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Review Article

A Review of the Traditional Uses, Medicinal Properties and Phytochemistry of *Centaurea benedicta* L.

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ABSTRACT

Centaurea benedicta L. is an annual herbaceous plant which belongs to the Asteraceae family. It is native to the Mediterranean region and western Asia and is commonly known as blessed thistle, holy thistle, St Benedict's thistle or spotted thistle. Traditionally, it has been used to treat bubonic plague and possesses diuretic, galactagogue, liver-strengthening and wound healing properties. Recent research studies have investigated its anticancer, anti-inflammatory, antioxidant and other therapeutic properties. Several studies have also reported its antimicrobial activity against a range of bacterial pathogens. However, most of these studies were preliminary and only tested relatively high concentrations of the extracts. Additionally, most studies screened a limited number of pathogens. Cnicin is the main chemical compound present in *C. benedicta* and it has been widely investigated. However, few other compounds from this plant have been identified and/or investigated, and further phytochemical studies are warranted. Interestingly, pure cnicin has good anticancer activity, whilst the crude extracts lack cytotoxic properties. Phytochemical analyses of *C. benedicta* extracts reveal the presence of multiple flavonoids, tannins, terpenoids and lactones, although few specific phytochemicals within these phytochemical classes have been identified. A limited number of research studies have determined the toxicity profile of *C. benedicta* in order to evaluate its safety for human use. Substantially more detailed studies are required to rigorously investigate the therapeutic properties and phytochemistry of *C. benedicta,* which may ultimately lead to the development of new plant-based therapeutic medicines.

Key words: Asteraceae, Blessed thistle, St Benedict's thistle, Flavonoids, Terpenoids, Tannins.

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INTRODUCTION

Humans have used traditional plant-based medicines to alleviate and treat diseases since ancient times. Fossil records indicate human use of plants as herbal medicines as long ago as 60,000 years.[1] Plant-based medicine systems including Ayurveda, traditional Chinese Medicine (TCM), Kampo, traditional Korean medicine and Unani, have long been practiced by many cultures. Furthermore, numerous allopathic medicines such as atropine, colchicine, digoxin, quinine, and morphine are derived from *Atropa belladonna* L., *Colchicum autumanle* L., *Digitalis purpurea* L., *Cinchona legeriana* L. and *Papaver somniferum* L. respectively. These drugs are now commonly used globally for the management and treatment of multiple diseases.[2] Compounds derived from traditional plant-based remedies possess significant biological activities and drug-like properties due to their unique chemical diversity and thus are a promising resource for the discovery and development of effective therapies.

In this review, we examine the traditional use, phytochemical composition and medicinal properties of *Centaurea benedicta* L (*C. benedicta*). This plant is commonly known as blessed thistle, St Benedict's thistle, holy thistle, or spotted thistle. It has been used traditionally for the management and treatment of multiple pathogenic and non-pathogenic conditions. It is an annual herbaceous plant of the family Asteraceae and is native to the Mediterranean region and western Asia, although it has now been widely naturalised globally.[3] *Centaurea benedicta* has a particularly long history of medicinal usage, with the plant tops, leaves and stems used for a wide variety of therapeutic uses (Table 1). It is perhaps best known for its use in Europe in the Middle Ages for the treatment and prevention of the bubonic plague, which is caused by the bacterium *Yersinia pestis*.[4,5] Presently, *C. benedicta* is commonly prepared and consumed as an infusion to stimulate appetite and to treat dyspepsia. The common name (blessed thistle) is believed to derive from its beneficial effects in the treatment of many different diseases, since it possesses diuretic, galactagogue, liver-strengthening and wound-healing properties, among others.[5-8]

Ethnobotanical knowledge of *C. benedicta* use has been handed down orally in many cultures and, as such, there is relatively little documentation of its traditional uses. Additionally, for most therapeutic uses there is little clinical evidence to support its efficacy.[4,9] In contrast, the phytochemical composition of this species is relatively well reported. Furthermore, the therapeutic properties of many of the individual components have been examined and are relatively well known. This review describes the traditional uses of *C. benedicta* and summarises previous studies involving the screening of *C. benedicta* preparations

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Table 1: Ethnopharmacological uses of *C. benedicta*.

Traditional Uses	Preparation and Uses	References
Abortifacient	Reported to be used as an abortifacient. Preparation and usage are not specified.	18
Aids digestion	The bitterness of the cnicin component stimulates saliva flow and gastric acid secretion	14, 16, 17
Appetite booster	Powdered whole plant is consumed.	14, 16, 18
Boils, wound and skin ulcers	Decoctions are directly applied to treat bacterial skin diseases and skin sores.	8, 15, 29
Bubonic plague sores,	Decoctions were applied directly to treat bubonic plague sores.	14, 15, 115
Cardiovascular disease and hypertension	Preparation and treatment not specified.	116
Contraceptive	Leaves stems and flowers were used to prepare decoctions or infusions which are consumed orally.	14
Decrease flatulence	Decoctions or infusions prepared from the whole plant are consumed orally.	14
Diabetes	The plant is powdered, and an infusion is created using boiling water. This infusion is taken orally before meals.	116, 117, 118, 119
Diarrhoea	Decoctions and infusions have astringent properties and help relieve diarrhoea.	14
Diuretic	Decoctions are consumed orally. The plant part used was not specified.	14, 18
Expectorant	Useful as an expectorant. Preparation and usage is not specified.	14, 18
Eye infections	Prepared as a decoction and used as an eye wash to treat bacterial, fungal and viral eye infections.	11
Fungal skin disease	Decoctions are directly applied to treat ringworm and other fungal skin diseases.	6, 116, 119
Galactagogue	Powdered whole plant is consumed orally.	4, 14, 18
Gall stones	Decoctions or infusions prepared from the whole plant are consumed orally.	14
Gastrointestinal issues	Aids digestion, settles stomach upsets. A decoction of the whole plant is consumed as needed.	17, 18, 120
Hypertension	Decoctions or infusions prepared from the whole plant are consumed orally.	117
Inflammation	An infusion of the whole plant is taken to treat inflammation and arthritis.	34, 38, 121
Liver diseases	A decoction is consumed to prevent and treat liver disease. Diminishes jaundice.	6, 14, 18, 122
Memory enhancer	Decoctions or infusions prepared from the whole plant are consumed orally.	18, 123
Menstrual pain	Decoctions or infusions prepared from the whole plant are consumed orally.	14, 18
Relieve symptoms of malaria	Decoctions are consumed orally. Plant part was not specified. Relieves fever.	14, 15, 116, 122
Respiratory disease	Used against multiple viruses including influenza. Used as an infusion or tincture. Useful in clearing virus due to its expectorant properties. Relieves fever.	14, 18, 124
Urinary tract infections	Plant part, preparation and treatment not specified.	116

(and isolated compounds) against various diseases, while identifying gaps in the literature and proposing future studies. The phytochemistry and bioactivities of identified *C. benedicta* compounds have also been reviewed and where known, the mechanisms of action are reported.

METHODS

The medicinal properties, pharmacology and phytochemistry of *C. benedicta* are discussed. Peer-reviewed journal articles and books on herbal and traditional medicine were consulted.[10,11] Google-Scholar, PubMed, Scopus and Science-Direct databases were used to source original scientific research papers. The following terms were used as filters and were searched both alone and as combinations: "blessed thistle", "St Benedict's thistle", "holy thistle", "spotted thistle", "traditional medicinal plant", "herbal medicine", "antibacterial", "inflammation", "anti-inflammatory", "antiviral", "bubonic plague", "*Yersinia pestis*". "appetite stimulant", "dyspepsia", "fever" and "diarrhea".

Eligibility criteria

To meet the eligibility criteria for inclusion in this review, all published studies were required to be English language publications published prior to September 2020. Publications with the following criteria were excluded from this study:

• Studies where the species identity was in doubt. Where possible, the species names were confirmed using the Plant List website (http://www.theplantlist.org/). Where the taxonomic identity of the species could not be definitively verified, the study was omitted from this review.

• Studies describing the usage of milk thistle (*Silybum marianus* (L.) Gaertn.), Scotch thistle (*Onopordum acanthium* L.) and other thistles were excluded from the review.

PLANT PROFILE AND TAXONOMY

Classification

Centaurea benedicta L. is classified as kingdom plantae; clade tracheophytes; order Asterales; Family Asteraceae; genus *Centaurea*; species *Centaurea benedicta* L.

Synonyms

Centaurea benedicta L. has also been known as *Benedicta officinalis* Bernh., *Calcitrapa benedicta* (L.) Sweet, *Calcitrapa lanuginose* Lam., *Carbeni benedicta* (L.) Arcang., *Carbeni benedicta* (L.) Adans, *Cardosanctus officinalis* Bubani, *Carduus benedictus* Auct. ex Steud., *Carduus benedictus* (L.) Garsault, *Centaurea centriflora* Friv. ex Gugler, *Centaurea pseufobenedicta* (Asch.) E.H.L.Krause, *Cirsium horridum* (Adams) Petr., *Cnicus benedictus* var. *kotschyo* Boiss., *Cnicus bulgaricus* Panov, *Cnicus kotschyi* Sch.Bip., *Cnicus microcephalus* Boiss., *Cnicus pseudo-benedictus* Asch. and *Epitrachys microcephala* K.Koch.

Nomenclature and common names

The Latin name *C. benedicta* is derived from the use by St. Benedict for its healing properties.[12] *Centaurea benedicta* was well known in Europe in earlier times and is mentioned in William Shakespeare's play "Much Ado About Nothing" (written in 1598-1599 CE).

Common names in various traditional healing systems include:

Arabic: farasion, kanterion mubark, shok mubark, shok marimi, shok bari

English: blessed thistle, St. Benedict's thistle, holy thistle, spotted thistle

French: chardon bénit

German: benediktenkraut, bitterdistel

Portuguese: cardo-bento, cardo-santo

Russian: benedikt aptečnyj, knikus blagoslovennyj

Spanish: Cardo santo

Swedish: kardbenedikt

Chinese: cang ye hua, 祝福薊

Distribution

Centaurea benedicta is native to the Mediterranean regions of Europe and is particularly prevalent in Portugal and Spain.[13,14] It is also native to the northern African regions of Libya, Egypt, and the Middle Eastern regions of Iran, Iraq, Israel, Jordan, Lebanon and Syria, as well as Pakistan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan and China. *Centaurea benedicta* has also been widely distributed and naturalised globally and is now common in most regions of the world.

PHARMACOLOGICAL EFFECTS

Traditional uses

Historically, there has been a myriad of uses for *C. benedicta*. Some of the more common uses are summarised in Table 1. The stems, leaves and flowers have been used to prepare "bitter" tonic drinks for oral consumption to treat bubonic plague sores and to relieve the symptoms of malaria,[15] and to increase appetite and aid digestion.[14,16,17] It is also used to relieve gastrointestinal distress and as an expectorant.[14,18] *Centaurea benedicta* is also used to treat liver diseases including jaundice. It is also useful for improving memory, as a galactagogue to increase milk production in nursing mothers, as a diuretic for increasing urine output, and for relieving menstrual pain.[18] When applied to the skin, it is an effective treatment for boils, wounds, and skin ulcers.[8,15]

The traditional uses of *C. benedicta* originate from European healing systems, where the uses have been extensively verified and modified. However, despite the European origin of this plant, its widespread uses have attracted the attention of other healing systems including Ayurveda, Unani, Siddha and traditional Chinese systems of medicine. Indeed, it has now been included in these systems although it is generally considered by practitioners of these systems to be a "Western herbal galactagogue".[19,20]

Despite its wide range of traditional applications, surprisingly few studies have rigorously examined the medicinal properties of *C. benedicta* and many therapeutic effects are yet to be verified. Studies have reported the antimicrobial,[21-23] antiinflammatory[24,25] and anticancer[26-28] properties of *C. benedicta* preparations. However, many of these studies are preliminary and the plant preparations were screened against limited panels of pathogens/cell lines, or with limited and/or high doses of extracts. The MIC (minimum inhibitory concentration) and IC_{50} values have often not been measured, making comparisons between studies impossible. Substantially more work is required to verify the medicinal properties of *C. benedicta* preparations, to quantify their efficacy and to determine the mechanisms of action. In contrast, the phytochemistry of *C. benedicta* has received substantially more consideration and many of the individual components have been screened for therapeutic properties. We will firstly review the traditional uses of crude *C. benedicta* preparations. The structure of the individual phytochemical constituents and their bioactivities will be summarised in a later section of this review.

Antimicrobial activity

Aqueous *C. benedicta* flower extracts have been reported to inhibit the growth of numerous bacterial pathogens including *Salmonella typhimurium, Salmonella enteritidis, Shigella sonnei, Staphylococcus aureus, Streptococcus pyogenes, Proteus vulgaris, Enterococcus faecalis, Pseudomonas aeruginosa* and *Escherichia coli*.[29] Extracts were prepared using 40% ethanol and were diluted to 10% and 20% of the original concentration in aqueous solution for both the immature and mature *C. benedicta* flowers. Unfortunately, the concentration of the stock extracts was not specified in that study, so it is not possible to determine the concentrations tested in the bioassay. The diluted extracts exhibited good antimicrobial activity against both Gram-positive coccus species and Gram-negative bacillus microbes. Interestingly, both concentrations of diluted extract produced from mature flowers showed substantially greater antimicrobial activity than the extracts prepared using the immature flowers, highlighting the need to document such details in ethnopharmacological studies. Furthermore, the extracts produced from the mature flowers showed particularly promising antimicrobial activity against reference strains of *Staphylococcus aureus*, *Streptococcus pyogenes* and *Escherichia coli*. The extracts produced from both the mature and immature flowers also displayed significant antimicrobial activity against a clinical *Bacillus proteus* strain in agar disc diffusion assays, with zones of inhibition ranging from 22-32 mm in diameter. In future studies, MIC values need to be determined using more quantitative assay methods. Chromatographical, spectrophotometric and gravimetrical methods were used to characterize these extracts. Both contained an abundance of polyphenolic compounds, flavonoids, and tannins. Each of these classes of compounds have been shown to possess antibacterial activities and are likely to contribute to the growth inhibitory efficacies of the extracts.

Ethanolic extracts prepared from the roots of *C. benedicta* have been tested against *Escherichia coli, Staphylococcus aureus* and *Micrococcus luteus*.[30] A zone of inhibition of 12 mm against *E. coli* was observed, despite the organism being resistant to ceftriaxone and gentamicin. However, the extracts were screened at very high concentrations (75 mg/mL) and thus the reported bioactivity does not provide definitive proof of antibacterial activity of the extracts, nor does it allow for comparison with other studies. Furthermore, the lack of growth inhibition by the "positive antibiotic controls" also places the results in doubt. The concentrated extracts inhibited *S. aureus* growth with a 20 mm zone of inhibition, compared with 8 mm and 5 mm zones of inhibition reported for ceftriaxone and gentamicin, respectively. Qualitative phytochemical analysis of the extracts indicated the presence of flavonoids, alkaloids, carbohydrates, coumarins, lignin, terpenoids and phenolic compounds, but the authors did not conduct further analysis to identify the specific molecular compounds present within those phytochemical classes.

One of the most studied phytochemical constituents of *Centaurea* species is the sesquiterpene lactone compound, cnicin. One study screened cnicin against a panel of pathogenic Gram-positive and Gram-negative bacterial strains and reported significant antimicrobial activity, with MIC values ranging from 42-124 µg/mL against *B. subtilis, S. epidermis, E. coli, K. pneumoniae, P. aeruginosa* and *S. aureus*.[31] Interestingly, cnicin also inhibits the growth of methicillin-resistant *Staphylococcus aureus* (MRSA), further highlighting its medicinal potential. Cnicin has been found to be a potent inhibitor of MurA,[32] a bacterial enzyme that catalyses the first committed step in peptidoglycan synthesis, indicating this is a likely mechanism of action for the compound.

Anticancer activity

The anticancer properties of *C. benedicta* extracts remain largely unreported. In contrast, the anticancer properties of individual *C benedicta* compounds have been relatively well documented, particularly for cnicin. Cnicin induces cell death in primary multiple myeloma cell lines, even in the presence of the tumour microenvironment and in the presence of survival cytokines.[33] In addition, stromal and endothelial cell lines were unaffected by exposure to cnicin, although increases

Table 2: Selected studies on the therapeutic properties of *C. benedicta*.

Medicinal properties	Therapeutic effects	Efficacy	References
Antimicrobial activity	40% ethanol extracts showed promising activity against *S. aureus*, *S. pyogenes, B. proteus* and *E. coli*	High concentrations of extracts (10-20%, or 100-200 mg/mL) were screened in the agar diffusion assays. ZOIs ranged from 18-32 mm	29
	Ethanolic extracts showed good activity against *E. coli, S. aureus*	Resuspension solvent not stated. High concentrations of extracts (25-75 mg/mL) used in agar disc diffusion assays, yielding 10-15 mm zones of inhibition	30
	Cnicin (a major component of *Centaurea* plant species) inhibits *B. subtilis, S. epidermidis, E. coli, K. pneumoniae, P. aeruginosa* and *S. aureus* growth	Cnicin was purified from *C. benedicta* chloroform extracts and tested in disc diffusion assays. Cnicin (50 µg) produced zones of inhibition of 10-20 mm	31, 32
Anticancer activity	Cnicin is a potent irreversible inhibitor of bacterial enzyme MurA	IC_{50} of 10-17 µM for cnicin towards *E. coli* or *P. aeruginosa* MurA enzyme.	32
	Cnicin showed antitumor activity against multiple myeloma cell lines	Cnicin IC_{50} values towards cell lines were 3.4–14.7 µM, with accompanying reductions in tumor sizes	33
	General cytotoxic effects of cnicin against breast ductal carcinoma (BT-549) and kidney epithelial (LLC-PK11) cells	IC_{50} values of 18.5 µM against BT-549 cells and 23.3 µM against LLC-PK11 cells	34
	Cnicin is moderately active against HeLa, MCF-7 and A431 cells	IC_{50} values for various cell lines between 16-35 µM	35
	C. benedicta showed no cytotoxic effects against DU-145 prostate cancer cells, MDA-MB-231 or MCF-7 breast cancer cells	Aqueous extracts (50 µg/ml) showed minimal reductions in cell proliferation	14, 36
Anti-inflammatory activity	Cnicin showed significant inhibition of NF-κB in PMA-induced SW1353 cells and iNOS activity in lipopolysaccharide-induced RAW264.7 cells	Cnicin inhibits NF-κB (IC_{50} = 1.8 µM) and iNOS (IC_{50} = 6.5 µM)	34
	Cnicin inhibited inflammation in rat paw induced by *Macrovipera lebetina* obstusa venom	2.5, 5 and 10 mg/kg doses of cnicin reduced inflammation by up to 28% in experimental animals	37
Antioxidant	*C. benedicta* contains high flavonoid and phenolic content (TPC), and ferric reducing antioxidant power (FRAP)	Methanolic extracts prepared from the consumable parts of the plant (leaf and root) were resuspended in distilled water. They inhibit xanthine oxidase (IC_{50} = 18-20 µM) and possess radical scavenging activity	38
	A nanofiltrate extract of *C. benedicta* contained significant amounts of polyphenols	Aerial segments of the plant extracted with 50% ethanol and were concentrated by nanofiltration and tested for antioxidant activity. IC_{50} values of 8.1 µg/mL were determined for scavenging activity and 82 µg/mL for reducing power	39
Antidiabetic activity	Treatment with a saline suspension of *C. benedicta* leaves extracted with methanol significantly reduced plasma glucose levels in fasted normal and streptozocin-induced diabetic rats	Doses of 100-400 mg/kg reduced fasting plasma glucose levels by 84% and streptozocin-induced diabetic plasma glucose levels by 45-66%, compared to 250 mg/kg chlorpropromide (72%)	40
Antinociceptive activity	A saline suspension of *C. benedicta* leaves extracted with methanol significantly reduced the number of writhes in albino rats compared with paracetamol and indomethacin	Doses of 35-400 mg/kg reduced the number of writhes by up to 75%, compared to 20 mg/kg indomethacin and 500 mg/kg paracetamol	40
Wound healing effects	A combination of *C. benedicta* root powder and Vaseline induced potent wound healing activity compared with Baneocin ointment	Wound healing activity of almost 99% occurs with root powder, compared with the reference ointment (~96%)	14, 41

in cell death occurred when cnicin was used in combination with standard therapeutic agents. The cytotoxic effects of cnicin have been reported to result from the increased production of reactive oxygen species, activation of caspases, and the downregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). A microarray analysis study reported that cnicin treatment induced the downregulation of Pim-2 (a serine/threonine kinase), which functions *in vitro* as a survival kinase for myeloma cells.[14] The downregulation results in the increased mortality of the myeloma cells. The antioxidant, cytotoxic and *in vitro* anti-inflammatory activities of cnicin have been studied[34] and reveal general cytotoxic effects against mammalian kidney fibroblasts (Vero) and kidney epithelial (LLC-PK11) cells. Additionally, *in vitro* anticancer properties of cnicin were demonstrated against four human solid tumor cell lines: breast ductal carcinoma (BT-549), ovary carcinoma (SK-OV-3), oral epidermal carcinoma (KB) and malignant melanoma (SK-MEL) cells. Mild cytotoxicity was observed for cnicin toward LLC-PK11 cells (IC_{50} = 23 µM), but no significant effects were noted against Vero cells. Antitumor effects were observed for cnicin towards SK-MEL and BT-549 cancer cell lines, with IC_{50} values of 14 and 18 µM, respectively.

When cnicin was tested against HeLa, MCF-7 and A431 carcinoma cells, moderate cytotoxic activities were evident against all cell lines.[35] In contrast, aqueous *C. benedicta* extracts failed to induce cytotoxicity *in vitro* towards DU-145 prostate cancer cells, MDA-MB-231 and MCF-7 breast cancer cells, or against a non-malignant breast cancer cell line.[14,36] This is an interesting finding, and it highlights differences between the effects of the purified components and the crude plant extracts on cancer cell lines.

Anti-inflammatory activity and immunomodulation

The anti-inflammatory activity and the effects of *C. benedicta* preparations on immunomodulation are yet to be examined thoroughly. However, cnicin has been found to inhibit NF-κB production in PMA-induced SW1353 cells with an IC_{50} of 1.8 µM, which compares

favourably to the control anti-inflammatory drug parthenolide (IC_{50} 6.4 μM).[34] Cnicin also inhibits the pro-inflammatory mediator iNOS in LPS-induced macrophages but does not affect PMA-induced intracellular generation of ROS in HL-60 cells.[34] In rats challenged with snake venom (which induces necrosis, pain and local oedemas), cnicin doses (2.5-10 mg/kg) reduced inflammation, indicating its effectiveness as an anti-inflammatory agent *in vivo*.[37]

Antioxidant activity

The leaves of *C. benedicta* contain approximately twice the content of phenolics and flavonoids as the roots. However, both parts of the plant possess considerable ferric reducing antioxidant power (FRAP) and 2,2 diphenyl-1-picryhydrazyl (DPPH) free radical scavenging activity, in addition to xanthine oxidase inhibition properties.[38] Microfiltration and nanofiltration processes can be used to prepare extracts with substantially higher polyphenol content, DPPH scavenging activity and ferric reducing power.[39]

Other therapeutic properties

The antidiabetic and antinociceptive effects of a methanolic leaf extract of *C. benedicta* were investigated using an albino rat animal model.[40] The animals were fasted overnight, and diabetes was induced with streptozotocin (STZ). *Centaurea benedicta* extracts (100-400 mg/kg, i.p.) significantly reduced blood glucose levels by 46-79% in the fasted normal rats and by 45-66% in STZ-induced diabetic rats. Furthermore, in oral glucose tolerance tests, administration of *C. benedicta* leaf methanolic extract reduced blood glucose concentration by 42-71%. Antinociceptive activity was also investigated using the acetic acid writhing test. Leaf *C. benedicta* extract (25-400 mg/kg, i.p.) significantly reduced the number of writhes, with the percentage inhibition ranging from 68–74% compared with indomethacin (20mg/kg, i.p.) and paracetamol (500mg/kg, i.p.) controls, which showed 69-75% inhibition. *Centaurea benedictus* root powder also possesses wound healing properties *in vivo*,[14,41] showing a 99% wound reduction over 2 weeks in a rat model. This is similar to levels obtained in rats treated with Baneocin® ointment. Powdered *C. benedicta* was also used in combination with other medicinal plants to restore normal liver function.[14] LIV-A is a product that consists of a combination of different herbs (including *C. benedicta*) and is used enhance digestion by increasing the secretion of bile.

DOSAGE, TOXICITY, AND INTERACTIONS WITH OTHER MEDICINES

Dosage and toxicity

Despite the long history of use of *C. benedicta* in traditional medicine, there is surprisingly little information on the dosage and toxicity of the plant. Generally, 4-6 g per day of cut herb or dried extract is believed to be adequate for most therapeutic purposes. When consumed as an infusion, it is recommended that 0.5-3 g of dried blessed thistle flowering tops be steeped in 150 mL of boiling water and consumed as a tea three times a day.[18] Alternatively, if an aqueous extract (prepared with equal amounts of dried plant material and water) or tincture (prepared with 1 part plant material to 5 parts alcohol) are used therapeutically, 1.5-2 mL or 7.5-10 mL respectively are recommended to be taken orally three times daily.

Limited data is available on the safety and toxicity of *C. benedicta* for human use and there are no definitive guidelines. Most commercially available supplements range from 300 mg to 450 mg per dose, and three doses per day is considered to be safe. Worsening side effects, including gastric irritation and vomiting, have been reported when the daily doses exceed 5 g.[42] In contrast to the whole plant and its preparations, toxicity data on some of the constituents is available. Cnicin, the major sesquiterpenoid component of *C. benedicta*, has an LD_{50} value of 1.6-3.2 mmol/kg body weight in mice.[14] *Centaurea benedicta* is not significantly mutagenic in the Ames test, with no mutagenicity observed in aqueous extracts at amounts up to 200 μL per disc.[43] However, mild mutagenic effects have been noted in alcoholic extracts at quantities of 400 μL per disc.[44]

Adverse effects

Centaurea benedicta is generally considered safe when used in moderation and administered as an infusion. However, it can cause gastrointestinal distress, nausea and vomiting if consumed in excess.[45] *Centaurea benedicta* ingestion should be avoided in people with inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, as it has been shown to increase the severity and duration of the symptoms.[42,46]

Interactions with other medicines

Several interactions have been reported between *C. benedicta* preparations and other therapies. The concurrent use of these therapies should therefore be avoided. Since the bitter phytoconstituents of *C. benedicta* (including cnicin) stimulate gastric acid production, they may reduce the effectiveness of antacids, rendering them ineffective while exacerbating gastric acidity and reflux.[47] Therefore, the use of *C. benedicta* in individuals with heartburn and gastric reflux is discouraged. Similarly, *C. benedicta* has platelet activating factor (PAF) antagonist properties and can therefore prevent platelet aggregation, increasing the risk of bleeding.[24] Its use should be avoided in individuals prescribed commercial anti-coagulants such as warfarin.[48]

C. benedicta constituents may also potentiate the activity of some other medicines. Indeed, the root and leaf extracts synergise the bactericidal activity of some antibiotics towards several bacterial pathogens.[29,30] The use of these therapies concurrently would therefore be beneficial. Similarly, cnicin inhibits proliferation and metastasis of some tumour cells and potentiates the activity of some antitumour drugs.[35] Whilst *C. benedicta* components are known to exert other therapeutic effects, their interaction with allopathic drugs is less well documented and substantially more work is required to understand these interactions. For example, cnicin has anti-inflammatory effects and may interact with NSAIDs.[37,49] However, it is not known whether these interactions result in potentiation or in antagonism. Similarly, some *C. benedicta* lignans inhibit the replication of some human viruses[50,51] and it is likely that they may interact with conventional antiviral agents. However, any such interactions have not yet been reported and this needs to be explored further.

PHYTOCHEMISTRY

The phytochemistry of *C. benedicta* preparations has been relatively well reported. The plant is relatively rich in sesquiterpenoid glycosides, particularly cnicin (0.2-0.7%), polyacetylen and absinthin,[52] as well as lower relative amounts of salonitenolide and artemisiifolin. These compounds are believed to be largely responsible for the bitter flavour of *C. benedicta* extracts.[53] An abundance of triterpenoids, including a-amyrenone, a-amyrin acetate, a-amyrine and multiflorenol acetate have also been reported.[39] Additionally, the levels of tannins in *C. benedicta* extracts have been found to be as high as 8%.[54] The lignans trachelogenin, nortracheloside and artigenin are also present in relative abundance in *C. benedicta* extracts,[55] together with lower levels of flavonoids[56] and essential oils.[57] Additionally, *C. benedicta* has a high mineral content and is particularly high in potassium, manganese, magnesium and calcium.[58]

Sesquiterpene lactones

Sesquiterpene lactones (SLs) are a category of terpenoids that contain a lactone ring. They are particularly prevalent in plants of the family Asteraceae, including *C. benedicta.* Extracts produced from this species contain multiple sesquiterpene lactones including cnicin (0.2- 0.7%) (Figure 2a), polyacetylen (Figure 2b)[41] and absinthin (Figure 2c).[59] A recent study has also identified two new sesquiterpene lactone glycosides, melitensin 15-O-β-D-glucoside (Figure 2d) and 11β,13-dihydrosalonitenolide 15- O-β-D-glucoside (Figure 2e).[52] Interestingly, dried *C. benedicta* plant material, volatile oil produced from the leaves, and isolated cnicin all have potent antibacterial activity against multiple pathogenic species (Newall et al., 1996).[54] The sesquiterpene lactone structure of cnicin allows it to form covalent bonds with bacterial proteins, thereby disrupting the bacterial membrane structure and function.[60] Furthermore, cnicin and its polyacetylene derivatives can inhibit quorum sensing in bacteria, thereby blocking biofilm formation and rendering the bacteria more sensitive to bactericidal treatments.[61,62] They have been shown to affect cancer cells via multiple mechanisms, such as inducing cell cycle arrest, apoptosis, and angiogenesis, as well as enhancing reactive oxygen species-associated cancer cell death, inhibiting telomerase activity and preventing metastasis.[63] Sesquiterpene lactones (particularly cnicin) also contribute to the bitter flavour of *C. benedicta* preparations.[53] These bitter agents induce increased salivary reflexes and gastric juice secretion, thereby stimulating appetite.[16] Therefore, *C. benedicta* sesquiterpene lactones are also good appetite stimulants.

Triterpenoids

The basic terpenoid structure has been identified in almost 30,000 natural compounds and can be divided on the basis of the number of isoprene units into mono-, sesqui-, di-, sester-, tri, tetra-, and poly-terpenes.[64] It has been reported that oleanane, ursane, lupine and dammarane-euphane triterpenoid structures are the most important for biological applications. Indeed, some of these triterpenoids have anti-inflammatory, hepatoprotective, antimicrobial, antimycotic, analgesic, virostatic, immunomodulatory and tonic properties.[64] Ulubelen and colleagues[65] extracted different triterpene and steroidal compounds from the light petroleum and chloroform extracts of *C. benedicta*. The triterpenoid compounds α-amyrenone (Figure 3a), α-amyrine acetate (Figure 3b), α-amyrine (Figure 3c), multiflorenol acetate (Figure 3d), oleanolic acid, multiflorenol and sitosteryl-3 β-D-glucoside were identified by using UV, IR, NMR and mass spectral methods. Another study investigated the effects of four triterpenoids on a 12-O-tetradecanoylphorbol-13-acetate multiple dose model of skin chronic inflammation, and both erythrodiol and ursolic acid displayed substantial anti-inflammatory activity.[66] A different study focused on the uses of the triterpenoids asiatic acid celastrol, oleanolic acid, ursolic acid and erythrodiol to protect the brain against neurodegenerative diseases including Parkinson's disease, Alzheimer disease, Huntington's disease, multiple sclerosis and amyotrophic lateral sclerosis.[67] Furthermore, the hepatoprotective effects of 350 natural triterpenoids with diverse structures have been documented.[68] Triterpenoid mechanisms of action have been suggested based on experimental data that has shown they downregulate cytokines to prevent inflammation,[69] halt bacterial protein synthesis and reduce biofilm formation as antibacterial agents[70,71] and reduce neuronal apoptosis to and improve cognitive impairment.[72]

Lignans

The lignans are a large group of polyphenols found in a wide variety of plant species. Interestingly, diets that are rich in plant lignans have been associated with decreased risks of cardiovascular disease.[73-75] However, there is insufficient evidence to determine if lignans themselves are responsible for this cardioprotective activity, or if other plant components contribute. Furthermore, the intake of lignans reduces the incidence of hormone-related cancer,[47] although some studies have provided conflicting results. One study reported no association between breast cancer and total lignan intake in premenopausal women.[76] However, the same group reported that dietary lignan intake in postmenopausal females resulted in a 17% decrease in the incidence of breast cancer in another study.[77] More research is required to confirm the effects of high dietary intakes of lignans on hormone-related cancers and to determine their mechanism(s) of action. Several lignans have been reported in *C. benedicta* preparations in relative abundance. These include trachelogenin (Figure 4a), arctigenin (Figure 4b) and nortracheloside (Figure 4c) and these compounds may contribute to some of the therapeutic properties of this plant. One possible mechanism of action of trachelogenin in cancer cells is the induction of autophagy in carcinoma cells via light chain 3 (a microtubule-associated protein) activation.[78]

Flavonoids

Flavonoids are polyphenolic compounds that are ubiquitous in plants and have important roles in traditional therapies against a wide variety of diseases. Indeed, multiple studies have reported antibacterial, antiviral, antiinflammatory, anticancer and anti-diarrhoeal effects for flavonoids.[79,80] Interestingly, *C. benedicta* is rich in bioactive flavonoids including apigenin-7-O-glucoside (Figure 5a), luteolin (Figure 5b) and astragalin (Figure 5c). Bioflavonoids can prevent the oxidation of LDL cholesterol through their free radical scavenging activity and can inhibit endothelial cell growth and platelet aggregation.[48,81,82] The antioxidant and free radical scavenging activities of flavonoids are due to their multiple hydroxyl groups and their location within the molecule.[83] Examples of antibacterial mechanisms of action for the flavonoids include the attenuation of bacterial growth and pathogenicity by altering cytoplasmic membrane function and permeability, and inhibition of the bacterial DNA gyrase enzyme.[84-86]

Tannins

From a chemical point of view, it is difficult to define tannins, as the term is used to describe a wide variety of variable oligomers and polymers of gallic acid and/or ellagic acid.[87] Tannins can be divided into four categories based on their structural characteristics: gallotannins, ellagitannins, complex hydrolysable tannins and condensed tannins.[88-90] The structural characteristics of typical tannins within each of the classes are shown in Figure 6. Tannin and tannin-containing traditional medicines have a wide range of therapeutic uses. They are particularly important in Asian traditional medicine as astringents, to treat diarrhoea, as diuretics, and for the treatment of stomach and duodenal tumours.[91] They are also used as anti-inflammatory, antiseptic, antioxidant and hemostatic therapies across multiple different cultures throughout the world.[92] Furthermore, epidemiological studies have reported decreased frequencies of chronic diseases in individuals whose diet comprises a high consumption of tannin rich plants.[93] There are several mechanisms by which tannins can act as antibacterial agents, such as altering osmotic and pH regulation, interfering with metabolic pathways, and through the inhibition of the bacterial catalase enzyme.[94,95]

Essential and volatile oils

Essential and volatile components account for approximately 0.3% of the weight of *C. benedicta* plant material.[21] Extracts from this plant are particularly rich in n-nonane, n-undecane, n- tridecane, citral (Figure 7a), dodeca-l,ll-dien-3,5,7,9-tetrain (polyyne), p-cymene (Figure 7b), fenchon (Figure 7c) and cinnamaldehyde (Figure 7d).[21] Monoterpenes including citral have been reported to exert a wide variety of biological effects including antibacterial, antifungal, anti-inflammatory and antitumour activities. Citral is also cytotoxic towards some cancer

cell lines. Indeed, both citral and 1,8-cineol can induce apoptosis in several human leukemia cell lines.[96] Multiple other monoterpenoids also induce apoptosis and potentiate doxorubicin induced cytotoxicity in MCF-7 adenocarcinoma cell lines.[97] The monoterpenes citral and pinene also induce apoptosis in melanoma cells.[98] Similarly, multiple sesquiterpenoids have cytotoxic activities against cancer cells.[99-103] Whilst we were unable to find reports of some of these terpenoids in *C. benedicta* extracts, this plant has not been thoroughly evaluated and it is possible that they may be reported in future studies.

Similarly, multiple mono- and sesquiterpenoids have been reported to suppress NF-κB signaling (the major regulator of inflammatory diseases and cancer).[104] In particular, citral, limonene[105,106] and α-pinene[107] have been reported to inhibit NF-κB signalling pathways. These terpenoids also block inflammatory diseases and cancer by inhibiting p65 translocation into the nucleus in LPS-induced NF-κB signalling.[107] Interestingly, many terpenoids including citral, p-cymene, fenchon and cinnamaldehyde also have good antibacterial activities.[79] Thus, it is likely that *C. benedicta* terpenoids and volatile components contribute to the therapeutic properties of this species.

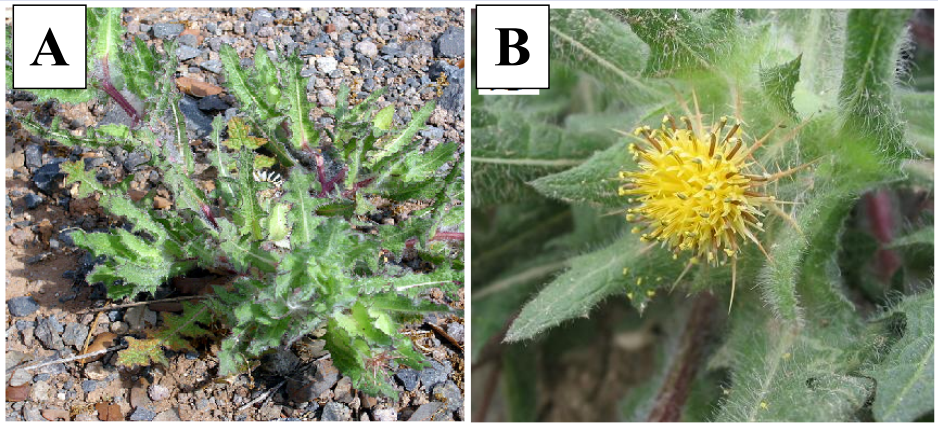

Figure 1: *C. benedicta* (a) whole plant and (b) a closer examination of the leaves and flower. Photographs are sourced from Wiki commons (https://commons.wikimedia.org/wiki/File:Cnicus_benedictus_flor.jpg; cited 27 November 2020) and are reproduced here with all relevant permissions.

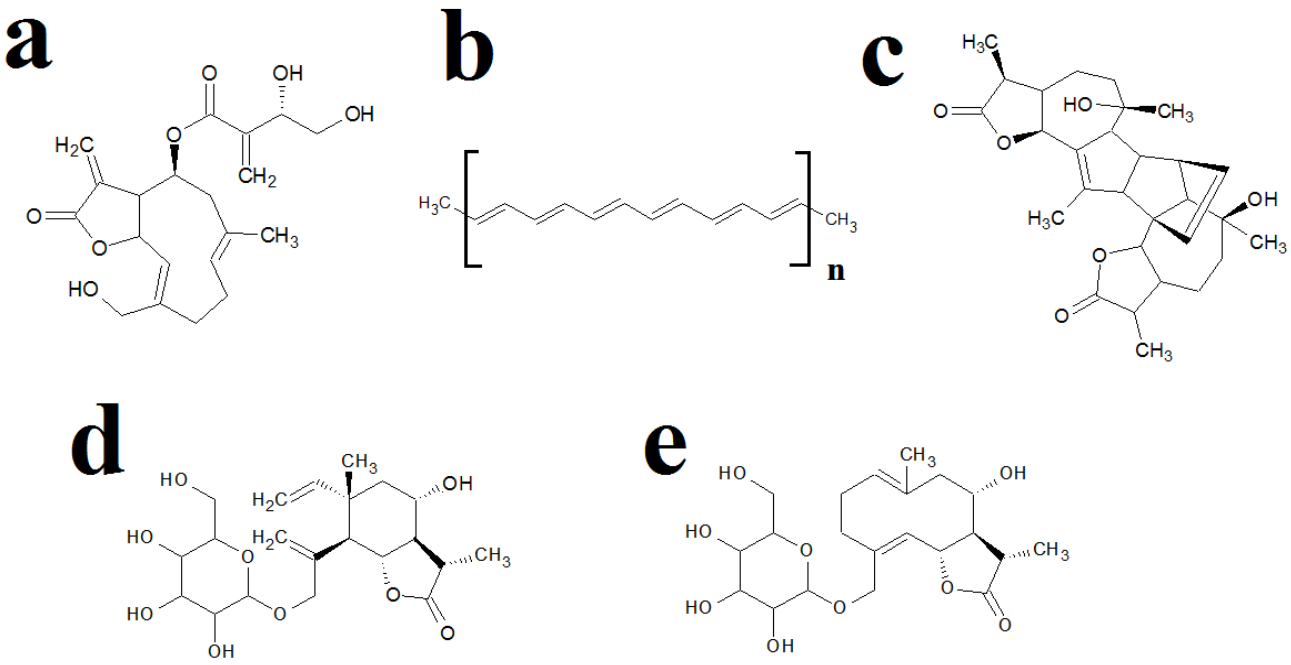

Figure 2: Chemical structures of selected sesquiterpene lactone molecules identified in *C. benedicta*: (a) cnicin, (b) polyacetylen, (c) absinthin, (d) melitensin 15-O-β-D-glucoside, (e) 11β,13-dihydrosalonitenolide 15-O-β-D-glucoside.

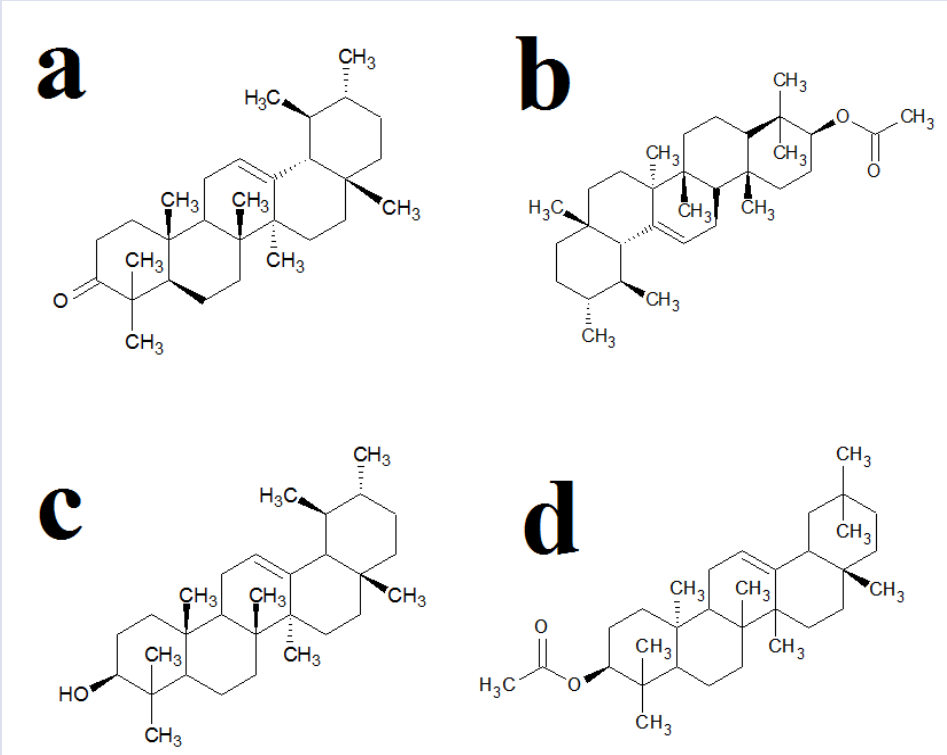

Figure 3: Chemical structures of selected triterpenoids molecules identified in *C. benedicta*: (a) a-amyrenone, (b) a-amyrin acetate, (c) a-amyrine, (d) multiflorenol acetate.

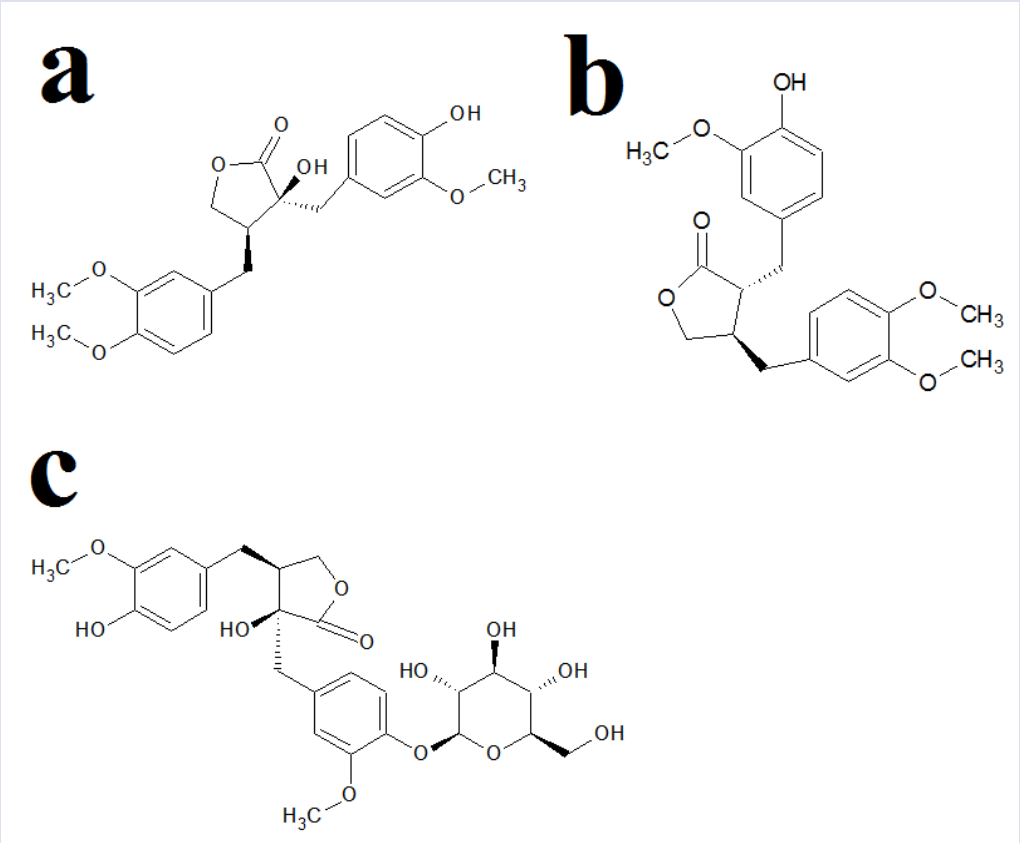

Figure 4: Chemical structures of selected lignan molecules identified in *C. benedicta*: (a) trachelogenin, (b) arctigenin, (c) nortracheloside.

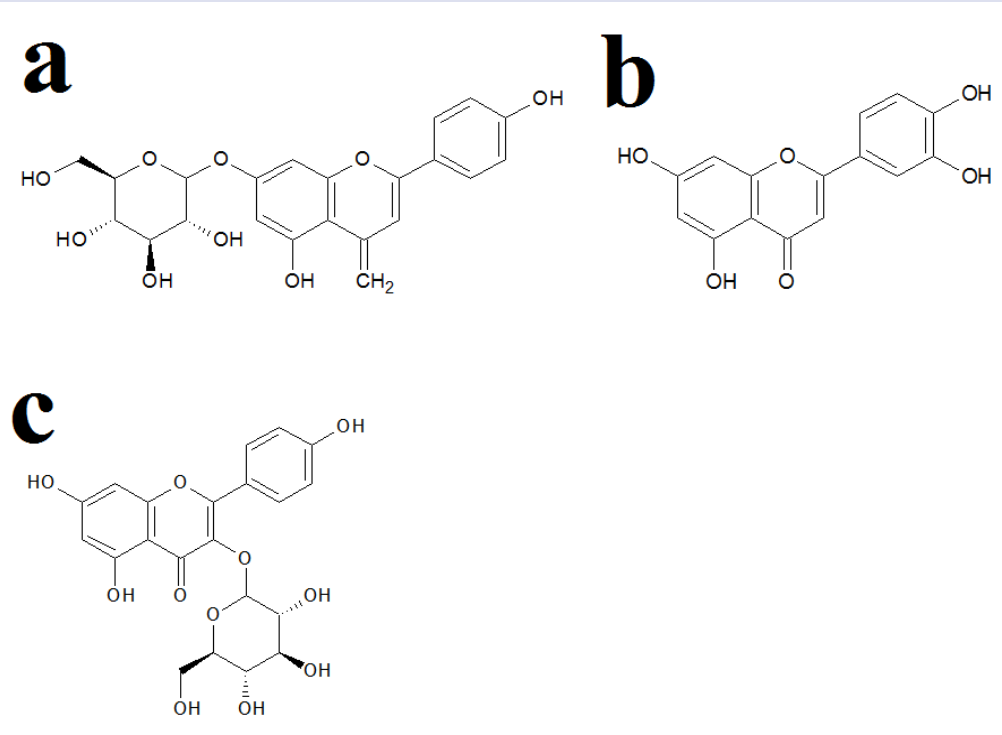

Figure 5: Chemical structures of selected flavonoids molecules identified in *C. benedicta*: (a) apigenin-7-O-glucoside, (b) luteolin, (c) astragalin.

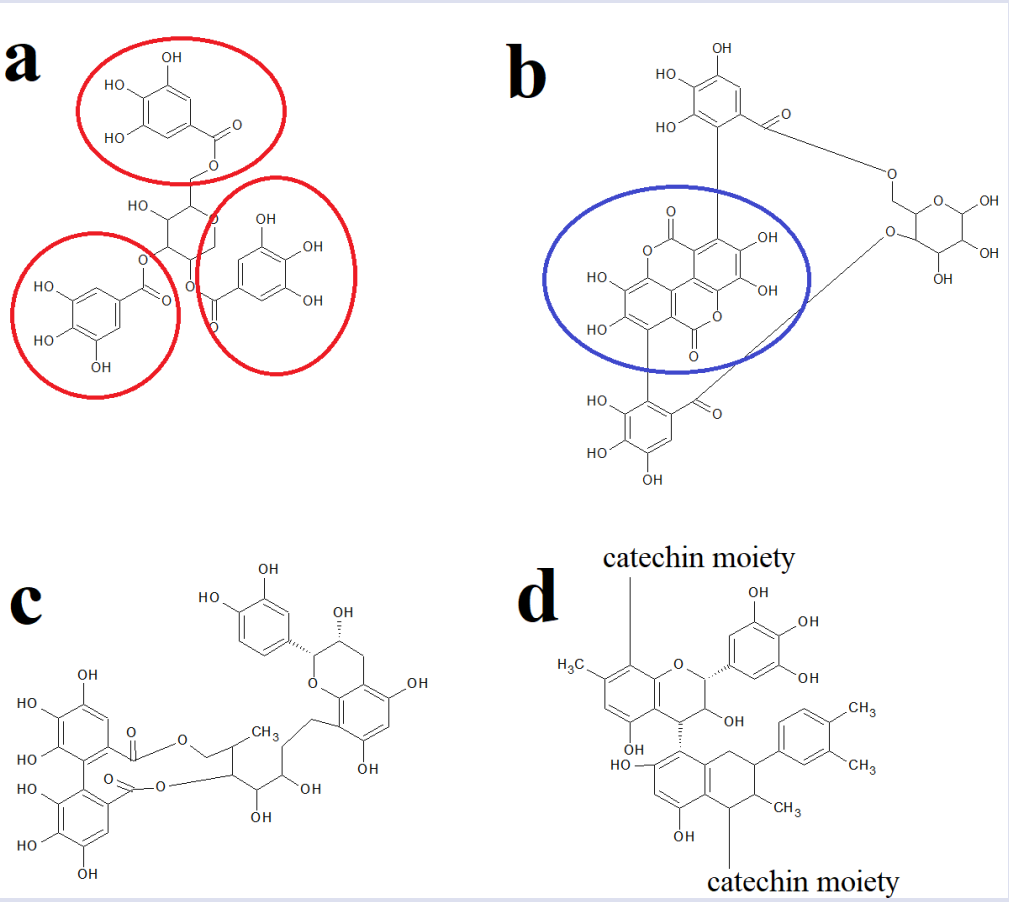

Figure 6: Classification of tannins: (a) gallotannin (gallic acid moieties indicated in red), (b) ellagitannin (ellagic acid moiety indicated in blue), (c) complex hydrolysable tannin, (d) condensed tannin.

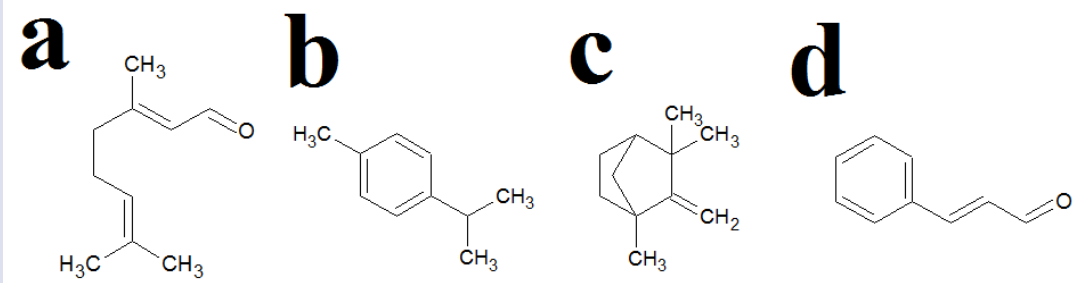

Figure 7: Chemical structures of selected essential and volatile oils molecules identified in *C. benedicta*: (a) citral, (b) p-cymene, (c) fenchon, (d) cinnamaldehyde.

DISCUSSION

The presence of chemically diverse compounds in plants has provided them with chemical defense systems against microbial infections and animal foraging. These phytochemicals can be utilised for novel natural drug discovery to develop semi-synthetic agents with high medicinal efficacy. Traditional medicines are currently attracting increased interest to treat health-related conditions due to their wide range of uses, availability, low cost, and perception of safety. Traditional medicine systems including Ayurveda, TCM, Unani are not only popular in their native countries, but are also gaining widespread acceptance and increased usage in Western medicinal systems. Recently, there has been an increase in awareness in plant-based medicines from regions including Africa, South America and Australia. A large number of drugs including atropine, caffeine, curcumin, colchicine, codeine and digoxin are used therapeutically and are derived from plant species. Furthermore, the anticancer drugs paclitaxel and camptothecin were discovered in a program sponsored by National Cancer Institute (NCI) in the United States and the Central Drug Research Institute (CDRI) in India, which screened almost 35,000 plants species from 1960-1981.[108]

Of the approximately 250,000 higher plant species (angiosperms and gymnosperms) that occur globally, only 6% have been investigated for any therapeutic activities. However, the advent of more efficient screening methods should increase the numbers of these studies, thus promoting the discovery of new drugs. Most pharmaceutical and biotechnology companies screen many thousands of plant-based compounds expediently via high throughput *in vitro* assay methodologies.[109,110] The goals of using plant-based traditional medicines for drug discovery is to isolate bioactive chemical constituents with high activity and low toxicity.[111] Alternatively, the whole plant may be used as a herbal medicine for holistic health promotion. *Centaurea benedicta* possesses notable phytochemicals including flavonoids, tannins, lignans, triterpenoids, sesquiterpene lactones, as well as essential and volatile oils, which may contribute to the antimicrobial, anticancer, anti-inflammatory, antioxidant, immunomodulatory and other therapeutic properties of this species.[8,29,38,55] Cnicin is present in significant quantities in *C. benedicta*.[112] Interestingly, cnicin has potent antibacterial activity against numerous Gram-positive and Gram-negative bacteria, including antibiotic resistant strains, and possesses cytotoxic properties against cancer cell lines.[17,34,54] Numerous studies have reported additional properties such as antioxidant, anti-inflammatory, antidiabetic and antinociceptive activities.[14,40,41] Together, these findings indicate that *C. benedicta* and its phytochemical constituents are a potential rich source of novel drug candidates.

Previous research studies have shown antimicrobial activities of blessed thistle using highly concentrated extracts (up to 70 mg/mL in some studies). Given the high concentrations/doses tested, it is not surprising that good activity was reported. However, screening such high doses may not indicate antibacterial activity, and would be classed as inactive in most other studies. Additionally, many of these studies reviewed herein tested only one or two different doses, and MIC values were not reported. These studies should be repeated to evaluate the efficacies of the *C. benedicta* extracts, allowing it to be benchmarked alongside other studies on the plant and other species so that appropriate comparisons can be made. It should also be noted that, in some of these studies, the extracts used in testing contained high concentrations of organic solvents such as methanol and ethanol, which would undoubtably complicate the analysis due to the inhibitory effects that these solvents exert on the cell lines being tested. Researchers should ensure that extracts are devoid of such solvents and are resuspended in aqueous solutions, and that they conduct control experiments with the resuspension solution to confirm that it does not contribute to the effects observed in the assays. As such, the activities of *C. benedicta* extracts in many of those studies are unreliable and should be repeated under these conditions. In any event, since research on crude extracts is already rather limited for this plant, this work would help increase our understanding of the properties of these preparations and thus provide a stronger platform for drug discovery efforts.

Although some studies have indicated antimicrobial properties of *C. benedicta*, relevant models of diseases should be implemented in each study to ensure that *C. benedicta* possesses activity against the causative agent(s) of that disease. For example, Staphylococcal and Streptococcal species cause skin disease, as do ringworm fungi, and thus collectively these pathogens should be tested for inhibition by *C. benedicta* to determine its potential applications in treating epidermal diseases. Urinary tract infections are caused by *E. coli* and *Proteus mirabilis*, and these species should be tested in the same way, as well as studies on pathogenic gastrointestinal bacteria (e.g. *Salmonella* spp. and *Shigella* spp.) which trigger diarrhoea. Any viral or parasitic organisms that cause these diseases should also be tested. Together, this would provide a more comprehensive analysis of the properties of *C. benedicta* in treating infectious diseases and thus provide a more expansive insight into the roles of the plant in human health.

Whilst some examination of *C. benedicta* antimicrobial, anti-inflammatory, antioxidant and anticancer activities has been conducted, the plant is most commonly used as a galactagogue and yet there are no studies seeking to verify this therapeutic effect. Studies relevant to its galactagogue properties should therefore be undertaken. This is also true for studies to validate *C. benedicta* preparations for the treatment of specific types of cancers. To date, studies on the effects of *C. benedicta* using cancer cell lines has been quite broad, with testing being performed on a number of different cell lines, without focus on a specific cancer type (such as breast cancer, cervical cancer or prostate cancer). More focused approaches should be undertaken to determine the anticancer properties of *C. benedicta* on specific types of cancers, with a more extensive investigation that provides evidence of potential

roles of the plant extracts or compounds isolated from the plant in treating certain cancers.

Phytochemistry studies reveal that *C. benedicta* contains a variety of flavonoids, coumarins, lignans, alkaloids, carbohydrates, terpenoids and polyphenols. Among these is the sesquiterpene lactone molecule cnicin, which has received considerable attention for its potential as a medicine. While some other compounds have been isolated and tested, it is interesting that investigation in this area has received limited attention. It is noteworthy that the activities of isolated compounds may be reduced or lost when purified, whilst they remain active in crude extracts, and act as potentiators of other compound(s) within extracts. Alternatively, they may have their activity potentiated by another molecule(s). Thus, it is possible that therapeutic properties can be missed by separating the various active phytochemicals. For example, *Artemisia annua* L. infusions (used in the treatment of malaria) have the same level of activity as a five-fold higher concentration of pure artemisinin when used as a monotherapy.[113] A well-documented example of a synergistic relationship between two individual compounds in therapy is Augmentin™, which contains both the antibacterial agent amoxicillin and a β-lactamase inhibitor, clavulanic acid. There are numerous other examples involving the use of plant-derived compounds in combination with currently available drugs to inhibit pathogenic microorganisms, including some antibiotic-resistant species.[114] The use of different extracts and/or molecules isolated from *C. benedicta,* both alone and in combinations, may reveal similar synergistic relationships inhibiting the growth of pathogenic microbes. Similarly, this work could also be conducted with cancer cell lines using combinational assays (combining *C. benedicta* extracts and/or individual molecules) which could reveal far more powerful inhibition of cancer cell growth than using single compounds isolated from plant extracts.

To date, the vast majority of work conducted with C. *benedicta* has involved *in vitro* experimentation. It should be noted that as the extracts and isolated compounds are more rigorously characterized in terms of their activities and subsequent potential as medicinal agents, *in vivo* testing using whole animal studies will be required to determine both their efficacy and toxicity. A detailed analysis of their pharmacodynamic properties and their pharmacokinetic parameters should be performed alongside toxicity studies to more clearly define their mechanisms of action, distribution, efficacy and safety. Compound(s) or other preparations derived from *C. benedicta* that demonstrate favorable profiles may then be taken forward for early phase clinical trials in order to establish their usefulness in the treatment of human illnesses.

CONCLUSIONS

Ethnomedical knowledge is indispensable in the search for botanical resources for the development of new drugs. It has become widely apparent that plants which have been used traditionally for thousands of years are a promising source of potential new drugs and therapies. *Centaurea benedicta* is a promising plant species in this regard and evidence has emerged documenting its medicinal properties that support its traditional use. However, much work remains to uncover its hitherto undiscovered or uncharacterized properties. Research should be focused on the pathogens that are responsible for specific diseases, so that downstream therapies can be tailored to treat infections triggered by the relevant invading prokaryotic, viral and eukaryotic (fungi, parasites and cancer cells) organisms. Similarly, the likely complex interplay between *C. benedicta* and disease-triggering inflammatory agents or oxidant species should be more closely examined. In all cases, combinations of extracts, fractionated extract samples, and/or individual molecules derived from the plant should be explored to identify possible instances where synergistic enhancements of efficacy occur. Moreover, drugs that are currently in use may be included in these combinatorial studies on *C. benedicta* to ascertain if improvements to current therapies are possible. An increased therapeutic effect elicited by the inclusion of *C. benedicta* would allow the doses of the conventional drug to be reduced, thus lowering drug toxicity risks. Furthermore, toxicity studies on *C. benedicta* and its components must also be conducted in parallel with the bioactivity experiments and the associated combination studies to provide a safety profile for the plant components involved. This should be conducted alongside detailed phytochemical analyses to identify the active molecular candidates involved, including those that may be potentiating the bioactivity of other plant components or conventional drugs. Together, this may lead to the development of effective drug therapies for the treatment of numerous ailment types, many of which are already purported to be ameliorated by the traditional uses of *C. benedicta*.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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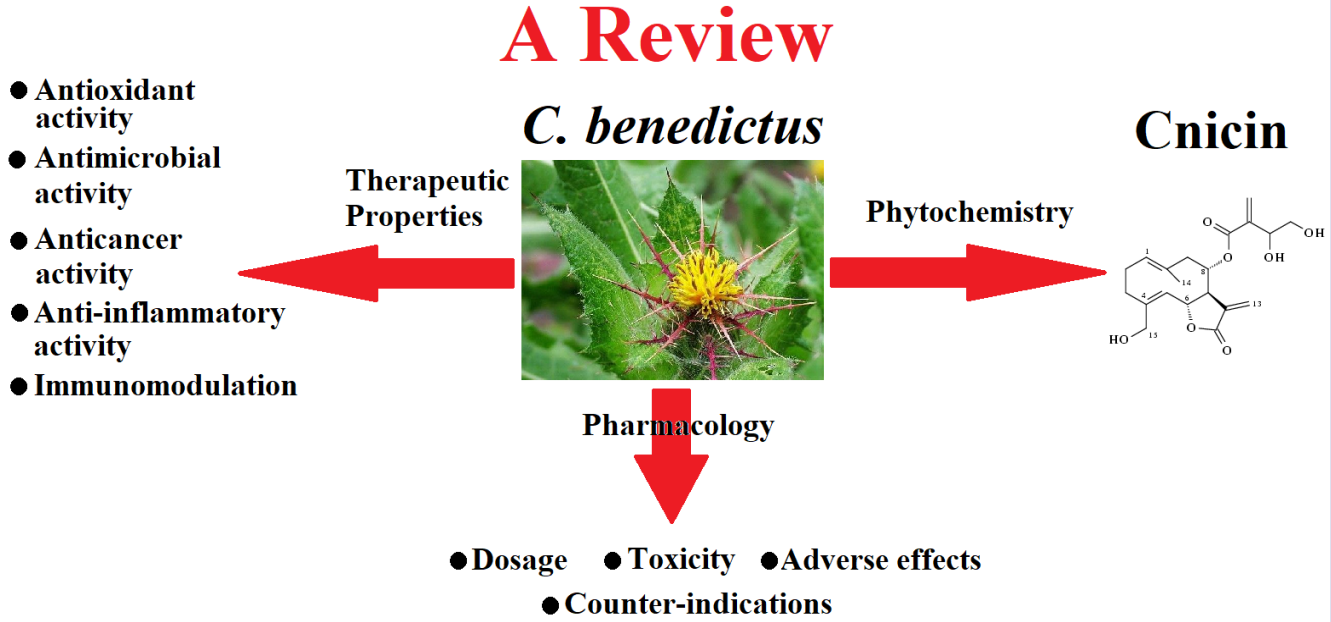
GRAPHICAL ABSTRACT



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  Mr Gagan Tiwana completed a Master of Pharmacy project on the medicinal properties of plants. He is seeking to begin a PhD in the area of traditional medicines in order to explore their potential in treating infectious diseases.

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  Jiahe Fua undertook an undergraduate project into the therapeutic properties of blessed thistle in our group and has recently graduated with degrees in science from Griffith University (Australia) and Nanjing University of Chinese Medicine (China).

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- **Dr Ian Cock**

  Dr Ian Cock leads a research team in the Environmental Futures Research Institute and the School of Natural Sciences at Griffith University, Australia. His research involves bioactivity and phytochemical studies into a variety of plant species of both Australian and international origin including *Aloe vera*, South Asian and South American tropical fruits, as well as Australia plants including *Terminalia ferdinandiana* (Kakadu plum), *Tasmannia lanceolata*, *Scaevola spinescens*, *Pittosporum phylliraeoides*, Australian *Acacias, Syzygiums, Petalostigmas* and *Xanthorrhoea johnsonii* (grass trees). This range of projects has resulted in more than 200 scientific publications in a variety of international peer reviewed journals. Dr Cock is also active in the administration and editorial aspects of scientific publication. He is currently on the editorial boards of 9 international peer reviewed journals. Of these, he is the editor in chief and foundation editor of the journal Pharmacognosy Communications.

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