NATIONAL UNIVERSITY OF PHARMACY
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COURSE PROJECT IN PHARMACOGNOSY

PHARMACOGNOSTIC STUDY OF FRESH LETTUCE LEAVES OF "LOLLO ROSSO" VARIETY

Prepared by: 3rd year student, A-02 group
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INTRODUCTION

Leafy vegetables are common food items in a well-balanced diet, and increased consumption of fruit and vegetables is a general goal in public health work in Western countries since diets rich in fruits and vegetables are associated with a lower risk of cancer and cardiovascular diseases [18].

Lollo rossa is part of the Lettuce genus and is a Lettuce variety. Its scientific name is *Lactuca sativa 'Lollo rossa'*. Lollo rossa is generally thought of as a heirloom open-pollinated variety.

Lollo Rosso lettuce is a classic Italian lettuce, with dark copper red fading to bright green, finely crinkled frilly leaves which are crisp, almost brittle when snapped.

This lettuce is appreciated for its unique shape and refreshing taste. It holds well in summer heat and in the cold. Harvest outer leaves or the entire plant.

In addition to its usual purpose as an edible leafy vegetable, lettuce has had a number of uses in ancient (and even some more modern) times as a medicinal herb and religious symbol. For example, ancient Egyptians thought lettuce to be a symbol of sexual prowess and a promoter of love and childbearing in women. The Romans likewise claimed that it increased sexual potency. In contrast, the ancient Greeks connected the plant with male impotency and served it during funerals (probably due to its role in the myth of Adonis's death), and British women in the 19th century believed it would cause infertility and sterility. Lettuce has mildnarcotic properties; it was called "sleepwort" by the Anglo-Saxons because of this attribute, although the cultivated L. sativa has lower levels of the narcotic than its wild cousins. This narcotic effect is a property of two sesquiterpene lactones which are found in the white liquid (latex) in the stems of lettuce called lactucarium or "lettuce opium". The cultivated lettuce does not contain as much lactucarium as the wild species, most being produced when the plant is in flower.

Some American settlers claimed that smallpox could be prevented through the ingestion of lettuce and an Iranian belief suggested consumption of the seeds when afflicted with typhoid. Folk medicine has also claimed it as a treatment for pain, rheumatism, tension and nervousness, coughs and insanity; scientific evidence of these benefits in humans has not been found. The religious ties of lettuce continue into the present day among the Yazidi people of northern Iraq, who have a religious prohibition against eating the plant.

The plant has been known for its properties since ancient times, and now is widely cultivated worldwide, having great number of varieties. Thus, the **objective** of our work was to carry out pharmacognostic study of lettuce of "Lollo Rosso" variety which is widely used for its culinary properties.

We have set the following **tasks**:

- To carry out literature review on lettuce, its botanical description, chemical constituents and medicinal and other uses, as well as detiled description for its "Lollo Rosso" variety;
- To determine the main macroscopical and microscopical features of lettuce leaves;
- To determine the main technological parameters of the plant material studied;
- To confirm the presence and determine the quantity of some groups of biologically active compounds in fresh lettuce leaves of "Lollo Rosso" variety.

CHAPTER I

LETTUCE AS A VALUABLE SOURCE OF BIOLOGICALLY ACTIVE COMPOUNDS

1.1. History of using lettuce

Lactuca sativa is a member of the *Lactuca* (lettuce) genus and the Asteraceae (sunflower or aster) family. The species was first described in 1753 by Carl Linnaeus in the second volume of his *Species Plantarum*. Lettuce is closely related to several *Lactuca* species from southwest Asia; the closest relationship is to *L. serriola*, an aggressive weed common in temperate and subtropical zones in much of the world.

The Romans referred to lettuce as *lactuca* (*lac* meaning milk in Latin), an allusion to the white substance, now called latex, exuded by cut stems. This word has become the genus name, while *sativa* (meaning "sown" or "cultivated") was added to create the species name. The current word *lettuce*, originally from Middle English, came from the Old French *letues* or *laitues*, which derived from the Roman name. The name *romaine* came from that type's use in the Roman papal gardens, while *cos*, another term for romaine lettuce, came from the earliest European seeds of the type from the Greek island of Cos, a center of lettuce farming in the Byzantine period.

Lettuce's native range spreads from the Mediterranean to Siberia, although it has been transported to almost all areas of the world. Plants generally have a height and spread of 6 to 12 inches (15 to 30 cm). The leaves are colorful, mainly in the green and red color spectrums, with some variegated varieties. There are also a few varieties with yellow, gold or blue-teal leaves. Lettuces have a wide range of shapes and textures, from the dense heads of the iceberg type to the notched, scalloped, frilly or ruffly leaves of leaf varieties. Lettuce plants have a root system

that includes a main taproot and smaller secondary roots. Some varieties, especially those found in the United States and Western Europe, have long, narrow taproots and a small set of secondary roots. Longer taproots and more extensive secondary systems are found in varieties from Asia.

The largest producer of lettuce in the world is China, which produces mainly a stem lettuce (*L. sativa* L. var. *angustana*) not commonly consumed in the US or Western Europe [39]. The US and Western Europe contribute about 22% and 13% of the total lettuce production worldwide, respectively [39]. In the US, lettuce ranks as the 3rd most consumed vegetable [58].

1.2. Modern lettuce types class

Lettuce comes in a variety of colors, sizes and shapes and because of this diversity lettuces can be grouped by their types. A type is a group of cultivars that are morphologically similar. A type can be further subdivided into subtypes which shares more morphological and genetic similarities. A cultivar is a variety selected for desirable traits for cultivation. A variety is a taxonomic rank below species and subspecies. Although there have been different classification systems proposed by different groups of researchers over the years [39], there is no standardized classification system, due to high genetic and morphological diversity among lettuce cultivars.

Fig. 1.1. Crisphead lettuce variety

1. **Crisphead** (iceberg types; var. *capitata* L. *nidus jaggeri* Helm) - large, heavy, tightly folded heads; brittle or crisp textured; prominently veined leaves; wrapper leaves green; inner leaves whitish-yellow; predominantly outdoor types; widely used in N. America.

The crisp head or cabbage lettuces are the most popular lettuces in American supermarkets and restaurants. There are hundreds of cultivars, some of which form heads no larger than a tennis ball ('Tom Thumb', 'Mini Green') and are well suited for the home garden. Some are red ('Rosa', 'Rosy'). Typical "iceberg" type heading lettuces are 'Ithaca', 'New York', 'Great Lakes'.

Fig. 1.2. Buttterhead lettuce variety

2. Butterhead (bibb or Boston lettuce types; var. *capitata* L. *nidus tenerrima* Helm) - soft leaves; smooth texture; varieties bred for both outdoor summer conditions and greenhouse winter conditions; summer butterheads larger and firmer than the winter types; winter butterheads smaller and less compact; popular in N. Europe.

Fig. 1.3. Romaine lettuce variety

The butterhead or bibb lettuces have small, roundish heads with loosely packed leaves that are thick and succulent. Among hundreds of cultivars are 'Buttercrunch', 'Bibb', and 'Perella Red'.

3. **Cos** (romaine; var. *longifolia* Lam., var. *romana* Hort. in Bailey) - elongated leaves developing into large loaf-shaped heads; slower to bolt than other lettuces; useful as a warm-weather crop; popular in S. Europe and the U.S. The many cultivars include 'Parris Island', and 'Valmaine'.

Fig. 1.4. Leaf lettuce variety

4. **Leaf** (cutting; var. *acephala* Alef., syn. var. *secalina* Alef., syn. var. *crispa* L.) - local marketing and home garden lettuce; grown mostly in greenhouses in the winter in northern and eastern regions. The curled or loose leaf lettuces are non-

heading types with loose rosettes of crinkled leaves. These are the easiest to grow and the most popular with the home gardener. Popular cultivars include 'Black Seeded Simpson', 'Ibis', 'Red Oak Leaf', 'Red Sails'. This morphotype is extremely heterogeneous. Cultivars may have entire, curled or fringed leaves, from non-lobed to deeply incised margins. The leaves are elongated or broad, having various shades of green, and various patterns and intensities of anthocyanin pigmentation. The Greeks and Romans cultivated cutting lettuces [27].

5. **Stem** or stalk (Asparagus) lettuce (var. *angustana* Irish ex Bremer, syn. var. *asparagina* Bailey, syn. L. *angustana* Hort. In Vilm.) – consists of a tuft of dark green leaves resembling Romaine lettuce atop a long thick stem. The leaves and stem are both edible, but are usually prepared in different ways. The outer leaves are relatively tough and bitter, and they are often discarded. The mild-tasting leaves at the tip of the asparagus lettuce look and taste like lettuce [29].

Fig. 1.5. Stem lettuce variety

1.3. Chemical constituents of lettuce

The study of polyphenol profiles by HPLC-DAD-MS/MS ESI allowed the identification of two compounds, quercetin and luteolin rhamnosyl-hexosides, not previously reported in lettuce. Caffeic acid derivatives were the main polyphenols in green varieties, while flavonols were observed in higher quantities in red varieties, and anthocyanins were only present in red-leafed varieties.

Lettuce flavonoids have been studied [10], showing that quercetin-3-O-(6”-O-malonyl)-glucoside, is the main phenolic compounds with other quercetin and luteolin derivatives also detected in smaller amounts.

As a general rule, red-leafed vegetables showed a higher content in both flavonol and caffeic acid derivatives than green lettuce varieties. Red-leaf varieties also contain quercetin-7-O-glucuronide-3-O-(6”-O-malonyl)-glucoside and quercetin-7-O-glucoside-3-O-(6”-O-malonyl)-glucoside [33]. The red oak leaf cultivar contained twofold more dicaffeoyl tartaric acid and 10-fold more chlorogenic acid than the green cultivars [40].

In Lollo Rosso lettuce, the total flavonoid content was the highest in red, followed by green and then white parts of leaves [13]. Generally, lettuces grown in an open field system had significantly higher flavonol content compared to lettuces in high tunnel due to higher solar radiation level [62]. Total phenolics, anthocyanin, and quercetin levels in Lollo Rosso lettuce were all increased by altering the level of UV using blocking film, low UV transparency film, and high UV transparency film [62].

Quercetin-3-O-glucuronide, quercetin- 3-O-glucoside, quercetin-3-O-rutinoside, luteolin-7-O-glucuronide, luteolin-7-O-glucoside and luteolin-7-O-rutinoside are not always detected in all lettuce cultivars, and are usually found in trace amounts with the exception of red lettuce cultivars. In red lettuce varieties, cyanidin-3-O-(6”-O-malonyl)-glucoside was also identified [32].

Concerning vitamin C, red-leafed salads showed higher content than green-leafed salad vegetables with the exception of the continental variety which showed the highest level [32].

Since lettuce passes through a long supply chain (figure 1.6.) before it gets to the consumer, it is highly important to evaluate the amount of biologically active compounds in it and influence of storage conditions on the resulting antioxidant activity.

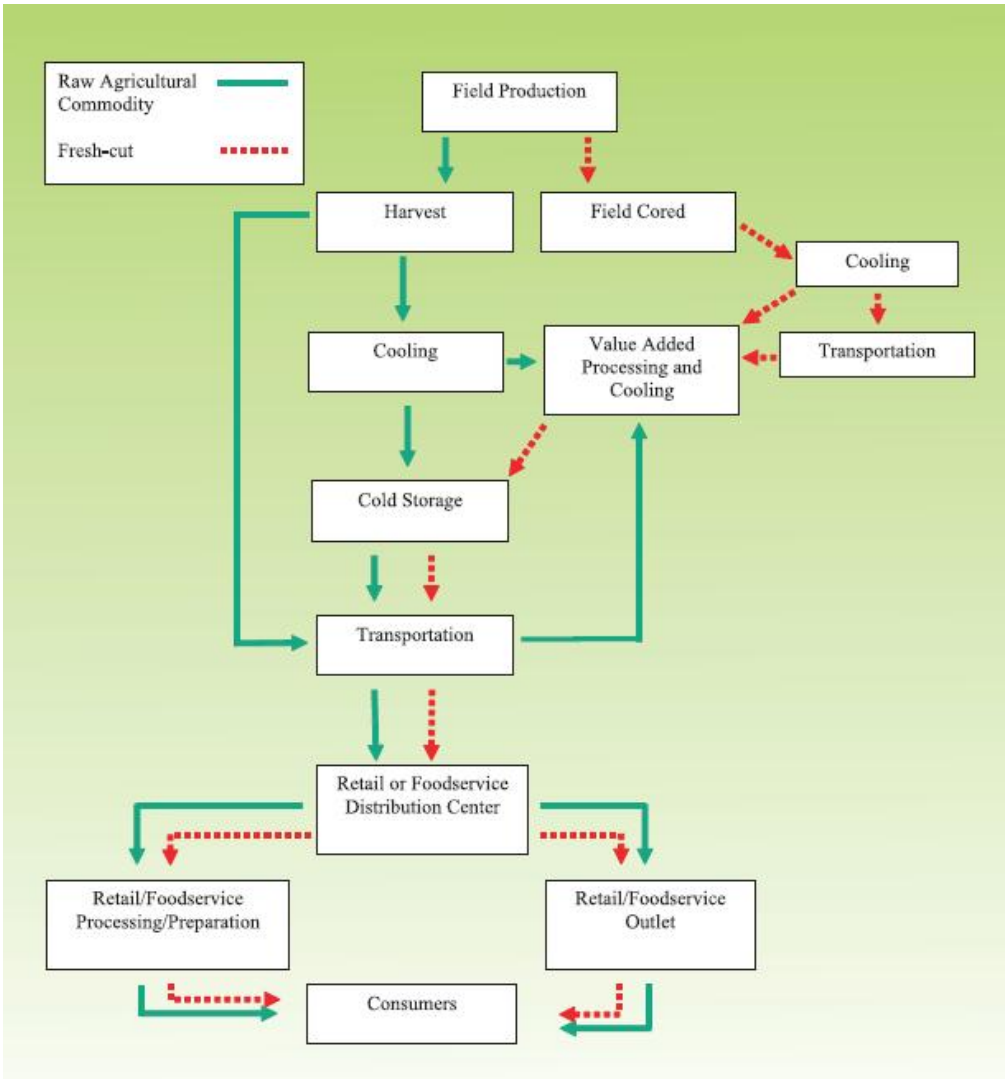


Fig. 1.6. General Supply Chain Flow for Lettuce

Concerning the correlation between storage and the content of phenolic compounds, although midrib showed brown discoloration and, therefore, phenolics should be decreasing, wounding induced phenolic metabolism and increased phenolic content throughout the storage. Phenolic acids and the anthocyanin cyanidin 3-malonylglucoside increased in midrib during cold storage, while flavonoids did not change. Finally, the total content of phenolic acids and flavonoids in both green and red tissues was maintained throughout the storage, but the anthocyanin concentration decreased [13]. It was also determined that after ingestion of fresh lettuce, plasma total radical-trapping antioxidant potential is higher than after ingestion of stored samples [50]. Major losses of antioxidants

(ascorbic acid, total phenolics) were recorded after 6 days and for temperatures above 2 °C for lettuce cultivars [51].

Lutein was the main carotenoid found in all cultivars, together with another xanthophylls [40].

53 volatile organic compouns were detected and successfully identified in a study showing the compounds that are responsible for certain smell of lettuce [34]. Four of the compounds obtained were reported as lettuce volatile emissions: hexanol and benzaldehyde, ethanol and nonanal.

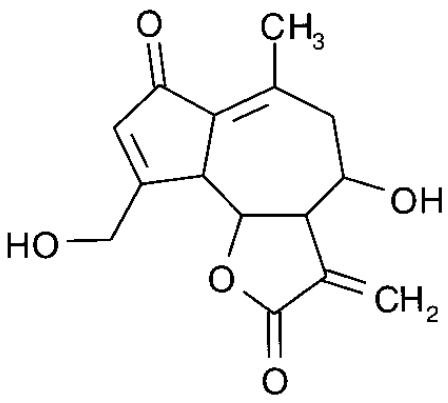
Five identified phenols and a quinone (benzoquinone) are substrates of polyphenol oxidase (PPO), an enzyme responsible for browning [5]. Two volatile chlorinated compounds were identified: 1,4-dichlorobenzene and 1-chlorododecane. These emissions could have been produced as a result of the chlorine treatment, reinforcing the idea that potentially harmful chlorinated compounds can be formed during minimal processing [48].

Four main categories of odors were distinguished: fresh, green, musty and rotten. Four green smelling-compounds (limonene, (+)-cyclosativene, copaene and caryophyllene) were terpenes. Three phenolic compounds (4-ethylbenzaldehyde, 2,5-dimethylbenzaldehyde and trans-cinnamaldehyde) were perceived as fresh aromas, while two others (benzoquinone and ester benzoic acid) contributed to the musty odor. These results confirmed that enzymatic browning was accompanied with the release of odors via the action of the polyphenol oxidase (PPO) on phenols and quinines [42].

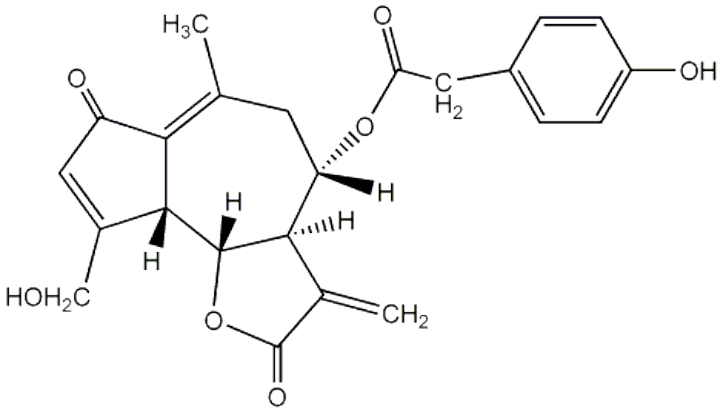
Some of the compounds can be considered as quality markers as they correlated with the same sensory attributes. 1,4-Dichlorobenzene, perceived as fresh, was a marker of odor changes, loss of green color and browning. The terpene limonene was a marker of the loss of green color. (+)-cyclosativene, copaene and caryophyllene, perceived as green aromas of leafy green vegetables, were correlated with fresh aroma. α-Longipinene, associated with a rotten odor, was a marker of the loss of green odor and the development of rotten off-odor [34].

Characteristic of the Asteraceae and sporadically occurring in other plant families, sesquiterpene lactones are interesting from the chemical and chemotaxonomic point of view, and show anti-tumour, anti-leukaemic, cytotoxic, antimicrobial activities and allergenic properties [36;55]. Sesquiterpene lactones have been also indicated as responsible of bitterness [49], a property connected to appetite and digestion promotion in humans [26, 1, 37]

The guaiane-type sesquiterpene lactone lactucin and its derivatives are characteristic bitter constituents of *Lactuca* species, and some other members of the tribe Lactuceae of the family Asteraceae. Lactucin was first discovered in latex of wild lettuce (*Lactuca virosa* L.) in the middle of the 19th century. The latex released from damaged lactifers of leaves or stems of the flowering plants, when left in the open, dries into a brown gummy product, known as lactucarium or lettuce opium. Analgesic, antitussive and sedative properties of the lettuce opium, used throughout Europe for centuries, had been attributed to the presence of lactucin and its ester lactucopicrin long before their structures were known [2].



Lactucin



Lactucopicrin

Other sesquiterpene lactones found in lettuce, were 11β,13-dihydrolactucin, melampolide, and 3β,14-dihydroxy-11β,13-dihydrocostunolide, 8-Tigloyl-15-Deoxylactucin [35, 3].

Methanolic extracts of Lactuca runcinata was reported to contain alkaloids [21], as well as *Lactuca serriola* L. [38].

Although low in fat, lettuce contains polyunsaturated fatty acids (PUFA) which are important for health. The omega-6 PUFA, linoleic acid (LA) and omega-3 PUFA, a-linolenic acid (ALA), are essential fatty acids that must be obtained from the diet [23].

Lettuce also provides carbohydrates with lower digestibility and, in turn, lower caloric content such as sugar alcohols. Lettuce also provides dietary fiber [58]. Health benefits reported for increased dietary fiber intake include weight loss due to its low caloric content, lowering risk of cardiovascular diseases by reducing low density lipoprotein (LDL) cholesterol and blood pressure, reducing risk of diabetes by improving glucose metabolism, and lowering risk of colon cancer [16; 19; 59; 60]. 100 g of fresh lettuce can provide up to 10% of the daily recommended intake of fiber for adults – 21–38 g/day [19].

Mineral analysis showed lettuce was a relatively good source of Fe and low in Na [25].

Reported values suggest lettuce is a rich source of folates, with butterhead, romaine, and red leaf lettuces being particularly good sources [20,25].

1.4. Medicinal effects of lettuce cultivars

The antioxidative activity of dietary phytochemicals has been linked to reductions in human degenerative diseases in populations that consume high amounts of fruits and vegetables. In particular, the ability of plant phenolic compounds or their possible human metabolites to scavenge various oxygen and nitrogen free radicals has suggested mechanisms for the human health benefits of diets rich in fruits and vegetables [7]. [31]

The values of content of phenolic substances and total antioxidant activity of the vegetables correlate very well. The very high values of antioxidant activity were found in intensely colored vegetables [32].

Evidence from in vitro, preclinical, and clinical studies suggested that lettuce has potential anti-inflammatory, cholesterol lowering, anti-diabetic, and anti-cancer properties.

Polyphenols have been described to have greater antioxidant activity than vitamin C and E. Individual phenolic compounds and vegetables that contain phenolic compounds have shown beneficial effects against oxidative stress, inflammation, cancer, diabetes, age-related neurodegeneration, and cardiovascular diseases [9 ;48; 52; 53; 61].

The anti-inflammatory activity of lettuce extract can also be related to its phenolic compounds [45], as well as its terpenoid componenets [3].

A study carried out in rats has shown that lettuce consumption increases the total cholesterol end-products excretion and improves antioxidant status due to the richness in antioxidants (vitamins C, E and carotenoids). Therefore regular consumption of lettuce should contribute to improve protection against cardiovascular diseases, with red lettuce cultivars showing the highest results [41]. The authors attributed the cholesterol-lowering effects of lettuce to synergistic effects of bioactive compounds such as a-tocopherol, b-carotene, antho-cyanins and phenolic compounds [30].

Phenolic compounds, such as chlorogenic acid in ‘Rutgers Scarlet’ lettuce, were suggested to have played a role in lowering blood glucose [8].

Potential nutrients in lettuce showing a significant association with reduced colorectal cancer were b-carotene and ascorbic acid, whereas, Ca, vitamin E, and folate showed no significant relationship to colorectal cancer [12].

Lettuce has acquired a folk reputation as an aphrodisiac, anodyne, carminative, diuretic, emollient, febrifuge, hypoglycaemic, hypnotic, narcotic, parasiticide and sedative [8].

Folates present in lettuce leaves are effective for reducing the risk of birth defects, such as neural tube defects [56].

Lettuce is popularly consumed in salad mixes and consumption of salads is increasing. Therefore, lettuce can contribute significantly to the nutritional content of diets. Since lettuce is generally eaten raw, more nutrients are retained compared to other vegetables that are cooked or processed, such as potatoes. [24]

CONCLUSION

1. The literature review concerning lettuce and its cultivars and varieties was carried out.
2. In spite of public perception that lettuce is low in nutritional value, nutritional data from various studies support that lettuce can provide considerable amounts of healthy nutrients, especially folate, carotenoids and phenolic compounds.

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