



The Constituents and Pharmacology of *Cnicus Benedictus*- A Review

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Abstract The chemical constituents of *Cnicus benedictus* showed that it contained sesquiterpene lactone glycosides, cnicin, polyacetylen, absinthin, salonitenolide and artemisiifolin. Triterpenoids such as a-amyrenone, a-amyryn acetate, a-amyryne, and multiflorenol acetate. Lignans such as trachelogenin, nortracheloside and arctigenin. Flavonoids, including apigenin-7-O-glucoside, luteolin and astragaline. Tannins contents reached (8%). essential and volatile oils (0.3%) including n-nonane, n-undecane, n- tridecane, dodeca-1,11-dien-3,5,7,9-tetraen (polyene), p-cymene, fenchon, citral, cinnamaldehyde, were also isolated from the plant. It was also contained many nutritional components, minirals and trace elemints. The previous pharmacological studies showed that *Cnicus benedictus* possessed antimicrobial, cytotoxic, anti-inflammatory, wound healing, enhancing digestion and increasing bile secretion. This review was designed to highlight the chemical constituents, pharmacological and toxicological effects of *Cnicus benedictus*.

Keywords constituents, pharmacology, toxicology, *Cnicus benedictus*.

Introduction

As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. 75% of the world's population used plants for therapy and prevention. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [1-30].

The chemical constituents of *Cnicus benedictus* showed that it contained sesquiterpene lactone glycosides, cnicin, polyacetylen, absinthin, salonitenolide and artemisiifolin. Triterpenoids such as a-amyrenone, a-amyryn acetate, a-amyryne, and multiflorenol acetate. Lignans such as trachelogenin, nortracheloside and arctigenin. Flavonoids, including apigenin-7-O-glucoside, luteolin and astragaline. Tannins contents reached (8%). essential and volatile oils (0.3%) including n-nonane, n-undecane, n- tridecane, dodeca-1,11-dien-3,5,7,9-tetraen (polyene), p-cymene, fenchon, citral, cinnamaldehyde, were also isolated from the plant. It was also contained many nutritional components, minirals and trace elemints. The previous pharmacological studies showed that *Cnicus benedictus* possessed antimicrobial, cytotoxic, anti-inflammatory, wound healing, enhancing digestion and increasing bile secretion. This review will highlight the chemical constituents, pharmacological and toxicological effects of *Cnicus benedictus*.

Plant profile

Synonyms:

Carduus benedictus (L.) Thell. and *Cirsium pugnax* Sommier & Levier [31-32].

Taxonomic classification:

Kingdom: Plantae; **Subkingdom:** Tracheobionta; **Superdivision:** Spermatophyta; **Division:** Magnoliophyta; **Class:** Magnoliopsida; **Subclass:** Asteridae; **Order:** Asterales; **Family:** Asteraceae / Compositae; **Genus:** *Cnicus*; **Species:** *Cnicus benedictus* L.⁽³¹⁾.

Nomenclature and common names:

The Latin name *benedictus* was derived from blessed thistle's immense healing properties implying its sacred virtues. By the early sixteenth century, it had securely gained footing in European folk medicine and was cultivated widely in monastery gardens. Even the famous poet Shakespeare mentioned blessed thistle in his play *Much Ado about*



Nothing (written in 1598-1599 CE). Spiritually, it was associated with purification and therefore used in purification baths. It was also believed that wearing a bit of it would protect one from evil. Furthermore, it was associated with the planet Mars, the zodiac of Aries, and the element fire [33-36].

The plant common names were: **Arabic:** farasion, kanterion mubark, shok mubark, shok marimi, shok bari; **Chinese:** cang ye hua; **English:** blessed thistle; **French:** chardon bénit; **German:** Benediktenkraut, Bitterdistel; **Portuguese:** cardo-bento, cardo-santo; **Russian** benedikt aptečnyj, knikus blagoslovennyj; **Spanish:** Cardo santo; **Swedish:** kardbenedikt [32, 37].

Distribution

Blessed thistle is native to the Mediterranean. It was also said that it was native in **Africa:** Algeria, Libya and Egypt; **Asia:** Afghanistan, Iran, Iraq, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, Jordan, Lebanon, Palestine, Syria, Turkey, China and Pakistan; **Europe:** Albania, Bosnia and Herzegovina, Bulgaria, Greece, Italy, Macedonia; Serbia, France, Portugal and Spain. It was stated that it was neutralized in a wide areas in Asia, Europe, Australia, North America (Canada and USA) and South America (Ecuador, Argentina, Chile and Uruguay) [32, 38].

Description:

The thistle grows to 30 to 50 cm high. The stems are heavily branched, thistle-like, villous and glutinous pubescent. The leaves are oblong, emarginated to pinnatifid, thorny-dentate, and roughly reticulate. Flower and Fruit: The blossom is a pale yellow composite, its solitary flower sessile on the tips of the twigs. The florets are tubular. The few lateral florets are sterile, have 3-part borders and are smaller than the numerous androgynous florets. The epicalyx is ovate. The inner bracts end in a long, rigid and pinnatifid thorn. The outer bracts terminate in a simple thorn. They are broad, leafy and connected with the cordate-oblong leaflets of the epicalyx by numerous web-like hairs. The fruit has a tuft of hair [39].

Traditional uses:

Blessed or holy thistle (leaves, stems, and flowers has been used to stimulate appetite, enhance bile secretion, strengthen the liver, diminish jaundice, decrease flatulence, and aid digestion. It was used for this purpose in both European traditional herbalism and in the Ayurvedic medicine system of India over the generations. It was also used to support and regulate the female reproductive system due to its emmenagogue action. It was also used as galactagogue in nursing mothers to increase and enrich milk flow [33-34, 40-41].

Blessed thistle leaves, stems, and flowers have traditionally been used in "bitter" tonic drinks and in other preparations taken by mouth to enhance appetite and digestion. It was also historically used as a diuretic, diaphoretic, emmenagogue, contraceptive, and antipyretic, as a cure for the plague and malaria, and as a general tonic. Nowadays, it was mainly used as a bitter tonic to treat dyspepsia, flatulence and indigestion; some herbalists also recommend it as an astringent (to treat diarrhea or hemorrhage), vulnerary, galactagogue, and remedy for dysmenorrheal [38, 42-46].

Homeopaths use the plant for nausea, left-sided stomach pain, gallstones, homesickness, intermittent fever, and enlarged liver, especially when eye symptoms are present and there is a sensation of contraction in many parts [37].

Part used:

The dried leaves and upper stems, including the inflorescence, and the flowering parts of the plant were used medicinally [39].

Chemical constituents:

The chemical constituents of *Cnicus benedictus* were included sesquiterpene lactone glycosides such as cnicin (0.2-0.7%), polyacetylen, and absinthin, additionally, salonitenolide and artemisiifolin. Triterpenoids such as a-amyrone, a-amyrin acetate, a-amyrine, and multiflorenol acetate. Lignans such as trachelogenin, nortracheloside and arctigenin. Flavonoids, including apigenin-7-O-glucoside, luteolin and astragaline. Tannins contents reached (8%). Essential and volatile oils (0.3%) including n-nonane, n-undecane, n-tridecane, dodeca-1,11-dien-3,5,7,9-tetraene (polyene), p-cymene, fenchon, citral, cinnamaldehyde. Lignans such as trachelogenin as well as cnicin contribute to the bitter characteristics of blessed thistle. The plant also contained phenolic compounds, saponins, alkaloids, starch, glycosides, triterpenes and coumarins [39, 47-51].

Blessed thistle (*Cnicus benedictus* L.) was cultivated as an alternative oil crop in central Europe. Fruit yields of approximately 2.0–2.5 t/ha and oil yields of 500–700 kg/ha result from sowing in early autumn. *Cnicus benedictus* oil is a good source of linoleic acid (>70% of total fatty acids) and α -tocopherol (>90% α -tocopherol of total tocopherols). The oil appears attractive for cosmetics and for technical applications (e.g. as a coating agent). *Cnicus benedictus* oil may also be suitable for human nutrition. In addition, *Cnicus benedictus* oil cake can be exploited as a source for the lignan glycoside arctiin [52].



Light petrol and chloroform extracts of the herba of *Cnicus benedictus* yielded α -amyrenone, α -amyrine acetate, α -amyrine, oleanolic acid, multiflorenol acetate, multiflorenol, sitosterol-3 β -D-glucoside and salinonolide [50,52].

The plant contained higher mineral contents: K (6300 mg/kg), Ca (923.61 mg/kg), Na (584.95 mg/kg), P (587.52 mg/kg), Mg (153.02 mg/kg), Fe (35.60 mg/kg), Zn (11.34 mg/kg), B (2.77 mg/kg), Cu (2.88 mg/kg), Mn (1.69 mg/kg), Cr (0.16 mg/kg), Co (0.09 mg/kg), Mo (0.08 mg/kg) and Se (0.04 mg/kg). According to these results, blessed thistle is a good natural source of mineral contents and can be included in the daily diet for alternative vegetable and functional foods [53].

Pharmacological Effects

Antimicrobial Effects

The antimicrobial effect of the aqueous solutions obtained from the soft extract of *Cnicus benedictus* flowers was investigated. The test was performed on Mueller - Hinton and blood-agar culture medium, on 8 standardized bacterial strains (*Salmonella typhimurium* ATCC 14028, *Salmonella enteritidis* ATCC 13076, *Staphylococcus aureus* ssp. ATCC 25923, *Staphylococcus aureus* ssp. ATCC 29213, *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 35218, *Streptococcus pyogenes* Gp ATCC 19615, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212 and *Shigella sonnei* ATCC 25931) and microbiological strains (*Staphylococcus aureus*, *Streptococcus pyogenes* and urine *Escherichia coli*) obtained from infected secretions, using the diffusimetric method. The antimicrobial action of the plant extracts was confirmed against all bacterial strains, it exerted inhibition zones, of approximately the same values, at solutions with different concentrations. However, the values obtained revealed significant differences of the intensity of the antimicrobial activity of the mature and immature flowers extract [54].

The antimicrobial activities of the main sesquiterpene lactones, onopordopicrin and cnicin, were assayed. Results showed that cnicin possessed antibacterial activities against a panel of Gram-positive and Gram-negative bacteria. Remarkable antibacterial activity against methicillin-resistant *Staphylococcus aureus* was also recorded [55].

The sesquiterpene lactones cnicin and cynaropicrin were potent, irreversible inhibitors of the bacterial enzyme MurA. They covalently bind to the thiol group of Cys115. Judging from the structure-activity relationships, the ester side chain of cynaropicrin and cnicin is of particular importance for the inhibition of MurA [56].

Some ester derivatives prepared from cnicin, a germacranolide sesquiterpenoid were tested for their antibacterial activity. The 8,15-diester showed a good activity, comparable with that of cnicin [57].

Cytotoxic Effects

Aqueous extracts prepared from *Cnicus benedictus* showed no cytotoxic effect *in vitro* against three human cancer cell lines: DU-145 prostate cancer cells, MDA-MB-231 and MCF-7 breast cancer cells and a non-malignant breast cell line, MCF-12A [58]. Cnicin and 4'-acetylcnicin were evaluated for their tumour cell growth inhibitory activities on HeLa, MCF-7 and A431 cells. It appeared that they were moderately active compounds [59].

Investigation of cytotoxic activities of the pure sesquiterpene lactones, cnicin showed that it possessed high cytotoxicity against human-derived macrophages [55].

Cytotoxic activity of cnicin was observed toward pig kidney epithelial (LLC-PK₁₁), human malignant melanoma (SK-MEL) and human ductal carcinoma (BT-549) cells with IC₅₀ values of 23.3, 14.0 and 18.3 μ M, respectively [60].

The cytotoxic effect of cnicin was evaluated in multiple myeloma. Cnicin treatment revealed potent antiproliferative effects and induced cell death in cell lines and primary myeloma cells even in the presence of survival cytokines and the tumor microenvironment. Other cell lines of hematopoietic origin also succumb to cell death whereas stromal cells and endothelial cells were unaffected. Combining cnicin with current standard or experimental therapeutics leads to enhanced cell death. The activation of caspases, accumulation of reactive oxygen species and downregulation of nuclear factor kappa-light-chain-enhancer of activated B cell contribute to the cytotoxic effects of cnicin. Microarray analysis reveals downregulation of Pim-2, a serine/threonine kinase. Pim-2 constitutes a new survival kinase for myeloma cells *in vitro* and is highly expressed in malignant but not in normal plasma cells *in vivo*. The authors concluded that cnicin induces myeloma cell death via several pathways and revealed Pim-2 as a novel target [61].

Cnicin also inhibited the root growth of lettuce. Growth, particularly of the roots, was retarded in a concentration of 1 and 4 mg of cnicin [62].

Antiinflammatory Effect

In investigation of anti-inflammatory effect of cnicin, cnicin was subjected to a panel of cellular assays to test for inhibition of nuclear factor κ B (NF- κ B), inducible nitric oxide synthase (iNOS) and reactive oxygen species. Cnicin showed inhibition of NF- κ B and inhibition of iNOS activity with IC₅₀ Values of 1.8 and 6.5 μ M, respectively [60].



Wound healing:

10g of the plant root powder was added to 50g Vaseline to prepare a cream used for treatment of wound induced in rats. The dorsal skin of rats was shaved, a wound was made in the dorsal area of the rats (1cm²). Wound healing effect of *Cnicus benedictus* root ointment was checked daily, the results indicate that treatment of rats with the test product isolated from root's powder shows a total wound healing after 14 days against more than fourteen days by the ointment control (Baneocin®). However, the comparison of the activity of the plant powder with the reference product on rats showed that the cream of *Cnicus benedictus* has a potent activity with a percentage reduction of wound (98.81 %) at day 14, against those treated by (Baneocin®) ointment (95.69%) [48].

Enhances digestion and increase bile secretion:

LIV-A is a combination formulated by the late Paavo Airola. This combination contained (for each capsule) (*Petroselinum crispum*) leaves, 19.8 mg of blessed thistle (*Cnicus benedictus*) herb, 16.8 mg of angelica (*Angelica archangelica*) root, 15.8 mg of chamomile (*Matricaria recutita*) flower, 12.9 mg of gentian (*Gentiana lutea*) root, 8.9 mg of goldenrod (*Solidaga virgaurea*). It was used to restore normal liver function. The herbs in LIV-A enhance the digestion and detoxifying functions of the body by working especially to increase the secretion and release of bile [63].

Toxicity and side effects:

Health risks or side effects following the proper administration of designated therapeutic dosages are not recorded. Allergic reactions have been seen only rarely. Persons with allergies to other members of the *Asteraceae* family (such as feverfew, chamomile, or Echinacea species) should exercise caution with Blessed Thistle as allergic cross-reactivity to *Asteraceae* plants was common. However, the only apparent side effects were allergic reactions in sensitive individuals and gastric irritation with very high dosages. Gastric irritation and vomiting have been reported from high doses (over 5 grams per cup of tea). It was not to be used during pregnancy as a result of its emmenagogue and abortifacient effects. In mice, the LD₅₀ of cnicin was 1.6 –3.2 mmol/kg body weight [39, 64-67].

Dose:

Infusions are prepared by pouring boiling water over 1.5 to 2 gm of drug, allowing to set, then straining after 10 to 20 minutes. Daily Dosage: Four to 6 g of drug. The dosage for the aromatic bitter is 1 cup 1/2 hour before meals. One cup of tea is taken 3 times a day. Tincture: take 1-2ml of the tincture three times a day. Liquid extract (1:1 in 25% alcohol): 1.5-3.0 ml, three times daily [68-69].

Conclusion

The current review discussed the chemical constituents, pharmacological and toxicological effects of *Cnicus benedictus* as a promising herbal medicine as a result of effectiveness and safety.

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