. *Euryale ferox* contains about 0.9% of phosphorous. Iron is the basic, structural and functional component of the hemoglobin it is the oxygen carrying molecule and transports oxygen by binding it with its heam group. Deficiency of iron in human body leads to anemia. Single seed of Phool makhana contains approximately 0.0014% of Fe. Systematic investigations have elaborated that Phool makhana seeds contain a specific quantity of water content. On moisture analysis it was proven that it contains 12.8% of moisture which is a small quantity so they can be stored for long time under room temperature due to relatively less moisture content present in it. Low moisture content makes the conditions unfavorable for microbial growth there by increasing the shelf life of the foxnut. Its seeds additionally contain some important nutrients including glucose which is the quick source of energy because it is the only molecule which is directly permissible in the blood stream. Important antioxidants that play significant role in reducing cellular stress by eliminating free radicals produced by incomplete oxidation of food are also contained within it. Phenols are the most prominent and abundant antioxidant present in foxnut. The most sensitive vitamin ascorbic acid conventionally termed as vitamin C is abundantly present in it which have remarkable role in nurturing the human body as well as in cosmetic industry for making dermatological products. Ascorbic acid also plays an important role in collagen formation and reducing aging symptoms. An intriguing finding in *Euryale ferox* is that it can fulfil its nutrient requirements even when it is grown in nutrient deficit soil. When this plant is grown in sodium deficit soil it was observed that it continue growing normally with its optimum sodium requirement. This proved that it can be grown in low mineral content areas successfully because it has the capability to adapt to poor soil conditions (Jha et al.,2018). On analysis of the seed extract of Foxnut it was noted that many secondary metabolites that are nutraceutically beneficial are present in it. Secondary metabolites not directly influence on growth but are significant in protection and survival. Steroids, Alkaloids, Glycosides, Phenols, Tannins, Saponins and Flavonoids are the seven major secondary metabolites present in *Euryale ferox* (Parry et al., 2011 ; Kumar et al., 2016). Kaempferol a well-

known flavonoid significant for neutralizing harmful molecules through its antioxidant activity is abundantly found in foxnut. It reduces irritation, swelling and pain in body and also slows down cell damage by neutralizing free radicals through its anti-inflammatory and anti-aging effect (Kaur et al., 2014: Jana et al., 2024).

Amino acids present in fox nut

A highly nutritious food *Euryale ferox* is superabundant in essential and non-essential amino acid which are indispensable for normal growth and development. Meticulous scientific investigation have revealed that foxnut contains 10 functionally important amino acids encompassing arginine, alanine, proline, cystine, glutamine, leucine, aspartic acid and serine. Arginine a semi essential amino acid which is essential in the developmental phase but once the body has been completely developed it becomes non-essential because human body adapts the mechanism for its production. It improves blood circulation because a molecule nitric oxide (NO) is produced under its influence which is responsible for vasodilation so it dilates the blood vessels and increases the blood supply rate. Moreover, it enhances the flexibility of arteries and veins through which the delivery of nutrients and oxygen to skin cells is enhanced it is also an anti-aging agent. Arginine acts as a natural booster for glowing skin and is widely used in cosmetic industry. Due to moisture capturing ability of arginine, it locks the water content and keeps the skin hydrated and fresh and is beneficial for repairing the barrier damage (Zhang M, et al 2004; Castillo L, et al 1993). An essential amino acid which is through out the life required by the human body named as methionine is vastly present in it. It is a Sulphur containing amino acid and plays a pivotal role in collagen and keratin production. Improves elasticity of skin through collagen production and prevents hair loss by strengthening hairs and preventing their breakage through enhancing keratin production. It is given as a supplement for hair strengthening (Williams JZ, et al 2002 ; Mathivanan, et al 2022). Cystine which is formed from cysteine and is essential structural component of keratin is found in Phool makhana it plays rebuilding role in repair of hairs and skin tissues. During arthritis which is the inflammation of joints this ammino acid is prescribed through medications to prevent swelling and reducing symptoms of this pathological condition (Govindarajan, et al 2021).

Table demonstrating essential bioactive components and their roles that are abundantly found in Euryale ferox

Bioactive Components	Substantial evidence	Experimental methodology	Therapeutic and physiological benefits	References
Flavonoids	129 flavonoids compounds including flavanols, flavanones, anthocyanins, flavonoid glycosides and isoflavones are pertained within *Euryale ferox.*	Employing catechin as equivalent standard quantitative absorbance assessment was performed at 510 nm on the methanolic extracts of Phool makhana treated with NaOH and $AlCl_3$.	They act as secondary metabolites through their oxidative stress mitigating potential, immunomodulatory activity and cardiovascular safeguarding properties.	Rebaya et al., 2015; Wu et al., 2021

Polysaccharides	EPJ(1) a polysaccharide present in *Euryale ferox* pertains glucose and rhamnose in its structure in 5.46:1 with molecular magnitude of 15.367 kDa.	For extraction and purification Sephadex G-100 column chromatography and DEAE-52 cellulose chromatography techniques were incorporated.	Have significant pharmacotherapeutic value and pathological management.	Chen et al., 2014
Dietary Fiber and Resistant Starch	High content of resistant starch and dietary fiber has been analyzed on statistical analysis Retro degraded starch is not digested and acts as a fertilizer for intestinal flora.	Popped seeds were converted into fine powder through milling and then were treated with amylopullunlanase for testing the presence of starch.	Highly preferred for the diabetic patients because of its glycemic index lowering impact and high satiety .	Biswas et al., 2020
Polyphenols	On HPLC analysis 1 flavonoid and 3 polyphenols were verified in the leaves, fruits, seed shell and roots of the Phool makhana.	HPLC was used for identification and Acoustic wave facilitated extraction techniques were involved.	Act as free radical scavenging agent and facilitate plant resilience under stress conditions.	Wu et al., 2021
Secondary metabolites	Flavonoids, saponins, tannins, phenols, alkaloids, glycosides and sterols.	Phytoconstituent characterization of seed extract.	Important for stress resistance plant viability and pharmaconutritional value.	Parry et al., 2011 ; Kumar et al., 2016
Minerals and Nutritional Components	Contains phosphorous=0.9%, calcium=o.02%, iron=0.0014% and moisture=12.8%. Additionally, vitamin C, phenols and glucose are also present in it.	On seeds nutrient and moisture analysis techniques were employed.	Phosphorous is the part of energy generating molecule (ATP) and is responsible for ATP production, calcium supports teeth and bones and crucial for excitation contraction coupling in muscles, iron prevents anemia and is constituent of erythrocytes, vitamin C have anti-aging	Jha et al., 2018

			impact through collagen formation. Low moisture content increases the shelf life.	
Kaempferol	Flavonoid are present in abundance in *Euryale ferox.*	Metabolic assessment of seed phytochemicals	Through neutralizing the impact of free radical species it exhibits anti-inflammatory, anti-oxidant and anti-aging impact.	Kaur et al., 2014; Jana et al., 2024
Cystine	Present in the structure of keratin which is the significant bioactive compound present in fox nut.	Analytical elucidation of amino acid composition	Helps in the strengthening and repair of hair and skin barrier and due to its immunomodulatory impact reduces the risk of inflammation during arthritis.	Govindarajan et al., 2021
Arginine	Conditionally essential amino acid found abundantly in fox nut.	Analytical investigation of nutritional and biochemical constituents.	It enhances the production of nitric acid which is mainly responsible for enhancing blood circulation throughout the body.	Zhang et al., 2004; Castillo et al., 1993
Methionine	Essential amino acid containing Sulphur as the main constituent found in *Euryale ferox.*	Biochemical nutritional investigation	Responsible for the production and synthesis of collagen and keratin which play pivotal role in maintaining skin elasticity and hair strength.	William JZ et al., 2002; Mathivanan et al., 2022

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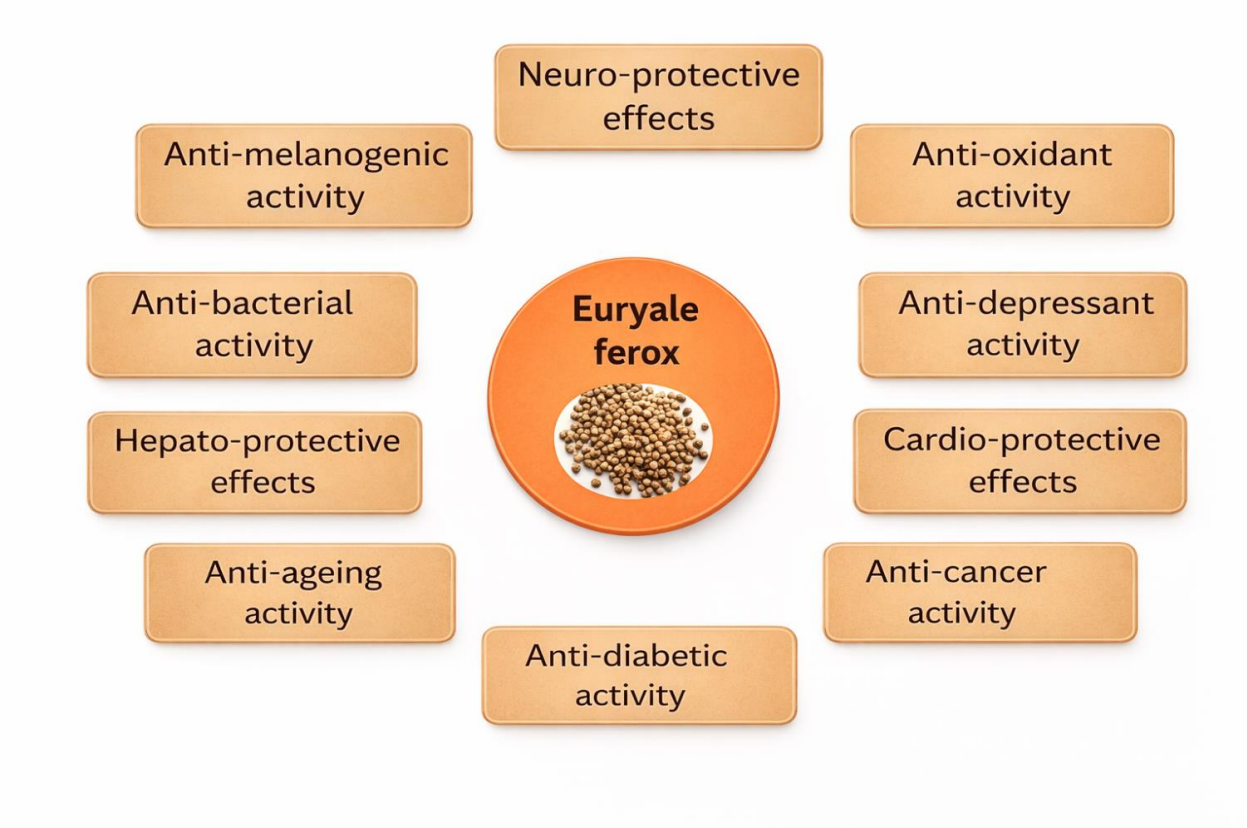


Figure Showing the overall Health Benefits of Euryale ferox

Anti-depressant Impact of Euryale ferox

According to statistical analysis it has been recently estimated that 50 million people residing in Pakistan are afflicted with mental health problems including post-traumatic stress disorder, drug addiction, anxiety and depression (Malik et al 2025). Pharmacotherapeutic analysis has revealed that bioactive compounds present in Phool Makhana encompassing flavonoids and polyphenolics have potent characteristics to neutralize the free radicals of oxygen and nitrogen thereby reducing the oxidative stress through there antidepressant and anxiolytic effect (Rendeiro C et al 2009). Glutamate is an important chemical messenger that assists brain in coordination of activities such as brain communication and learning it helps to keep the brain cells active. But if the concentration of Glutamate exceeds beyond optimum level it can damage the brain cells through its glutamate-induced toxicity. Excess glutamate in the brain cells is significant cause of oxidative stress. In order to illuminate the impact of *Euryale ferox* as anti- depressant methanol and ethanol extracts of fox nut were tested on special neurological cells referred as N18-Re-105 cells. High amount of glutamate 20mM was administered into the nerve cells usually without the assistance of methanol and ethanol extracts brain cells cannot survive so the foxnut extracts increased the life span of neurological cells through there neuroprotective impact. On frequent analysis it was concluded that on increasing the dosage of extract the neuroprotective impact was significantly increased (Vikram and Mishra DS 2021). Detailed analysis on fox nut extracts comprehended that the antioxidant property varies from part to part because of variation in the concentration of

bioactive and polyphenolic compounds present there. Seed coat, pedicles, leaves and petioles showed lower antioxidant impact as compared to the seed (Wu, C. et al., 2014). When germinated seed powder extracts were compared with the non-germinated seed powder extracts of fox nut it was discovered that upon germination the antioxidant capability of the *Euryale ferox* is enhanced.

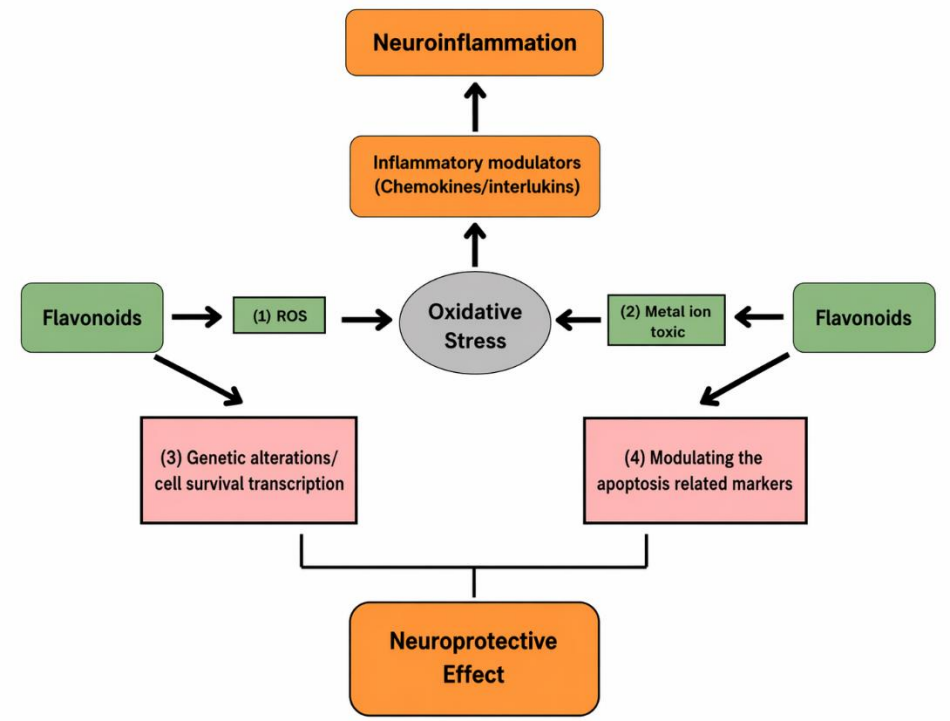


Figure illustrating the neuroprotective and anti-oxidant impact of Euryale ferox extracts

Cardio-protective Impact of Euryale ferox

According to computational analysis recorded by the experts approximately 85 % of the deaths related to cardiocirculatory disorders associated with heart and blood vessels. Stroke a life-threatening condition in which neuronal degeneration occurs because blood supply to the brain is cut off is intricately associated with the deficient vascular supply by the cardiovascular system. When coronary arteries become inefficacious to supply oxygenated blood to the heart due to fat deposition in them commonly referred as atherosclerosis is the leading cause of heart attack or myocardial infarction. In short myocardial infraction and stroke are lethal cardiovascular disorders (WHO 2017). Contemporary scientific investigations have demonstrated that therapeutic adjuncts isolated from pharmacologically active plants pertain therapeutically active constituents that play significant role in diminishing susceptibility to cardiac pathology. The chemical entities produced by the plants alongside with the indispensable metabolic compounds essential for plant growth referred as secondary metabolites are the dominant character that play paramount role in prevention of such life-threatening disorders. Secondary metabolites pertaining terpenoids, polyphenolics, fatty acids, flavonoids, saponins, alkaloids, carotenoids and cardio stimulatory glycosides are considered to be the most effective botanical bioactive compounds that contribute substantially to diminishing the risk of heart related chronic disorders (Rana, Goyal N et al

2015). In order to experimentally determine the impact of ethanolic extracts of *Euryale ferox* incorporating significant bioactive molecules an experimental frame work was designed. The experimental analysis was performed on rats and results were analyzed through acute treatment model and feeding model. In acute experimental model the impact of ethanolic extracts was tested by isolating the heart of rats and preserving its functional integrity in an experimental environment. After that makhana extracts were directly introduced to the hearts blood supply the results substantiated that the flow of blood through the coronary arteries was significantly improved lowering the risk of cardiovascular disorders. In the feeding model for 21 days rats were put in the optimum laboratory conditions and specific dosage of ethanolic extracts ranging from 250mg/kg and 500mg/kg was administered into the rats. After 21 days of the experimental analysis the rat's heart was separated and was exposed to lack of blood supply for 30 minutes in order to evaluate the strength of myogenic activity of the rat's heart and 2 hours were provided for the restoration of the blood flow called reperfusion. As a final point scientists quantified aortic and coronary circulation and compared the results with the control group. Makhana treated rats demonstrated substantial reperfusion of blood flow after 60 and 120 minutes. The experimental investigation also proved that the cardiac tissue damage zone during heart attack was reduced in the rats that were treated with ethanolic extracts. Thioredoxin-related protein-32(TRP32) and Thioredoxin-1(Trx-1) contribute substantially in protecting heart from fatal cardiovascular disorders were significantly increased in rats that were treated with the extracts of *Euryale ferox*. Antibody array technique was involved to test the presence of these proteins (Azhar M, et al 2015). Due to the abundance of TRP32 and Trx-1 in Makhana it protects the heart from myocardial ischemia-reperfusion injury. Due to free radical reducing impact of these proteins, they act as scavenger and reduce level of reactive oxygen species (ROS) by neutralizing their impact (Das, S et al 2006).

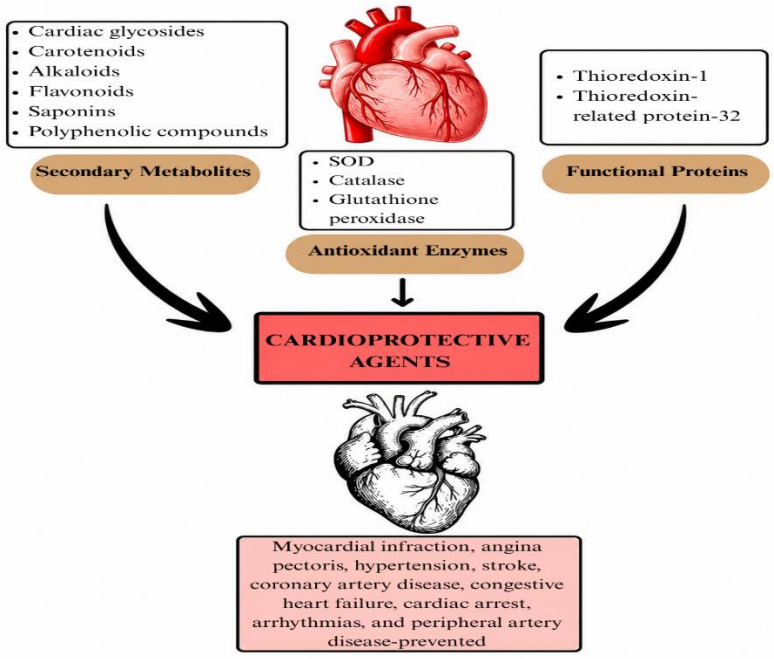


Figure showing cardio-protective agents present in Phool Makhana

Antihyperglycemic potential

Scientific studies on *Euryale ferox* have revealed that it is rich in oxidative stress-ameliorating biomolecules. They play significant role in reducing oxidative stress by scavenging free radicals that interrupt in normal physiological mechanisms. Oxidative stress is directly associated with diabetes because increase in the concentration of reactive oxygen species increases insulin resistance by making body cells least sensitive towards the elevated blood glucose level due to which they become resistant towards insulin. Diabetes directly impact on the normal functioning of nephrons within the kidney. Nephrons are the structural and functional units of the kidney. Pathophysiological impairment of nephron function due to diabetes leads to hyperglycemia-induced neural impairment. Ethanolic extracts of *Euryale ferox* pertains 2β-hydroxybetulinic acid 3β-caprylate (HBAC) an endogenous antioxidant constituent known for its glycemic index lowering ability. It lowers the elevated blood glucose level by stimulating the β cells of pancreas to secrete insulin and also reduces the insulin resistance by making cells sensitive towards the insulin uptake. Increased level of insulin lowers the risk of diabetes and hyperglycemia associated kidney disfunctions (Liaquat M, et al., 2022). On further studies when the extracts from germinated and non-germinated seeds were compared for phytochemical profiling it was evident that the germinated seeds have more concentration of bio functional polyphenolic compounds as compared to non-germinated seeds. Germination elevates the density of 27 therapeutically active polyphenols. Polyphenols reduce the oxidative stress through their radical detoxification potential. Renal biomarkers are the measurable substances in the urine which are used to evaluate the renal functioning. Germinated seed extracts of *Euryale ferox* enhanced renal biomarkers reflecting protective efficacy against nephrotoxicity. Certain metabolic pathways speed up while testing the germinated extracts which showed efficient metabolic functioning. AMPK/mTOR pathway associated with the energy metabolism and regulation of glucose level was significantly enhanced. Keap1/Nrf2/HO-1 is involved in reducing the oxidative stress by neutralizing the free radicals was significantly potentiated reflecting decrease in oxidative stress. As a consequence, it was proved that germination enhanced the therapeutic potential of *Euryale ferox* against diabetes and hypoglycemic linked nephronic functional impairment (Wang, Y and Yuan et al ., 2023). Makhana has gained global popularity due to enhanced nutraceutical and remedial potential. It is a low glycemic index food because it releases glucose slowly into the blood stream maintaining a stable blood glucose level there fore it is preferred for the diabetic patients due to its glucose modulatory impact. For several years it is being traditionally consumed in China and India but now a days it attained widespread recognition in Europe, North America and other countries (Kapoor et al., 2023).

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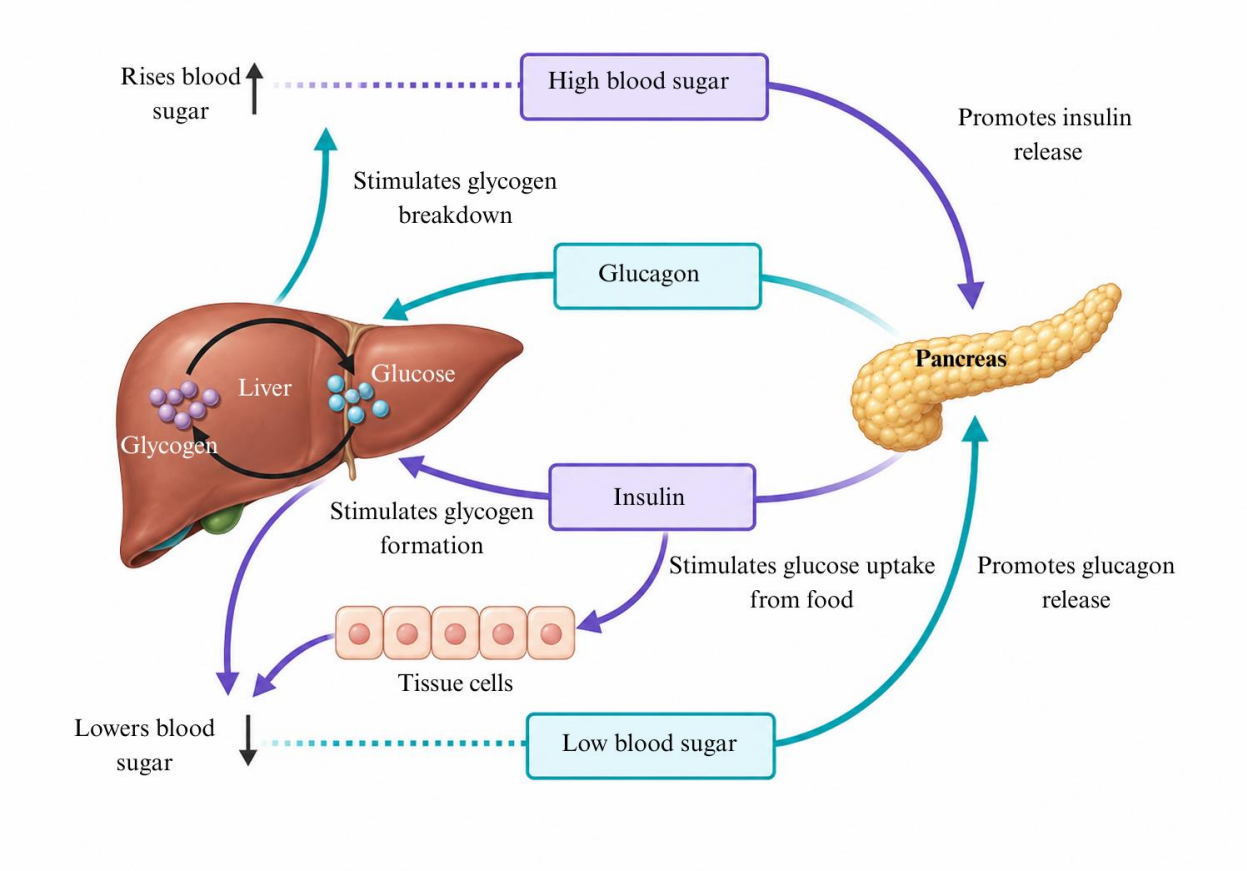


Figure illustrating the regulation of glucose in body by pancreas

Therapeutic potential in arthritis management

Rheumatoid arthritis is an immunologically driven inflammatory disorder. In this condition immune system starts to recognize body's own healthy tissues as foreign pathogen and starts to produce anti-bodies against it. Its main target area is synovial joints it starts to destroy the synovial membrane which leads to inflammation and stiffening of joints due to which the affected person feels difficulty in walking, running up to the stairs and feels pain even at rest. Due to widespread immunoinflammatory reaction it not only affects joints but also contributes to multi organ impairment including heart, lungs and blood vessels (Conrad N et al., 2023). It not only effects joints but is also responsible for emotional impairment there fore referred as systemic multisite involvement condition. Primary symptoms include articular inflammatory triad: pain, swelling and stiffness. These clinical indications further leads to articular deformation and compromised movement capacity of bones, joints and cartilage (Pop JE 2020). On clinical analysis it was evident that when 200mg/kg body weight fraction of *Euryale ferox* was administered into body already suffering from arthritis hemoglobin status and erythrocyte population density significantly increased which indicates improvement in blood profile of specie suffering from this chronic disease reverting conditions towards the normal. Phytochemical constituents present in *Euryale ferox* are responsible for the reduction of symptoms of arthritis and improving overall health profile (Ansar W and Gosh s 2016). On induction of EFCF (Euryale ferox chloroform fraction) into arthritic rats it was analyzed that the aberrantly elevated CRP concentrations start to normalize and an autoantibody produced by the immune cells that destroys health tissues commonly referred as Rheumatoid factor (RF)

starts to decrease. These two factors are the major cause of inflammation during arthritis and reduction in their levels is the indication that EFCF have potential to lower the risk of arthritis and recovers the conditions to optimum level. During the course of diseases decrease in body weight and wasting of body tissues is noted because there are elevated immunoinflammatory cytokine factors in blood. Initially during the experimental analysis reduction of weight in the rats was observed but later due to the impact of EFCF the lost weight was restored. Inconclusion the study verifies the therapeutic and recuperative efficacy of EFCF in arthritis-induced systemic dysfunction (Li Y, et al., 2016).

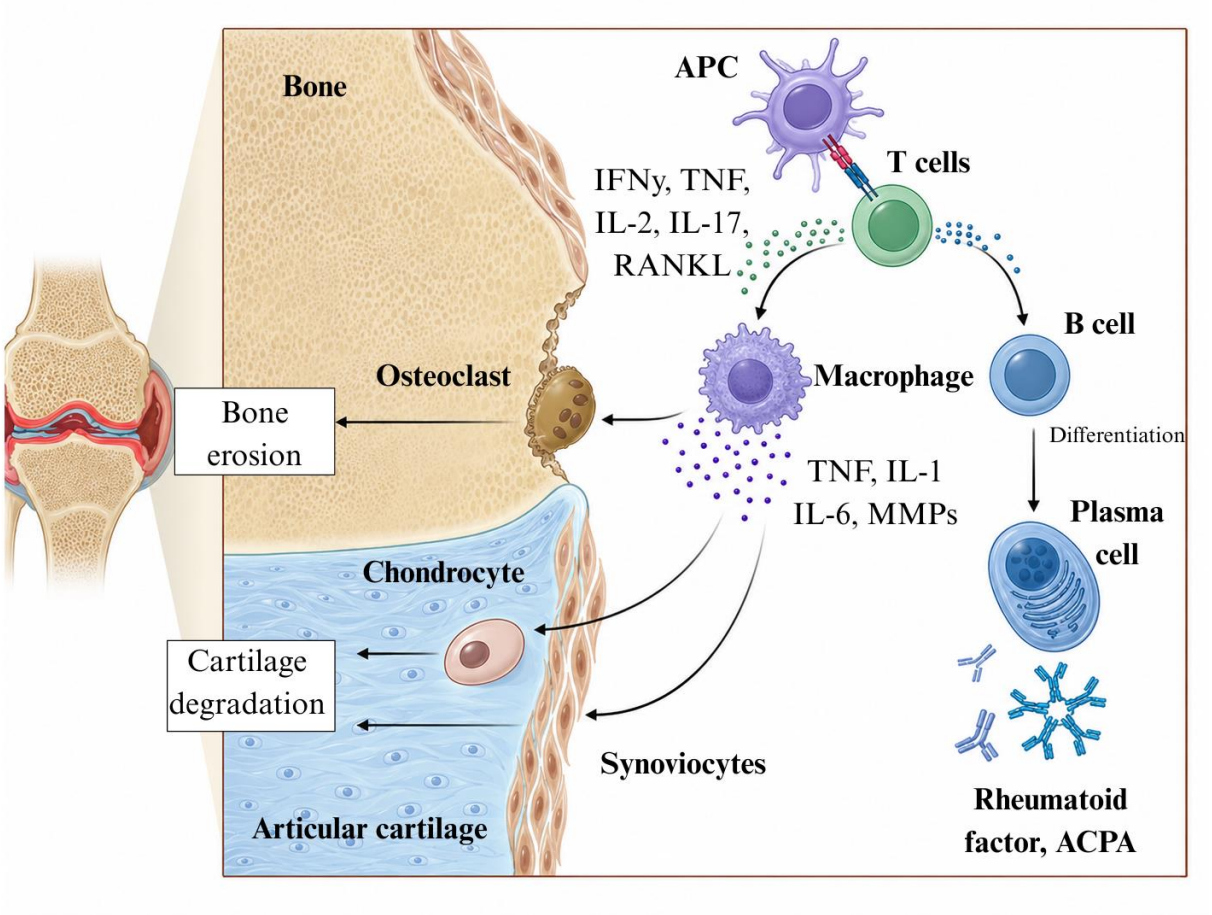


Figure Showing the mechanism of Rheumatoid arthritis

Anti-hepatotoxic potential

Fatty liver disease scientifically referred as hepatic steatosis is a pathological state in which there is excess deposition of unsaturated triglycerides within the liver cells. Hepatocytes (liver cells) have capacity to store fats up to a certain optimum level but when this level exceeds it leads to steatohepatitis which further progresses into fibrosis, cirrhosis and hepatocellular carcinoma. It is the dominant hepatic manifestation and approximately 25% of the global population is suffering from it. Due to its rapid epidemiological expansion and disease advancement, it has been predicted that by the year 2030 hepatic steatosis will be the root cause behind liver transplantation (Asrani and S.K et al., 2019). Depending on the alcohol consumption scientists have classified liver steatosis into two major types alcohol-induced hepatic steatosis and non-alcohol associated fatty liver disease (Inan-Eroglu, E. et al., 2022). When

the ethanolic extracts obtained from the seed coat of the *Euryale ferox* were tested on Wister rats that were already suffering from the non-alcoholic fatty liver steatosis it was evaluated that the symptoms of the diseases were remarkably reduced. For experimental investigation firstly, the disease was induced in the rats. For induction of the disease for 4 weeks rats were given high fat diet simultaneously so that accumulation of fat occurs in the liver cells as a result non-alcoholic fatty liver disease was successfully provoked within them. Their body weight and hepatic weight-to-body weight proportion increased which indicates impairment of lipid metabolism in the rats. Laboratory based biochemical assessment evidenced elevated level of acylglycerol, serum total cholesterol concentration, bad cholesterol referred as LDL (low density lipoprotein) on the other hand good cholesterol (High density lipoprotein level) in the blood was significantly decreased. These all were the signs of non-alcoholic fatty liver steatosis. Study also demonstrated reactive oxygen species-associated markers as a consequence high concentration of MDA (Malondialdehyde) and SOD (Superoxide Dismutase) was observed. SOD is a free radical scavenging enzyme and MDA is indicator of lipid oxidative damage their elevated level leads to reactive oxygen specie mediated stress. AST (Aspartate Aminotransferase) and ALT (Alanine transaminase) are the hepatic enzymes that are normally located within the liver upon hepatic injury they leak in to the blood stream and through there elevated concentration in blood hepatic injury and poor hepatic functioning is detected. For molecular level analysis western blotting technique was employed by the researchers to study specific proteins implicated in hepatic steatosis two proteins CYP2E1 and IRS-1 were studied trough this technique. CYP2EI elicits the formation of damaging oxidant species. Increase in its expression leads to increase in liver damage, fatty liver progression and increase in oxidative stress. Insulin Receptor Substrate-1 (IRS-1) facilitates insulin in its normal functioning dysregulated insulin receptor substrate signaling means the body cells become resistant towards blood insulin level, carbohydrate metabolic equilibrium is disrupted and pathogenesis of diabetes and fatty liver disease progresses. The ethanolic extracts of *Euryale ferox* normalized the conditions by reducing free radical stress, making cells sensitive towards insulin hence by promoting insulin sensitivity and inhibiting the conditions that promote insulin resistance. The efficiency of fat metabolism was enhanced and deposition of fats in hepatocytes was decreased reducing the risk of NAFLD. Bioactive components entailed within the extract protected and repaired hepatic injuries and restored the enzymatic balance (AST and MDA) of the liver. The extract restored physiological homeostasis by normalizing enzymes involved in carbohydrate metabolism. These enzymes include fructose-1,6-bisphosphatase, hepatic hexokinase, glucose-6-phosphatase and glucose-6-phosphate dehydrogenase (Shi, L et al., 2021). Using western boiling method deep analysis was performed on IRS-1(Insulin Receptor Substrate-1) and CYP2E1 when *Euryale ferox* extracts were given the expression of CYP2E1 was enhanced and IRS-1 expression levels were also evaluated under experimental conditions they mediated hepatic functional and structural modulation these changes were considered as positive because they lead to hepatoprotective effect (Roopal Mittal et al., 2020).

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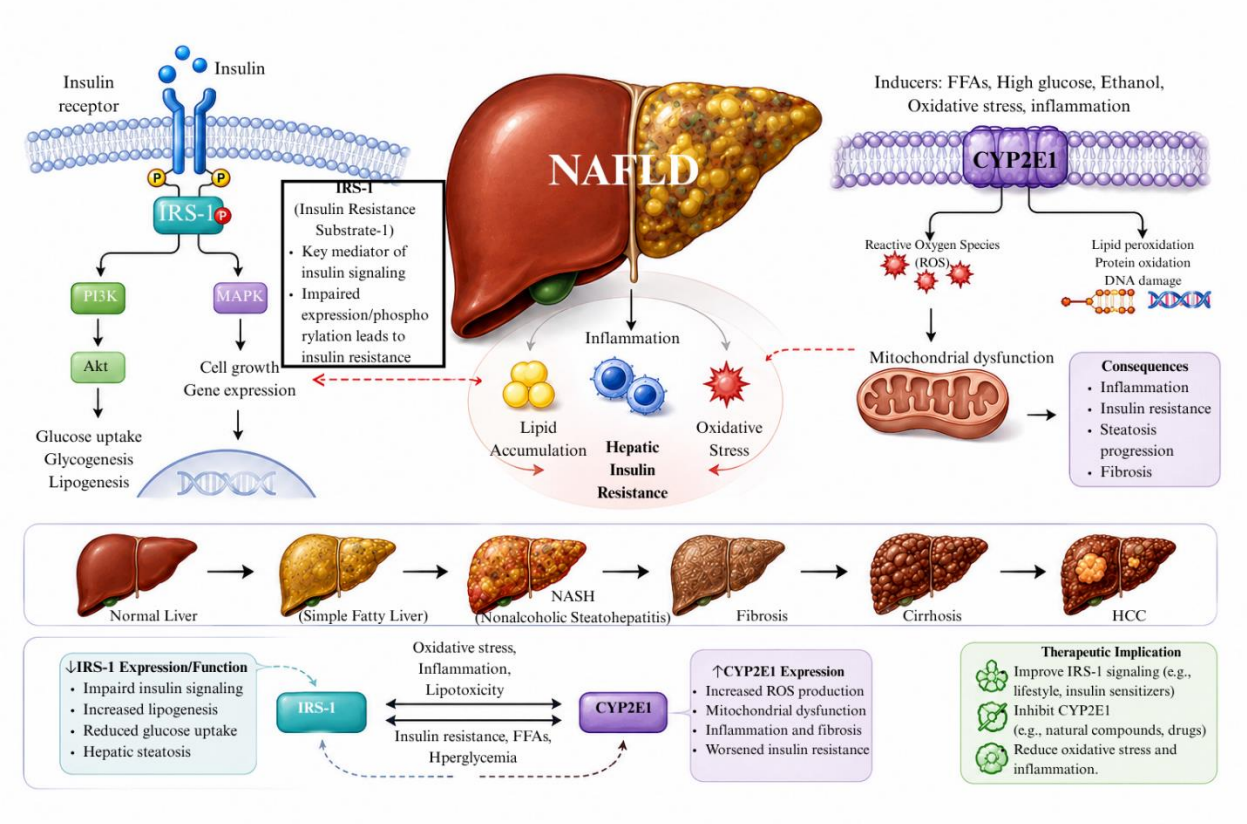


Figure showing the impact of IRS-1 and CYP2E1 on Non-Alcoholic Fatty Liver Disease

Anti-Aging Impact

Investigative experimentation has elucidated that aging is inevitable phase in trajectory of human life. During the course of aging the metabolism of the body weakens, skin sags, capacity to perform work is lowered, muscle strength is reduced and wrinkles appear on the skin these are the major signs of aging that intensify over the course of time (Halloran L 2012). The skin is the protective structure that encapsulates the whole body and it is resistant against the environmental changes. It protects the body from environmental pathogens. The outer most layer of the skin is epidermis which directly interacts with the external environment and maintains a barrier between external and internal environment the symptoms of aging first appear on the skin because of the environmental stress (de Szalay and Wertz 2023). Certain amino acids play crucial role in maintaining the structure, strength and flexibility of skin. Creatin protein is the basic structural component of skin, nails and hairs. The major structural block or precursors for the synthesis of creatin are methionine and arginine. Glycine/glutamine and arginine also act as biochemical antecedent for the synthesis of creatin. Creatin formed by the combination of glutamine and glycine plays important role in maintenance of healthy skin because they supply energy required by the skin to maintain its healthy activity. They assist in preventing aging symptoms by maintaining structural integrity of the skin through extracellular matrix synthesis, optimal cutaneous metabolism and cellular renewal. In-addition amino acids isoleucine and proline are important bioregulators. They promote overall physiological development through promoting repair of body tissues and body growth (William JZ et al., 2002). Scientific investigations on the extracts of *Euryale ferox* have demonstrated that it pertains amino acids that play significant role in delaying the symptoms of aging by maintaining

optimum cellular metabolism. These include cysteine, glutamine and methionine. On meticulous assessment it was evident that both roasted and unprocessed seeds contain notable proportion of essential amino acids which not only play important role in strengthening skin by boosting collagen production but also play substantial role in maintaining homeostatic metabolic regulation. It is significantly noted that people consuming *Euryale ferox* have substantially retarded symptoms of aging. In those people whitening of hairs, wrinkles and other symptoms were postponed through free radical suppressive effect of fox nut (Tehseen S et al., 2020). Amino acids present within fox nut serve as a key determinant for maintaining hemodynamic flexibility of vessels by preventing hardening of arteries and blood vessels and ensure that blood is being efficiently supplied by them through out the body. Efficient blood supply to skin and other connective tissues exerts a preventive effect against senescence indicators (Solano F, 2020).

Anti-proliferative activity against cancer cells

Cancer corresponds to spectrum of pathological conditions associated with uncontrolled cell division. Cancer tumor develops when cells continue to grow at abnormal level and cell to cell inhibition phenomenon is interrupted. It is unregulated neoplastic proliferation of cells. Cancer effects the cells and cells lose their proper functioning and become morphologically and functionally aberrant. These cells spread their illness to the neighboring cells and soon they lose their maximum physiological efficacy (Kaur C and Garg U 2021). Apoptosis is programmed cell death during which physiologically impaired and dead cells are killed in order to eliminate functionally compromised cells. During the course of cancer, the process of apoptosis is pathophysiologically altered due to which there is excessive tumor growth. Upon interaction of ethanolic extracts of *Euryale ferox* seeds with A549 lung cells suffering from cancer it was noted that the process of apoptosis speeds up for the elimination of cancer cells. It was a recovery sign and restoration of normal functionality of lung cells. It was analyzed that the extracts influenced mitochondrial membrane polarization and enhanced the production of reactive oxygen species. Although excess ROS production leads to oxidative stress but in this case increase in production of oxygen free radicals interrupted with the cell membrane of cancerous cells and altered there functioning promoting conditions toward apoptosis. On subsequent investigation it was discovered that there was increase in p53 protein which is a carcinogenesis-inhibitory protein it favors the programmed death of malignant cells. When ethanolic extracts of *Euryale ferox* were administered into Balb/c-nu mice engrafted with A549 tumor cells augmentation of p53 occurred for cytotoxic clearance of cancer cells this experiment confirmed the neoplasm-inhibitory activity of fox nut (Nam et al., 2019). Euryale ferox not only promotes apoptosis by activation of p53 protein but also suppresses the production of Akt protein. Akt protein promotes the proliferation of cancerous cells so for tumor suppression inhibition of Akt protein is mandatory (Lee Seet al., 2002).

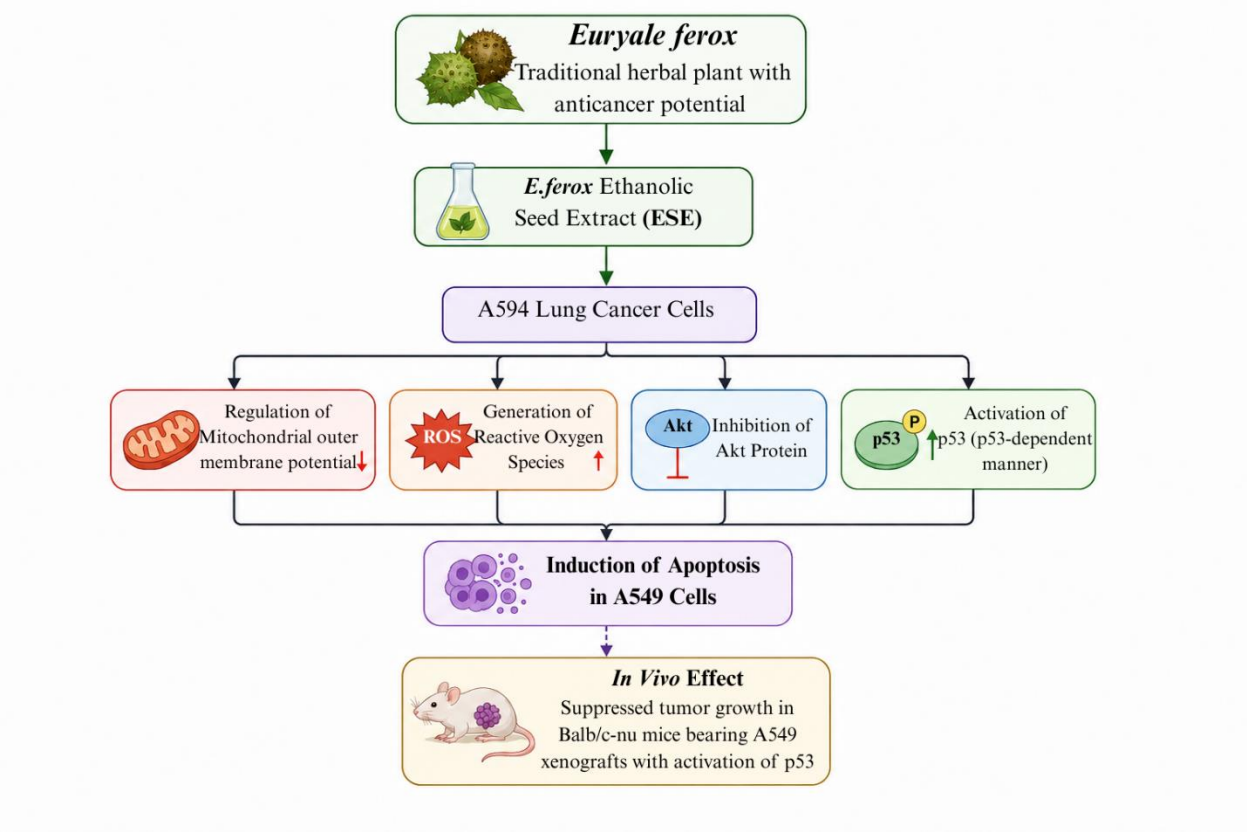


Figure showing the impact of ethanolic extracts of Euryale ferox on cancer proliferation

Nutraceutical benefits	Therapeutically active metabolites	Prominent experimental outcomes	Investigational framework	References
Neuropsychological protective activity	Kaempferol, vitamin, flavonoids, polyphenols, ethyl acetate and oxidative stress mitigating agents.	Counteracted glutamate-mediated neurodegeneration and oxidative impairment, through reduction of oxidative stress by demonstrating antioxidant cytoprotection in N18-RE-105 neuronal cells.	N18-RE-105 neurocellular model	Huang Z et al., 2018; Singh M et al; 2024; Vikram and Mishra; 2021
Oxidative stress mitigating effect	Flavonoids, phenolics, Euryalin B,	Activity and number of enzymes associated with reduction of	In vitro antioxidative evaluation using	Wu C et al., 2014; Singh M et al., 2024; Joseph

	syringaresinol, buddlenol E.	oxidative stress was increased. After germination of seeds total content of phenolic compounds pertained within it was increased.	mesangial cell models	A and Ramesh G; 2023
Hepatic cytoprotective potential	Phytochemical ethanolic seed extract associated with CYP2E1 augmentation, IRS-1 signaling modulation and oxidative stress attenuating enzymes.	Damage associated with NAFLD was significantly reduced through certain mechanism. Enzymes present within liver were restored and pathways associated with carbohydrate mechanism were enhanced.	Experimental hyperlipidemic diet was given to Wister rats already suffering from NAFLD	Shi L et al., 2021; Roopal Mittal et al., 2020; Inan-Eroglu E et al., 2022
Cardio protective pharmacodynamic effect	Oxidoreductive stress ameliorating phytochemicals, Thioredoxin-1(Trx-1) and TRP32 proteins.	Exhibited cardio protection against ischemic myocardial injury, ameliorated coronary and aortic blood flow impairment associated with ischemia-reperfusion.	Cardiac model of Sprague Dawley rat	Azhar M et al., 2015; Das S et al., 2006
Antihyperglycemic therapeutic efficacy	2β-hydroxybetulinic acid 3β-caprylate (HBAC), AMPK/mTOR, polyphenols and Keap1/Nrf2/HO-1 modulation.	Insulin release from beta cells of pancreas was enhanced along with enhanced carbohydrate metabolic control, oxidative defense status and nephrological parameters were also improved.	Animal models already affected with diabetes were used	Wang Y et al., 2023; Liaquat M et al., 2022; Kapoor et al., 2023
Rheumatoid arthritis attenuating activity	Inflammation suppressing	Reduction in concentration of	Arthritic rat models	Conrad N et al., 2023; Ansar W

	bioactive molecules and pro-inflammatory cytokine downregulation.	rheumatoid factor and CRP. Lost body weight was regained along with enhancement in blood hemoglobin level and RBC count.		and Gosh S., 2016; Li Y et al., 2016
Anti-aging Activity	Cysteine, arginine, glutamine, creatin, methionine and free radical scavenging agents.	Through antioxidant activity collagen production is enhanced which provides nourishment to the skin, strengthen connective tissues and promote synthesis of new tissues. These all processes collectively lead to delaying aging.	Phytochemical and nutritional assessments	Tehseen S et al., 2020; Solano F., 2020; Williams JZ et al., 2002
Antiproliferative anticancer effect	Akt inhibition, stimulation of p53, ROS-mediated apoptosis and flavonoids.	Programmed cell death activation in lung cancer cells named A549. In xenograft mice tumor growth was downregulated.	A549 lung cancer cells and Balb/c-nu mice	Nam et al., 2019; Lee S et al., 2002
Nephrocytoprotective potential	Naturally derived redox modulating phytocompounds and polyphenolic metabolites.	Diabetic induced nephron dysfunction is inhibited and renal injuries due to oxidative stress are cured and prevented.	Diabetic experimental models	Liaquat M et al., 2022; Wang Y et al., 2023

Conclusion

In conclusion *Euryale ferox* commonly referred as Phool makhana a hydrophytic plant specie have medicotherapeutic and industrial significance due to the chemical components present within it. It is widely grown in India because of suitable environment and commercial significance. India is among the largest exporters of Phool makhana. Raw materials obtained from Euryale ferox supports the cotton industries. In certain regions of the world, it is being used as medicine for treating certain diseases encompassing diarrhea, gonorrhea and spermatorrhea. It is useful in both raw and roasted form but there is difference in the

nutritional value in both the forms it has been noted that the nutritional value is significantly enhanced on roasting. It contains many important bioactive compounds including essential amino acids. It can be used as a heathy snack due to its low-fat content it plays significant role in growth and repair of body tissues. Therefore, it is very beneficial for growing children because during developmental period certain essential nutrients must be incorporated in the diet so that growth of brain, body tissues and bones takes place at optimum level. According to certain statistical analysis and scientific research it has been proven that Phool makhana is the best source of in dispensable nutrients along with that it is a good source of energy as well its nutritional value is near about that of carbohydrates and proteins. It can be utilized in making guilt-free snacks, yoghurt toppings, cookies, ice-creams and salad and trail mixes. It plays very important role in weight reduction and weight management because of its phytochemical content. Researchers have proved that it enhances cardiovascular supply and anti-oxidant activity through multiple experimentations. Certain experimental studies have proven that extracts of Euryale ferox play significant role in amelioration of arthritis, fatty liver, hyperglycemia, prevention of cancerous tumors and in delaying aging. Phool makhana can be grown in certain regions of Pakistan where environment is favorable for its growth it can be grown in marshes and swamps where there is moisture content because it is a water loving plant so water is the basic necessity for its survival. Certain areas of Sindh and Punjab including Thatta, Larkana, Sanghar, Bahawalpur, Muzaffargarh, Okara and areas along the Chenab River pertains the best optimum environment for its growth. Phool makhana harvesting and cultivation in Pakistan requires a lot of efforts and support of both government and people. If it is grown on large scale it will boosts up the Pakistani economy and nutraceutical industry as well because of the number of benefits associated with it. In short *Euryale ferox* is known globally not just because of its medicinal importance but also due to the commercial and economical benefits associated with it.

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