

Pharmacology, Phytochemistry, Pharmacognosy of Lettuce (*Lactuca sativa*)

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ABSTRACT

Lettuce is a recently popular plant that grabbed the attention of food interest worldwide. It is widely consumed a salad. There is more to the plant than just a to be used as a salad. It is great source of minerals and antioxidants. It is highly famous as minimally processed food. Lettuce has better sources of vitamin A, niacin, riboflavin, and thiamine, Ca, Fe, K, Mn, Se and Beta-carotene. The present publication emphasises on the pharmacognosy, phytochemistry and the pharmacological aspects of lettuce.

KEY WORDS: Lettuce, *Lactuca sativa*, Antioxidant activity, Polyphenols, Medicinal properties

INTRODUCTION

Lettuce is an annual plant mostly grown as a leafy vegetable. Along with Broad-leafed endive, Lettuce is the well-liked vegetables in salads that are eaten up by people all over the world in increasing amounts due to its impression as healthy food². It is a profitable vegetable next to tomato⁵. Lettuce, one of the most popular vegetables in terms of production and economic value, ranks second to potato in per capita consumption⁷. Modern city lifestyle is characterized by an increased demand for ready-to-eat fresh or minimally processed foods⁶. Lettuce, principally iceberg lettuce, is currently the main vegetable used during the manufacture of fresh-cut salads⁶. Lettuce contains substantial amounts of Vitamin C, polyphenols, vitamin E, B9 and carotenoids which are beneficial sources of antioxidants in vegetarian diets^{1,2,5,6}.

There are a variety of species of lettuce, typically at the level of phenotypic and phenological variation, variation in karyology and DNA content, biochemical traits, and protein and molecular polymorphism³. There are four varieties of Lettuce and Nutrient Value of lettuce varies depending on them 1. Celtuce, 2. Head lettuce, 3. Leaf or curled lettuce, 4. cos or romaine lettuce. From the ancient period of time Lettuce is known to reduce inflammation, pain, stomach problems as well as indigestion and lack of appetite⁴. The modern lettuce varieties were observed to be having a higher phenolic content than a traditional lettuce⁶. The traditional and modern lettuce both have the same antioxidant volume⁶. There are various other benefits of consuming lettuce; it improves health benefits such as higher dietary fiber content that aids in digestion⁵. The Romaine types of lettuce have better sources of vitamin A, niacin, riboflavin, and thiamine, Ca, Fe, K, Mn, Se and Beta-carotene⁵. All the antioxidants and phenolic content has proved to be having health benefits. They also help the plants to cope up with stresses.



Fig1-4: Image of Lettuce plant

HISTORY

Lettuce (*Lactuca sativa* L.) is considered a major food crop within Europe and North America. In ancient Egypt, Lettuce seeds were used to obtain oil. Later, Egyptians changed farming lettuce as an important food crop. Romans named Lettuce as *lactuca* (*lac* meaning “milk”) while it spread to the Greek and Roman. The English word Lettuce was derived from *lactuca*. In medieval writings, many types of Lettuce were described including several herbals. *Lactuca sativa* can be crossed easily within the species and with some other species within the genus *Lactuca*. Approximately 6000 years ago, lettuce was first domesticated in the Caucasus region in Egypt. The early cultivated lettuce was tall and upright, resembling modern romaine lettuce.

Romaine lettuce was primarily cultivated, with evidence of domestication dating back over 5000 years, mainly in ancient Egypt where it was valued for both its leaves and oil-rich seeds.

At that time, lettuce seeds were considered holy to God and also connected with fertility. Medicinally, latex obtained from lettuce was used as a painkiller and sedative. The Egyptian passed lettuce to the Greeks, who also utilized sap for medicinal purposes. Hippocrates even praised its sedatives qualities. They selectively bred lettuce for better-tasting leaves. Many varieties were recorded by the 1st century AD. Lettuce appeared frequently in medieval writings, often mentioned as a medicinal herb. From the 16th-18th Centuries, Europe saw the development of many new lettuce varieties, including emergence of firm-head types in France, Holland, and Italy. In the late 15th century, Christopher Columbus is credited with bringing lettuce seeds to the Americas. By the time of the Revolutionary war, lettuce was well-established in the American diet. Today there are hundreds of lettuce varieties, broadly categorized into types like butterhead, romaine, crisphead, loose leaf, and summer crisp. In 2021, China will be the world’s leading producer of lettuce and chicory. The evolution of lettuce led to loss of thorns and bitterness. The iceberg lettuce is the most recent development or modern form of lettuce in America.

CLASSIFICATION

| | |
|----------------------|---|
| Kingdom | Plantae |
| Subkingdom | Tracheobionta |
| Superdivision | Spermatophyta |
| Division | Magnoliophyta |
| Class | Magnoliopsida |
| Subclass | Asteridae |
| Order | Asterales |
| Family | Asteraceae |
| Genus | <i>Lactuca</i> L. (Lettuce) |
| Species | <i>Lactuca sativa</i> L. (Garden lettuce) |

Table 1: The classification of Lettuce

PHARMACOGNOSTIC ASPECTS

The Pharmacognosy of lettuce includes its microscopic and macroscopic characteristics.

Lettuce is an annual herb with a short stem and rosette of leaves that can vary in shape, size, and colour.

Macroscopical and Microscopical Characters of Lettuce

| Part | Description |
|------------|--|
| Fruit type | A small dry indehiscent one-seeded fruit. |
| Shape | Round to ruffled leaves. |
| Size | 527 to 2289 cm ² . |
| Color | Light green to dark green, with some varieties displaying red, pink, or even purple. |
| Seeds | Small, brown, oval shaped. |
| Taste | Mild and subtly sweet. |
| Flower | Yellow or white daisy-like flowers produced in a terminal cluster. |

Table 2: Macroscopical Characters of Lettuce

| Part | Under the Microscope |
|-----------------|---|
| Epidermis | A single layer of tightly packed, thin, translucent cells, with a cuticle, a waxy, transparent layer covering the outer surface of the epidermal cells. |
| Trichomes | Hair-like or glandular appendages extending from the epidermal cells. |
| Seed Coat | Combination of pericarp and remnants of the integument. |
| Crystals | Calcium oxalate crystals are seen. |
| Cotyledons | Dicotyledonous. |
| Vascular Tissue | Xylem tissue with tapered ends and pits in their walls, wider and shorter tracheids. Phloem tissue appears as small, more densely packed cells. |

Table 3: Microscopical Characters of Lettuce

PHYTOCHEMISTRY OF LETTUCE

Phytochemicals are naturally synthesized chemical compounds present in plants. These compounds are integral to the plant, often contributing to their characteristic colors and flavors, and playing a vital role in their defence mechanisms against diseases¹⁴.

Many of these phytochemicals are classified as secondary metabolites, which are organic compounds not directly involved in the primary growth, development or reproduction of the plant¹⁴. Instead, they serve functions related to a plant's interaction with its environment, such as defense against herbivores, insects, and pathogens, as well as protection from UV radiation and other environmental stresses¹⁴. There are several phytochemicals in lettuce: Phenolics, Tannins, Steroids, Carbohydrate Glycosides, Flavonoids, flavonol, quercetin, caffeic acid, ascorbic acid, Gum, Carotene, Alkaloid (Lactucarium, mixture of lactorin with three bitter principles lectucin, lectopicrin, and Lactic acid)⁹.

Phytochemical Components of Lettuce

| S. No. | Phytochemical Component | Main Components | Part of Plant Found | Key Function |
|--------|-------------------------|---|---------------------|--|
| 1 | Phenolic acids | Caffeic acid, chlorogenic acid, and their derivatives | Seeds, Leaves | Antidiabetic, antimicrobial, anti-inflammatory, skin care products, food preservatives |
| 2 | Carotenoids | Alpha-carotene, beta-carotene, lycopene, lutein, neoxanthin, lactucaxanthin, violaxanthin, zeaxanthin | Leaves | Hepatoprotective, antibacterial, anti-inflammatory, anti-cancer, antiviral, cardiovascular |

| | | | | |
|---|------------------------|--|---------------------------------------|---|
| | | | | protective, anti-obesity, pigment, antiproliferative |
| 3 | Chlorophyll | Chlorophyll A, Chlorophyll B | Leaves | Antioxidant, anti-cancer, stimulating immune system, pigment, normalize blood pressure |
| 4 | Vitamins | Folate, Vitamin C, Vitamin E, B-complex vitamins, Vitamin B1, B2, B3, B6, Biotin, Choline, Pantothenic acid, Vitamin A, Vitamin D | Darker green leaves | Antioxidant, shelf life, preserving phenolic compounds |
| 5 | Minerals | Sodium, Potassium, Calcium, Magnesium, Iron, Zinc, Boron, Calcium chloride | Leaf | Balance of water and electrolyte, metabolic functions, maintaining bone health |
| 6 | Anti-nutrients | Nitrates, phytates, tannins, oxalates, cyanogenic glycosides, alkaloids | Cell vacuole, xylem and phloem | Nutrition and function |
| 7 | Fatty acids | Omega-3 fatty acids, Linolenic acid, Alanine, Arginine, Aspartic acid, Cysteine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine | Chloroplast and endoplasmic reticulum | Energy storage, forming cell membranes, aiding in nutrient absorption, and acting as signalling molecules |
| 8 | Sesquiterpene lactones | Lactucin, lactucopicrin, and 11- β ,13-dihydrolactucin | Vascular system | Analgesic and sedative properties |

Table 4: Phytochemical aspects of Lettuce

Generally, Lettuce is cultivated annually. It requires relatively low temperatures to prevent it from flowering quickly. The yield is higher when lettuce is grown in a hydroponic system^[5]. The hydroponic system is a type of system which uses less water. Due to this, there is a continual recycling of nutrient solution. This reduces the risk of edaphic diseases and the yield of lettuce when cultivated in soil is more⁵. When osmotic or salt stress is induced along with a high nutrient solution, electrical conductivity (EC) in the root zone enhances the phytochemical constituents in fresh produce⁵. Anthocyanins protect the leaves from high radiation along with balancing photosynthesis⁷.

PHARMACOLOGICAL ASPECTS OF LETTUCE

Previously, considerable pharmacological studies have been conducted to evaluate therapeutic significance of the crude extracts of *Lactuca sativa* which showed its anticonvulsant, sedative-hypnotic and antioxidant properties⁴.

Anti-oxidant properties

Agents that reduce the oxidative stress is called antioxidants.²³ Oxygen is a highly reactive atom that is capable of becoming part of potentially damaging molecules commonly called "Free Radicals." Antioxidant Activity applied to components that can trap free radicals, thereby breaking the chain reaction that normally leads to extensive biological damage¹⁰. Free radicals are reactive molecules involved in many physiological processes and human diseases such as cancer, aging, arthritis, Parkinson syndrome, ischaemia, toxin induced reaction, alcoholism, liver injury etc¹⁰.

There are antioxidants that fight against cancer properties, such as beta-carotene with tocopherols, quercetin and ascorbic acid are present in lettuce⁹. Linoleic acid is an important nutrient with antioxidant and anti-inflammatory properties. The antioxidant properties of lettuce, it has significant oxygen free radical absorption capacity, prevents lipid oxidation in low-density lipoproteins⁹. Inhibition of ethylene production induced by hydroxyl radical absorption capacity and Cu²⁺ induced protein oxidation. Lettuce leaf extract has been shown to have antioxidant activity and helps preserve biomolecules⁹. According to certain reports, sleep deprivation may cause oxidative stress in the brain¹³. Romaine lettuce has been interestingly reported to show antioxidant polyphenols¹³. The brain uses the antioxidant polyphenols as natural defences against oxidative damage¹³.

Protective Activity

Cardio protective Activity

One of the biggest risks to people's health are cardiovascular diseases, which are not caused by infections⁸. These conditions are linked to a wide range of intricate factors such as diabetes, metabolic syndrome, hypertension, and hyperlipidaemia⁸. Consuming vegetables is positively associated with the treatment of CVD's, according to certain prior epidemiological studies, particularly when it comes to green leafy vegetables like lettuce⁸. Fibre and antioxidants are thought to have beneficial effects on cholesterol metabolism and CVD prevention. The fibre component of lettuce is responsible for its lower cholesterol impact⁸. It has been confirmed that pectin, a soluble fibre that influences lipid metabolism, decreases the absorption of cholesterol via the digestive tract⁸.

Protective effects: To find out how lettuce oil might shield rats from gamma radiation harm, a study was carried out. Following exposure, levels of glucose, triglycerides, total cholesterol (TC), malondialdehyde (MDA), and follicle stimulating hormone (FSH) rose, and superoxide dismutase (SOD) increased as well. The Hematocrit (%Hct), red blood cell (RBC), and white blood cell (WBC) percentages dropped⁹.

Neuroprotective Activity

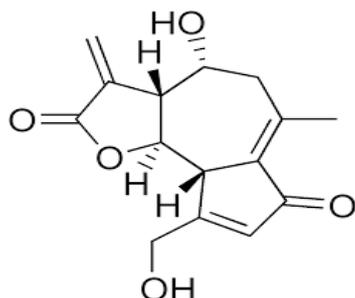
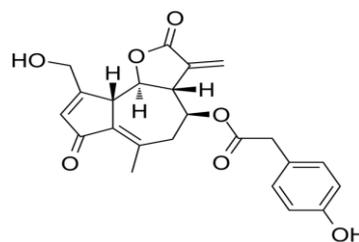
The neutral polar component of alfa's ethyl acetate part shields cells from harm brought on by the in vitro brain ischaemia model known as glucose/serum deprivation (GSD). Strokes and other neurological disorders can be treated with it⁹. Lettuce's ethyl acetate component inhibits pro apoptotic pathways and lowers oxidative stress, preventing neurotoxicity-induced glucose/serum deprivation (GSD). This medication can be used to treat ischemia-induced neuronal injury⁹. Lettuce, particularly romaine lettuce, may have neuroprotective properties¹³.

Analgesic, Antidepressant and Anticoagulant Activity

Extracts from lettuce leaves and seeds have been shown in rat studies to lessen discomfort in several experimental setups. Notably, in certain assays leaf extracts appear to have a greater analgesic impact than seed extracts. Due to presence of Lactucin and its derivatives guaianolides possess analgesic activities in thermal models of nociception similar to that observed for ibuprofen¹¹. Lactucin also has sedative properties¹¹.

Vitamin K is abundant in a variety of leafy green vegetables, such as lettuce. Maintaining a steady intake of vitamin K is essential for Warfarin patients in order to effectively control their anticoagulant medication. Unexpected increases or decreases in vitamin K intake may affect how well the medication works, increasing the risk of blood clots or causing excessive bleeding.

In order to treat and prevent thromboembolic diseases, anticoagulants are crucial mediators. There is strong scientific evidence that dietary anticoagulants and phytochemicals with anticoagulant properties can finally eradicate or lower the danger of thromboembolic illnesses⁴. According to the experimental results of several extracts, L.sativa is a broad-spectrum medicinal crop with important analgesic, anti-inflammatory, depressive, and anticoagulant qualities that could eventually take the place of manufactured medications⁴.

**Fig.1. Chemical structure of lactucin¹¹****Fig.2.Lactucopicrin chemical structure**

Sedative Properties

Mice's pentobarbital-induced sleeping behaviour is enhanced by romaine lettuce seed and leaf extracts. Extracts from romaine lettuce may have sleep-enhancing properties¹³. The leaves of the plant *Lactuca sativa*, commonly shown to have sedative-hypnotic and anticonvulsant properties¹².

Anti-cancer Properties

Lettuce induces certain phytochemicals that some clinical researchers have found to have health benefits, it can help prevent cancer. Reactive oxygen Species (ROS) are produced by cancer cells when they consume iodine-biofortified lettuce, which causes cancer cells to undergo programmed cell death, which has anticancer effects. First off, lettuce may include minerals like ascorbic acid and beta-carotene that can lower the risk of colon cancer¹⁴. Preventing cancer and chemotherapy is one of the most important uses of plant-derived medicines made of phenols. Polyphenols have an anti-cancer impact showing the growth of tumors. Phenols, such as antioxidants, are impacted by chemoprevention, lowering free radicals and ROS, hence lessening the harm they do to DNA¹⁴. Numerous biological and experimental studies have demonstrated the anti-cancer therapeutic properties of apigenin, a flavonoid derived from edible plants. By changing several signalling pathways, it stops cell development and triggers apoptosis in a variety of tumor types, such as breast, lung, liver, skin, and blood cancers as well as prostate, pancreatic, cervical, and stomach cancers. By triggering the extrinsic caspase-8 and TNF-alpha mRNA levels. Apigenin induces apoptosis¹⁴.

MEDICINAL VALUE

Lettuce is more than just a salad staple; it offers several medicinal benefits due to its rich nutritional profile and bioactive compounds⁸.

Nutritional Powerhouse: Romaine and red leaf are the darker varieties of lettuce which are packed with vitamins and minerals essential for overall health:

Vitamin A: Crucial for vision, immune function and cell growth. It also acts as an antioxidant⁸.

Vitamin K: Important for blood clotting and bone health. Adequate intake can reduce the risk of bone fractures⁸.

Vitamin C: A potent antioxidant that supports the immune system, promotes wound healing, and is vital for healthy skin and gums.

Folate (Vitamin B9): Essential for cell division and DNA synthesis, particularly important during pregnancy to prevent neural tube defects.

Potassium: An electrolyte that helps regulate blood pressure and supports heart health.

Calcium and Phosphorous: Important for bone formation and strength.



Iron: Necessary in muscle and nerve function, blood sugar control, and blood pressure regulation⁸.

Magnesium: Involved in muscle and nerve function, blood sugar control, and blood pressure regulation⁸.

Fiber: Promotes digestive health, prevents constipation, helps regulate blood sugar levels, and contributes to feelings of fullness, aiding in weight management.

Anti-inflammatory Effects: Certain compounds in lettuce may help manage inflammation in the body.

Hydration: With a high-water content (over 95% in raw lettuce), it contributes to overall hydration, which is vital for various bodily functions.

Support for Bone Health: Vitamin K, calcium, phosphorus, and magnesium in lettuce contribute to maintaining strong and healthy bones.

Eye Health: The vitamin A and carotenoids like lutein found in lettuce are beneficial for vision and may help prevent age-related macular degeneration and cataracts.

Blood Sugar regulation: The fibre content in lettuce can slow down the absorption of carbohydrates, helping to prevent rapid spikes in blood sugar levels, which is beneficial for individuals with diabetes or insulin resistance.

Sleep Aid and anxiety Reduction: some studies suggest that compounds like lactucarium, found in the white liquid released when lettuce leaves are broken, may have sedative and anxiolytic properties, potentially promoting better sleep¹⁵.

Skin Health: Antioxidants and vitamins A, C, and E in lettuce can protect skin cells from damage, promote healing, and contribute to skin hydration, potentially preventing premature aging¹⁶. These nutrients and chemicals are present in different levels in different varieties of lettuce. More nutrients are found in darker-leafed types than in lighter ones, such as iceberg lettuce. A greater range of these health advantages can be obtained by including a variety of lettuces in a regular diet⁸.

MISCELLANEOUS

Toxicity: The main component of lettuce that poses a risk to intake is anti-nutrient. Nitrate, which is a purely harmful dietary component, excessive consumption can result in infantile methemoglobinemia, carcinogenesis, and possibly even teratogenesis, even though its content is controlled at a dangerous level in lettuce cultivation.

MARKET VALUE

The global lettuce market was valued at \$3.7 billion in 2023 and is projected to grow to \$5.36 billion by 2032. The largest market share first goes to China, subsequently the US and India.

The FAO reports that 106 nations produced lettuce in 2017. Countries such as America, Asia, Australia, and Europe have become more vigorous markets for lettuce. The gross yield of lettuce in China is the maximum globally, occupying 56.4% of the harvesting market, followed by the United States (14.3%) and India (4.1%). In Australia, the production and consumption of lettuce have increased.

Summary Table of Pharmacological Activities of Lettuce Leaf Extracts

| S. No | Plant part | Activity | Extract | Model | Standard drug | Dose | Parameters | Mechanism | Stats P value | Author year | Reference |
|-------|------------|----------------------------|---|--|---------------|---------------|----------------------------------|---|---------------|-------------------------------|-----------|
| 1 | Leaf | Anti-inflammatory activity | 3,14-Dihydroxy-11,13-dihydrocostunolide | - | Baicalein | - | Enzyme Kinetics program | Lipoxygenase inhibitory activity | P<0.05 | K. Araruna Et al., 2010 | 19 |
| 2 | Leaf | Sedative Activity | Aqueous extract of lettuce | Caftaric acid, chlorogenic acid, chicoric acid | Phenobarbital | 42 mg/kg, i.p | Sleep latency and sleep duration | High lactucin content in romaine lettuce | P<0.05 | Hae dun Kim Et al., 2017 | 20 |
| 3 | Leaf | Antioxidant activity | - | - | Quercetin | - | - | - | P<0.05 | Mauro Serafini Et al., 2002 | 21 |
| 4 | Leaf | Antioxidant activity | - | - | Coumaric acid | - | - | - | P<0.01 | Mauro Serafini Et al., 2002 | 21 |
| 5 | Leaf | Analgesic effects | Lactucin | Nociception | Ibuprofen | 10 ml/kg | Tail flick and hot plate | - | - | Ashaolu Victoria Et al., 2023 | 9 |
| 6 | Leaf | Analgesic activity | Aqueous leaf extract | Hot plate analgesic assay | Aspirin | - | - | Halts prostaglandin synthase | P<0.05 | Hammad Ismail Et al., 2015 | 4 |
| 7 | Leaf | Antiinflammatory activity | Methanolic extract | Carrageenan-induced inflammation test | Carrageenan | 100 μ L | Digital plethysmometer | TRP reflects antioxidant activity via hydrogen donation | P<0.05 | Iqra Younus Et al., 2019 | 17 |



| | | | | | | | | | | | |
|----|-------|--------------------------|--------------------|---------------------------|----------------------|-----------|------------------------------------|---|--------|--------------------------|----|
| 8 | Shoot | Analgesic activity | Ethanollic extract | Thermal nociception model | Acetylsalicylic acid | 0.8 mg/mL | Time-dependent activity | Flavonoids inhibit prostaglandin synthetase | P<0.05 | Iqra Younus Et al., 2019 | 17 |
| 9 | Leaf | Anti-inflammatory | Methanolic extract | Biphasic model | Diclofenac | 8.4 mg/mL | 76.90% response vs callus | Phenolics, saponins, triterpenoids | P>0.05 | Iqra Younus Et al., 2019 | 17 |
| 10 | Leaf | Antiinflammatory effects | Aqueous extract | - | - | - | Attributed to quercetin glycosides | Nrf2 translocation, decreased ROS, NO inhibition, COX-2 suppression | - | Xiao Yang Et al., 2021 | 18 |

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