

RESEARCH PAPER

Lettuce: A Promising Leafy Vegetable with Functional Properties

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ABSTRACT

Lactuca sativa (lettuce) belongs to Asteraceae family important leafy vegetable known for its medicinal properties. The lettuce is a food that should not lack in our meals, we should keep in mind that its low fat and carbohydrate contents and its high contents of water, it provides caloric power of only 13 Kcal /100 gm are very appropriate for weight loss diets. It is rich in minerals, especially potassium that is very necessary to maintain appropriate levels of liquids in the body, together with calcium and phosphorus makes it especially for the correct well being of the bones. It contains selenium, an antioxidant that has a medicinal property in prevention of certain type of cancers, colon, prostate and lungs. It contains many necessary amino acids for the formation of the proteins, alanine, and necessary for the construction of muscular and nervous tissues, glycine for the correct operation of immunological system. The most of therapeutic properties of this plant is due to sesquiterpene lactones- lactucin, lactucopicrin the most bioactive compound of *Lactuca sativa*. This review mainly focuses on the pharmacological action of the Lettuce and active constituents for the wide spectrum biological properties, such as anti-oxidant, anti-inflammatory, anti-microbial, analgesic, neuroprotective and sedative properties, etc. Since Lettuce has medicinal therapeutic potential its usage in dietary supplementation can be exploited. Lettuce has also acquired a folk reputation. More clinical studies are needed to further assess the efficiency and safety in therapeutic application.

Keywords: *Lactuca sativa*; Sesquiterpene; Lactucin; Antioxidant; Neuroprotective and Antianxiety properties

1. HISTORY

Lettuce is native to the eastern mediterranean region and western Asia. With depictions appearing in ancient Egyptian tombs, the cultivation of lettuce is thought to date back to at least 4500 BC. Lettuce was held in high regard both as a food and for its therapeutic medicinal properties by the ancient Greeks and Romans. In China, where lettuce has been growing since the 5th century, lettuce represents 'good luck'. It is served on birthdays, new year's eve and other special occasions. Christopher Columbus introduced varieties of lettuce to North America during his second voyage in 1493. Lettuce was first planted in California, the lettuce capital of the United States, by the Spanish missionaries in the 17th century. Its popularity across the US did not become widespread until centuries later with the development of refrigeration and railway transportation. Lettuce has been described as a 'weedy Cinderella' by Whitaker¹ and as the 'queen of the salad plants' by Martin and Ruberté². *Lactuca sativa* belongs to family Asteraceae is an important leafy vegetable mainly consumed in salads. The plant originated in South Europe. Lettuce is considered to be a poor source of nutrients³ while it is rich in calcium, iron, vitamin A⁴. The whole plant is rich in a milky sap, sap contains lactucarium which is used in medicine for sedative, digestive, diuretic, narcotic properties. It is taken internally in the treatment of insomnia, anxiety, neurosis,

dry coughs, rheumatic pain, etc⁵. The whole plant has been used as a traditional medicine for the treatment of stomach problems, stimulate digestion and to enhance appetite and relieve inflammation⁶, chemical and biochemical assay have been done to isolate sesquiterpene lactones⁷, pharmacological investigation have proved the potential therapeutic effects of *Lactuca sativa* through various studies. Lactucarium is the milky fluid secreted by several species of wild Lettuce, usually from the base of the stems. Lactucarium is also known as lettuce opium, because of its opium like properties. More specifically, lactucarium bears physical resemblance to opium and can be consumed or smoked. It is said that consuming 'Lettuce Opium' can lead the user to a state of sedation as well as being a form of analgesic (painkiller). The objective of this review is to compile all this literature systematically to know their effects mechanism of action and safety for therapeutic application.

2. CLASSIFICATION

Varieties of lettuce are: Arugula (rocket or rockette), Belgian endive or French endive, Chicory or curly endive, Escarole, Mâche or lamb's lettuce or field salad, Raddicchio are as shown in Table 1.

3. TRADITIONAL USES

The lettuce is a food that should not lack in our meals, we should keep in mind that its low fat and carbohydrate contents and its high contents of water, it provides caloric power of only

Table. 1 Classification of Lettuce

Classification	Features
Romaine	Also known as Cos, this variety of head forming lettuce has deep green, long leaves with a crisp texture and deep taste.
Crisphead	With green leaves on the outside and whitish ones on the inside, this variety of head lettuce has a crisp texture and a watery, mild taste. The best known variety of crisphead lettuce is iceberg.
Butterhead	These types of lettuce feature tender large leaves that form a loosely arranged head that is easily separated from the stem, a sweet flavor and a soft texture. The best known varieties of Butterhead lettuce include Boston and Bibb.
Leaf	Featuring broad, curly leaf varieties that are green and/or red, the leaf lettuces offer a delicate taste and a mildly crispy texture. Best known varieties of leaf lettuce include green leaf and red leaf.

13 Kcal /100 gm. are very appropriate for weight loss diets. It is rich in minerals, especially potassium that is very necessary to maintain appropriate levels of liquids in the body, together with calcium and phosphorus makes it especially for the correct well being of the bones. It contains selenium, an antioxidant that has a medicinal property in prevention of certain type of cancers, colon, prostate and lungs. It contains many necessary amino acids for the formation of the proteins, alanine, and necessary for the construction of muscular and nervous tissues, glycine for the correct operation of immunological system. (www.botanical-online.com). The nutritional information is summarised in Table 2.

Table 2. Micronutrients and calories (per 100 g)

Nutrients	Amount
Protein	1.23 g
Carbohydrates	3.28 g
Fat – total	0.28 g
Dietary fibre	2.09 g
Calories	17.00 g
Ash	0.58 g
Micronutrients	
Carbohydrates	Total sugar 1.19 g
	Monosaccharides 1.19 g
	Fructose 0.79 g
	Glucose 0.39 g
Fate	Monounsaturated fatty acids 0.01 g
	Polyunsaturated fatty acids 0.15 g
	Saturated fatty acids 0.04 g
Water	94.60
Vitamins	
Water soluble vitamins	
B Complex vitamins	Vitamin B1 0.07 mg
	Vitamin B2 0.06 mg
	Vitamin B3 0.30 mg
	Vitamin B3 (Niacin) 0.45 mg
	Vitamin B6 0.07 mg
	Biotin 1.90 mg
	Choline 9.90 mg
	Folate 136.0 mcg
	Folate (DFE) 136.0 mcg
	Folate (food) 136.0 mcg
	Pantathenic acid 0.13 mg
Vitamin C	4.0 mg
Fat soluble vitamins	
Vitamin A	8710.00 IU
	Vitamin A mcg retinol activity equivalent (RAE) 435.50 mcg (RAE)
	Vitamin A mcg retinol equivalent (RE) 871.00 mcg (RE)

Carotenoid mcg retinol equivalent (RE)	871.0. mcg (RE)
Beta-Carotene	5226.00 mcg
Beta-Carotene equivalents	5226.00 mcg
Lutein and Zeaxanthin	2312.00 mcg
Vitamin D	0.00
Vitamin E	Vitamin E mg alpha tocopherol equivalents (ATE) 0.12 mg (ATE)
	Vitamin E (IU) 0.18 IU
	Vitamin E mg 0.18 IU
Vitamin K	102.5 mcg
Minerals	
Boron	83.74 mcg
Calcium	33.00mg
Chloride	57.00 mg
Chromium	1.32 mcg
Copper	0.05 mg
Iodine	3.29 mcg
Iron	0.96 mg
Magnesium	14.00 mg
Manganese	0.15 mg
Molybdenum	6.00 mcg
Phosphorus	30.00 mg
Potassium	247.00 mg
Selenium	0.38 mcg
Sodium	8.00 mg
Zinc	0.23 mg
Individual Fatty Acid	
Omega-3 Fatty Acids	0.11 g
Linolenic Acid (18:3)	0.11 g
Individual Amino Acids	
Alanine	0.05 g
Arginine	0.05 g
Aspartic acid	0.13 g
Cysteine	0.01 g
Glutamic acid	0.17 g
Glycine	0.05 g
Histidine	0.02 g
Isoleucine	0.04 g
Leucine	0.07 g
Lysine	0.06 g
Methionine	0.01 g
Phenylalanine	0.06 g
Proline	0.04 g
Serine	0.05 g
Threonine	0.04 g
Tryptophan	0.01 g
Tyrosine	0.02 g
Valine	0.05 g

Lettuce opium has been used in folk medicine for indications ranging from aiding circulation to treating swollen genitals. In Europe, it is used as a substitute for opium in cough mixtures⁸. In homeopathy, a tincture has been used for laryngitis, bronchitis, asthma, cough, and urinary tract infections⁹. The juice of the stem covering yields a medicinal extract known as thridace, the use and efficacy of which is widely discribed¹⁰. Lettuce Opium was used by the Ancient Egyptians and was introduced as a drug in America as early as 1799. The America hippie movement used it as a legal mind-altering drug or psychotropic, widely used. The dried juice has been recommended as a topical wound antiseptic, and the seeds have been used as a galactogogue (to increase the flow of milk in nursing mothers). It has been claimed that the flowers and seeds are effective in reducing fevers¹¹, lettuce opium products have been marketed as narcotic substitutes intended to be smoked alone or in combination with marijuana to enhance potency and flavor¹².

The interest in the plant at that time led to the first isolation of two major constituents of lactucarium – lactucin and lactucopicrin. Initial pharmacological and clinical studies were carried out and it was generally accepted that the compounds were responsible for the opiate resembling activity of the plant. In the 1930s, Knoll A.G. pharmaceutical company introduced Latucyl – an antitussic drug containing 0.2 g sesquiterpene lactones per dose.

Lactucarium was used unmodified in cough drop, 30 mg - 60 mg (0.5 grain to 1 grain), sometimes mixed with borax. However, it was found to be more efficient to formulate the drug in a cough syrup (Syrupus Lactucarii, U.S.P.) containing net 5 per cent lactucarium, 22 per cent glycerin, 5 per cent alcohol and 5 per cent orange flower water in syrup¹³.

4. CHEMICAL COMPOSITION AND ACTIVE COMPOUNDS

Lactuca sativa or garden lettuce is an annual plant. The stem, which rises above two feet, round, simple below, and branching in its upper part. The lower leaves are obovate, undulate and rounded at the summit; the upper are smaller, sessile, cordate, and toothed; both are shining, and of a yellowish-green color. The flowers are pale yellow, small, and-disposed in irregular terminal corymbs. Before the flower stem begins to shoot, the plant contains a bland pellucid juice, has little taste or odor, and is much used as a salad for the table, but during the period of inflorescence it abounds in a milky juice, which readily escapes from incisions in the stem. The variation in nutrition composition of *Lactuca sativa* varies from different origin is due to variation of cultivated region, storage condition, the leaves, seeds, is used for various medicinal purposes.

Leaves per 100 gm contain 96 per cent water, 1.4 gm protein, 2.2 gm carbohydrate, 1.1 gm dietary fibre, 0.2 gm fat, 1.2 gm ash. The leaves are rich source of vitamins, vitamin-A, vitamin-C, vitamin-K, niacin & folate, minerals particularly calcium, iron, phosphorous, sodium, potassium (USDA Nutrient database). The latex from *Lactuca sativa* contain 15 oxalyl and 8 sulfate conjugates of the guaianolide sesquiterpene lactones, lactucin, deoxylactucin and lactucopicrin^{14,15}. The guaianolide sesquiterpene lactones (Fig. 1.) phytoalexin from lettuce,

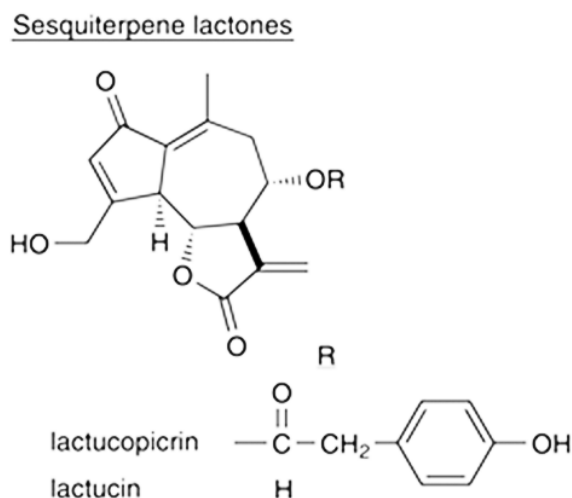


Figure 1. Structure of Sesquiterpene lactone.

lettucenin A is highly antimicrobial¹⁶. Medicinally lettuce leaf is used as mild sedative with other benefits. *Lactuca sativa* and its relatives contain sesquiterpene lactones which are active ingredients used as a sleep inducer and sedative¹⁷. Total polyphenolic content of *Lactuca sativa* was found to be 40 mg - 60 mg gallic acid per gram of vegetable. The active chemicals lactucin, lactucopicrin, etc are capable of inducing pharmacological effects in humans.

4.1 Lactucarium (U.S. Lettuce-opium)

The name of lactucarium has been given to the concrete milky juice of *Lactuca sativa*, or common garden lettuce, and of other species of *Lactuca* which are natives of Europe. It is procured from the stem, the leaves, which constitute all of the plant. They often have a narcotic property, and induce drowsiness when freely eaten. It should be collected about the time when the flowers begin to blow; for, if procured later in the season, though the juice may be thicker, it contains, less of the bitter matter on which its virtues probably depend. It is in small, irregular, light, and friable lumps, of a reddish-brown colour, a narcotic odour strongly recalling that of opium, and a bitter taste. It was this resemblance of its sensible properties to those of the medicine referred to, that gave origin to the name of lettuce-opium by which it has been occasionally designated.

It has a strong resemblance of the sensible properties of lactucarium to those of opium. The odorous principle distills over with water; but, though it is probably a volatile oil, and may have narcotic properties. A bitter, crystallizable, principle named lactucin is said to have been obtained from lactucarium; but its claims to be considered as the active constituent of the medicine have not yet been satisfactorily determined. Lactucarium yields its virtues to water and alcohol.

Dr J.R. Cox inferred, from his experiments, that it had the same stimulant properties as opium, Dr François, who used an analogous preparation of lettuce, under the name of thridace in France, found it to diminish the frequency and force of the pulse, and the temperature of the body. If, as stated by Fisher, it should be found to have the property of directly diminishing sensibility, without ever exciting the circulation and if Buchner be correct in comparing the influence of lactucin over the

pulse to that of digitalin, and in ascribing to it the properties of lowering the animal heat, dilating the pupil, and producing sleep; then we shall certainly be justified in placing lactucarium among the sedative. So far as can be inferred from other published accounts.

From its variable strength, lactucarium may be employed for calming nervous disquietude, relieving pain, and producing sleep, in cases in which, in consequence of the existence of some contraindication, opium cannot be used. Thus, having little or no stimulant influence over the circulation, it may be used in inflammatory and febrile conditions in which the excitant action of opium might prove injurious. Not having, at least in an equal degree, the property of checking the secretions, it is better adapted to the early stages of catarrhal disease; and, perhaps, it's most advantageous application is to the alleviation of cough. It is said, moreover, to be less than opium to cause headache, nausea or other disorder of digestion, and constipation; and may agree well with constitutions, which from idiosyncrasy may not be kindly affected by that narcotic.

It has been specially recommended to allay cough in phthisis, catarrh, and other pulmonary complaints; to compose nervous irritation and produce sleep in febrile diseases of all kinds, idiopathic, exanthematous, and symptomatic; to quiet palpitation of the heart; and to relieve pain in chronic rheumatism, colic, gastralgia, and excessive sensibility of the eyes. The dose of it is from five to fifteen or twenty grains; that of the alcoholic extract, from two to five grains. The Edinburgh College formerly directed a Tincture.

- a. *Lactucin* ($C_{11}H_{14}O_4$), one of the bitter principles of lactucarium, may be obtained by extracting lactucarium, with cold alcohol of specific gravity 0.85. It is a colorless, odorless, fusible, neutral substance, crystallising in rhombic plates, or in pearly-white scales. It dissolves in from 60 to 80 parts of water, is slightly soluble in ether, readily so in alcohol, and in acids. It reduces Fehling's solution, but yields no sugar upon hydrolysis.
- b. *Lactucic acid* is light yellow, very bitter, soluble in water and alcohol, and does not readily crystallise. Alkalies turn its aqueous solution red. This acid is considered a prominent active constituent.
- c. *Lactuco-picrin* ($C_{44}H_{32}O_{21}$). It is a brown, amorphous, bitter body, faintly acid in reaction, soluble in water and alcohol. It is probably an oxidation product of lactucin. Kromayer regards lactucic acid as the product of the oxidation of lactuco-picrin.
- d. *Lactucerin* (lactucon of Lenoir, 1846) ($C_{19}H_{30}O$) The most abundant substance in lactucarium is lactucerin, constituting half or more of its weight. It is obtained by extracting lactucarium with cold, then with boiling alcohol, which leaves undissolved; or by extracting lactucarium with a mixture of 1 part of chloroform and 3 parts of alcohol. It forms odorless, tasteless, colorless needles, soluble in alcohol, ether, benzene, benzol, chloroform, and volatile and fixed oils, but not soluble in water.

5. PHARMACOLOGICAL USES AND DOSAGE

It appears to be of use in insomnia, due to mental overwork.

Syrup of lactucarium is of value in the cough of phthisis, and even garden lettuce appears to exert a good influence in this disease, tending to allay the broncho-pulmonary irritation. Dose of lactucarium in pill or powder, which is the most efficient mode of administration, from 5 grains to 20 grains; of the tincture, 30 drops to 60 drops; of the alcoholic extract, 1 grain to 5 grains.

All over the world scientific research is getting momentum to evaluate the pharmacological activities, side effects and medicinal uses of *Lactuca sativa* against different diseases. On the basis of various experimental and clinical researches, the following pharmacological activities or medicinal properties of *Lactuca sativa* have been reported.

5.1 Anti-oxidant Property

Lactuca sativa have shown to prevent oxidative injuries, lettuce is a rich source of antioxidants which are considered to have anti carcinogenic properties, among antioxidant compounds in lettuce are β carotene¹⁸ combined antioxidative effects of lettuce extract and α tocopherol, quercetin, ascorbic acid were investigated for peroxidation of 1α phosphatidylcholine liposomes with oxidation initiated by lipophilic or by hydrophilic azo initiators¹⁹ heating of lettuce extract resulted in a increasing synergism for added quercetin and α tocopherol indicating that thermal inhibition of polyphenol oxidase increases antioxidant potential and interaction^{20,21}, antioxidant activity of lettuce has been reported that it can prevent chronic diseases related to oxidative stress such as cancer²², the lettuce is sequentially extracted with methanol and ethyl acetate, the extract were evaluated for their *in vitro* lipid peroxidation and cyclooxygenase enzyme inhibitory activities²³ methnolic extract of green lettuce contain linoleic acid, quercetin glycoside, chicoric acid, linoleic acid is considered as an essential dietary ingredient with antioxidant and anti inflammatory properties²⁴, Radical scavenging was determined by DPPH radical scavenging activity²⁵, the antioxidant extracts of lettuce exhibited significant oxygen radical absorbance capacity²⁶, prevention of lipid oxidation in lower density lipoproteins²⁷, inhibitory effects on ethylene formation induced by Chu²², *et al.*, hydroxyl radical absorbance capacity and inhibitory activity against Cu^{2+} induced protein oxidation²⁸. Antioxidant properties of *Lactuca sativa* leaf extract involved in the protection of biomolecules was as also reported²⁹.

5.2 Anti-inflammatory Property

The seeds of the lettuce plant were used for relieving of inflammation, anti inflammatory activities of a crude methanol/petroleum ether extract of the seeds have been evaluated dose dependent anti inflammatory activity in a carrageenan model of inflammatory activity³⁰, the seeds of the lettuce were traditionally used in Iran for relieving of inflammation, gastrodynia and osteodynia sesquiterpene lactones exert anti inflammatory properties by inhibiting the central transcription factor nuclear factor κ B (NF- κ B), this transcription factor promotes the expression of multiple inflammatory and immune genes and genes encoding enzymes such as Cyclooxygenase 2 (COX 2) and inducible nitric oxide synthase. reduction of

the PGE2 production it is possible that a prevention of the induction of COX2 protein expression mediated by the NF- κ B activation, may partly explain the inhibition of PGE2 synthesis by the guaianolides (Wesolowska³⁵, *et al.*), preliminary phytochemical analysis performed for seed extract of *Lactuca sativa*, triterpenoid, saponins and phenols were present³⁰, the anti inflammatory action of triterpenoids has been reported by many^{31,32,33} suppression of inducible nitric oxide synthase (i-NOS) and inducible cyclooxygenase 2 (COX2) enzymes has been showed for triterpenoids^{32,33}.

5.3 Analgesic Property

An analgesic potency of lettuce opium extracts was studied by³⁴ and a distinct inhibition of enkephalinase activity in a concentration dependent way was found. *Lactuca sativa* seeds were analysed for analgesic property by Formalin and Tail flick test. It has the property due to presence of triterpenoides and saponins³⁰, lactucin and its derivatives possess analgesic activities in thermal models of nociception similar to that observed for ibuprofen used as a standard drug³⁵.

5.4 Neuroprotective Property

Reports are available on neuroprotective effects of *Lactuca sativa*³⁶. The *Lactuca sativa* was designed to elucidate the protective effects of ethanolic extract on accumulation of lipofuscin granules in various regions of the brain of D galactose induced ageing accelerated female albino mice³⁷, *Lactuca sativa* has decreased the lipofuscin granules in cerebral cortex, hippocampus this might be due to formation of advanced glycation end products (AGEs) lettuce is rich in antioxidants³⁸, which together must have nullified the effect of D galactose and there by reduced the oxidative stress³⁹ have demonstrated the anti AGE effect of quercetin, vitamin C is a proven antioxidant⁴⁰, decreased lipofuscin granules in *Lactuca sativa* cotreated group indicate lysosomal clearance which indicate the healthy cell. *Lactuca sativa* has protected the neurons from accumulation of lipofuscin granules and thus proved as effective antioxidant³⁷. It has been showed that *L. sativa* protect neuron-like rat pheochromocytoma-derived cell line (PC12) cells against H₂O₂-induced cytotoxicity via anti-oxidant^{41,42}.

5.5 Sedative Property

Anticonvulsant and sedative hypnotic effects have been studied in the leaves of *Lactuca sativa* plant⁴³ sedative property of lactucin and some lactucin like guaianolides in mice was carried out sedative property was showed by lactucin, lactucopicrin in the spontaneous locomotor activity test⁴⁴. An alcoholic extract of a related species, *L. sativa*, has exhibited a sedative effect in toads, causing a reduction in motor activity and behaviour⁴⁵. The lettuce has a tranquilising effect. It helps to calm the nerves to control palpitations and sleep better at nights, avoiding the insomnia. *Lactuca* is used for insomnia and believed to help a weak memory⁴⁶, Metabolite profiling of sesquiterpene lactones from *Lactuca* species. Major latex components are novel oxalate and sulfate conjugates of lactucin and its derivatives⁴⁷. The component that grants this property is the lactucin, one of the main components of the juice of the lettuce.

5.6 Anti-anxiety Property

Lactuca sativa extract was found to improve exploratory behaviour and biochemical changes that occur due to anxiolytic condition. *Lactuca sativa* was fed to animals for two different treatment duration (15 days and 30 days) and subjected for a variety of behaviour parameters like elevated plus maze, elevated T maze, open field test, marble burying test, rat exposure test, novel object recognition test, hyponeophagia. The plant extract treated group found to improve exploratory behaviour, locomotory activity in mice^{48,49}.

5.7 Other Medicinal Properties

Lettuce has diuretic property; it stimulates the urine elimination in illness like: obesity, dropsy, arterial hypertension, kidney stones, inflammation in bladder, etc. it is equally it is used as a support in the diets dedicated to reduce the sugar of blood, by means of the elimination of corporal liquids. It improves circulation, prevents arteriosclerosis and diminishes cholesterol. The decoctions of lettuce leaves are used to combat cold, asthma attacks and bronchial spasms (www.botanical-online.com).

Lactucopicrin has also been shown to act as an acetyl cholinesterase inhibitor, anti-cholinesterase is a chemical that inhibits the cholinesterase enzyme from breaking down acetylcholine, increasing both the level and duration of action of the neurotransmitter acetylcholine⁵⁰. Uses of Acetyl cholinesterase inhibitors: Occur naturally as venoms and poisons, are used as weapons in the form of nerve agents.

6. SAFETY AND TOXICITY

The plant should be used with caution, and never without the supervision of a skilled practitioner. Even normal doses can cause drowsiness while excess causes restlessness and overdoses can cause death through cardiac paralysis (Lettuce and its legend). The Yazidi of northern Iraq consider eating lettuce taboo. Food taboos can be defined as a codified set of rules about which foods or combination's of foods may not be eaten⁵¹.

7. CONCLUSION

The lettuce seems to possess medicinal properties and have been worked out extensively. It is a rich source of many important nutrients, vitamins and minerals and sesquiterpenes. The main active compounds Lactucin, Lactucopicrin from this plant have been shown to possess beneficial therapeutic potential on human health as it is evident from a many research findings. However exploration into molecular mechanism for the active compounds needs research in future. A number of reports on this plant have shown great therapeutic value. Lettuce could be used to prepare multipurpose products for pharmaceutical applications and its usage as dietary source of antioxidant should be considered largely for ameliorating anxiety disorder conditions especially.

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