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An Evidence-Based Systematic Review of Blessed Thistle (*Cnicus benedictus*) by the Natural Standard Research Collaboration

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ABSTRACT. An evidence-based systematic review including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

KEYWORDS. Adverse effects, blessed thistle, dosing, evidence-based, interactions, pharmacodynamics, pharmacology, pharmacokinetics, systematic review

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INTRODUCTION

Systematic Aggregation, Analysis, and Review of the Literature

Search Strategy

To prepare each Natural Standard review, electronic searches are conducted in nine databases, including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT. Search terms include the common name(s), scientific name(s), and all listed synonyms for each topic. Hand searches are conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions are placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) are consulted for access to additional references or ongoing research.

Selection Criteria

All literature is collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, human data). Standardized inclusion/exclusion criteria are utilized for selection.

Data Analysis

Data extraction and analysis are performed by health care professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertain to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data are verified by a second reviewer.

Review Process

A blinded review is conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, complementary and alternative

medicine (CAM) research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addresses conflicts, and consults experts when applicable. Authors of studies are contacted when clarification is required.

Update Process

Natural Standard regularly monitors scientific literature and industry warnings. When clinically relevant new data emerge, best efforts are made to update content immediately. In addition, regular updates with renewed searches occur every 3–18 months, variable by topic.

Synonyms/Common Names/Related Substances

- Bitter thistle, cardin, Carbenia benedicta, Chardon Benit, Cardo Santo, carduus benedictus, Cnici benedicti Herba, *Cnicus*, holy thistle, Kardo-benedictenkraut, St. Benedict thistle, spotted thistle.
- **Combination product example**: Essiac® (blessed thistle, burdock root, Indian rhubarb, sheep sorrel, inner bark of slippery elm, watercress, red clover, and kelp).
- **Note**: Blessed thistle should not be mistaken for milk thistle *Silybum marianus* or other members of the thistle family.

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- Blessed thistle leaves, stems and flowers have traditionally been used in "bitter" tonic drinks and in other oral preparations to enhance appetite and digestion. Blessed thistle may also be included in the unproven anticancer herbal remedy, Essiac®. The herb has been tested in vitro for its antimicrobial, anticancer and anti-inflammatory effects, with some positive results. However, no controlled trials have documented clinical benefits in humans.
- Blessed thistle has been used traditionally to stimulate menstruation or induce abortion, and therefore should be avoided during pregnancy.

Indication	Evidence Grade
Abortifacient	C
Dyspepsia/indigestion/flatulence	C
Viral infections	C

Scientific Evidence for Common/Studied Uses

Natural Standard Evidence-Based Validated Grading Rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and folkloric precedent are not included in this assessment, and are reflected in a separate section of each monograph ("Strength of Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Historical or Theoretical Indications which Lack Sufficient Evidence

- Anorexia, antibiotic, anticancer, antimicrobial, antipyretic, appetite stimulant, astringent, blood purifier, boils, bubonic plague, cervical dysplasia, choleretic, colds, contraceptive (Krag, 1976), diaphoretic, diarrhea, digestive tonic, diuretic, dysmenorrhea (Novitch & Schweiker, 1982), emmenagogue (de Laszlo & Henshaw, 1954), expectorant, fever, galactagogue, gall bladder disease, hemorrhage, hepatic disorders, inflammation, jaundice, malaria, memory improvement, menstrual disorders, pneumonitis, rabies, salivary stimulant, skin ulcers, wound healing.

Expert Opinion and Folkloric Precedent

- Traditionally, blessed thistle leaves, stems and flowers have been used in "bitter" tonics to stimulate appetite and digestion. Preparations of

Level of Evidence Grade	Criteria
A (Strong scientific evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (Good scientific evidence)	Statistically significant evidence of benefit from 1 to 2 properly randomized trials, OR evidence of benefit from ≥ 1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/nonrandomized trials AND with supporting evidence in basic science, animal studies, or theory. *This grade applies to situations in which a well designed randomized controlled trial reports negative results but stands in contrast to the positive efficacy results of multiple other less well designed trials or a well designed meta-analysis, while awaiting confirmatory evidence from an additional well designed randomized controlled trial.*
C (Unclear or conflicting scientific evidence)	Evidence of benefit from ≥ 1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from ≥ 1 cohort/case-control/nonrandomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (Fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/nonrandomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit. *This grade also applies to situations in which >1 well-designed randomized controlled trial reports negative results, notwithstanding the existence of positive efficacy results reported from other less well-designed trials or a meta-analysis. (Note: if there is ≥ 1 negative randomized controlled trials that are well designed and highly compelling, this will result in a grade of "F" notwithstanding positive results from other less well-designed studies.)*
F (Strong negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from ≥ 1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

*Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al. (1996), in which a score below 4 is considered to indicate lesser quality methodologically.

†Listed separately in monographs in the "Historical or Theoretical Uses which Lack Sufficient Evidence" section.

blessed thistle have been used medicinally in Europe and India for multiple conditions, including anorexia, dyspepsia, flatulence, indigestion, and loss of appetite. The German expert panel, the Commission E, has approved the internal use of blessed thistle for loss of appetite and dyspepsia. The British Herbal Compendium indicates its use for loss of appetite, anorexia and "flatulent dyspepsia."

- Anecdotally, blessed thistle has also been recommended for cervical dysplasia, diarrhea, hemorrhage, wound healing, stimulation of lactation, and dysmenorrhea.

Brief Safety Summary

- **Likely safe**: When blessed thistle is used as flavoring agent, it is generally considered to be safe. In the United States it is an allowable flavoring for alcoholic beverages, such as Benedictine liqueur.
- **Possibly safe**: The above ground parts of blessed thistle may be safe when taken orally in recommended doses; allergic reactions have been reported.
- **Possibly unsafe**: Oral use of blessed thistle is possibly unsafe during pregnancy, due to potential emmenagogue (menstruation stimulant) or abortifacient properties. Gastric toxicity may occur with high doses.

DOSING/TOXICOLOGY

General

- Recommended doses are based on historical practice. With natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what are the active components of a product, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization

- There is no widely accepted standardization for blessed thistle, although there are assays available to determine the presence of the

"bitter" constituent cnicin. Pharmacopeial-grade blessed thistle herb is reported to require a "bitterness value" that is ≥800.
- Blessed thistle herbal preparations are often obtained from the leaves and flowers of the plant.

Dosing

Adult (Age ≥18)

Oral

- **Tincture**: 7.5–10 ml (1.5 g/L blessed thistle) three times daily has been used.
- **Liquid extract** (1:1g/ml in 25% alcohol): 1.5–3.0 ml has been used three times daily.
- **Infusion**: 1.5–2 g of blessed thistle in 150 ml water has been used three times daily.
- **Tea**: 1.5–3 g of dried blessed thistle flowering tops steeped in boiling water and taken as tea three times daily, or 1–3 tsp of dried blessed thistle herb in 1 cup boiling water for 5–15 min; 1 cup may be taken three times daily, recommended by some to be used 30 min before meals. May be bitter in taste.

Children (Age 18)

- Safety and efficacy data for children are lacking, and blessed thistle is generally not recommended in infancy or early childhood.

Toxicology

- **Acute toxicity**: Gastric irritation and vomiting have been reported from high doses of blessed thistle (>5 g per cup of tea).
- Water extracts of blessed thistle have exhibited no mutagenicity at concentrations up to 200 microliters/disc in the standard Ames test (Schimmer, Kruger, Paulini, & Haefele, 1994), although alcoholic extracts in concentrations of 400 microliters/disc possess mild mutagenic effects (in combination with other herbs, which reduces the clarity of this finding) (Goggelmann & Schimmer, 1983). The LD_{50} of cnicin, a constituent of blessed thistle, has been reported as 1.6–3.2 mmol/kg body weight in mice.

- In theory, tannins in blessed thistle may be hepatotoxic or nephrotoxic if ingested chronically.

PRECAUTIONS/CONTRAINDICATIONS

Allergy

- Allergy/hypersensitivity to blessed thistle has been reported, as well as cross-reactivity to mugwort and echinacea. In theory, cross-reactivity may occur to other plants in the Asteraceae/Compositae family. Cross-reactivity may occur with bitter weed, blanket flower, chrysanthemum, coltsfoot, daisy, dandelion, dwarf sunflower, goldenrod, marigold, prairie sage, or ragweed (Zeller, de Gols, & Hausen, 1985).
- Sesquiterpene lactones are the elements of Asteraceae/Compositae plants believed to be responsible for allergic cross-sensitivity. A study in guinea pigs using 20 different species of Compositae plants demonstrated blessed thistle to possess relatively strong sensitizing properties (Zeller et al., 1985).

Adverse Effects/Post Market Surveillance

- **General**: Blessed thistle is generally considered to be safe when used in recommended doses for short periods of time, with few reported adverse effects. Allergic cross-sensitivity may occur with other members of the Compositae family.
- **Dermatologic**: Blessed thistle may cause contact dermatitis. Cross reactivity may occur with other members of the Compositae family.
- **Gastrointestinal**: Anecdotally blessed thistle taken in high doses (greater than 5 g per cup of tea) may cause stomach irritation and vomiting. Blessed thistle contains approximately 8% tannins; notably, chronic ingestion of plants that contain $\geq$10% tannins may cause gastrointestinal upset, hepatic necrosis, or increased risk of developing esophageal or nasal cancer. Traditionally, blessed thistle is believed to stimulate gastric acid secretion, and use may be inadvisable in patients with peptic ulcer disease.
- **Hematologic**: Blessed thistle has been shown to possess platelet-activating factor (PAF) antagonist properties, which in theory may reduce PAF-stimulated platelet aggregation, increasing bleeding risk (Nose, Fujimoto, Nishibe, & Ogihara, 1993).

- **Ocular/Otic**: Direct exposure to growing blessed thistle plants may result in irritation of the eyes.
- **Renal**: Blessed thistle contains approximately 8% tannins; notably, chronic ingestion of plants that contain ≥10% tannins may result in nephrotoxicity.

Precautions/Warnings/Contraindications

Use blessed thistle cautiously in patients with peptic ulcer disease; based on the traditional belief that blessed thistle stimulates gastric acid secretion.

Pregnancy & Lactation

- Blessed thistle has been used traditionally to stimulate menstruation or induce abortion, and therefore should be avoided during pregnancy.
- Although blessed thistle has been used traditionally to stimulate lactation, it is not recommended during lactation due to insufficient available safety information.

INTERACTIONS

Blessed Thistle/Drug Interactions

- **Antacids, H2-receptor antagonists, proton pump inhibitors, sucralfate**: Traditionally, blessed thistle is believed to stimulate gastric acid secretion, and may reduce the efficacy of antacids.
- **Antibiotics**: Blessed thistle may have antibacterial effects (Vanhaelen-Fastre, 1972; Vanhaelen-Fastre, 1973; Vanhaelen-Fastre & Vanhaelen, 1976).
- **Anticoagulants and antiplatelets**: Blessed thistle has been shown to possess PAF-antagonist properties, which in theory may reduce PAF-stimulated platelet aggregation, increasing bleeding risk (Nose et al., 1993). Clinical effects in humans have not been assessed.
- **Antineoplastic agents**: Cnicin and arctigenin have exhibited cytotoxic activity against some tumor cell lines including leukemia (HL-60), hepatomas, and sarcomas via inhibition of cellular DNA, RNA, or protein synthesis (Barrero, Oltra, Morales, Alvarez, & Rodriguez-Garcia, 1997; Cobb, 1973; Eich et al., 1996; Hirano, Gotoh, & Oka, 1994; Moritani, Nomura, Takeda, & Miyamoto, 1996; Ryu, Ahn,

Kang, & Han, 1995; Vanhaelen-Fastre & Vanhaelen, 1976). Arctigenin has been noted to induce differentiation in mouse myeloid leukemia cell lines (Umehara, Sugawa, Kuroyanagi, Ueno, & Taki, 1993). Blessed thistle is included in some brands of the unproven anticancer herbal remedy, Essiac®.

- **Antiviral agents, antiretroviral agents**: Lignans in blessed thistle may have antiviral activity (particularly anti-HIV) and may theoretically interact with other antiviral agents (Pfeiffer, Trumm, Eich, Schroder, & Muller, 1999).
- **Nonsteroidal anti-inflammatory agents (NSAIDs)**: In the standard rat paw model of inflammation, cnicin had mild anti-inflammatory effects (Mascolo, Caspasso, Menghini, & Fasulo, 1987). Lignans such as arctigenin and trachelogenin appear to exert inhibitory effects on cyclic AMP, phosphodiesterase, and histamine release in rat mast cells (Nose et al., 1993). Antagonist activities against calcium ions and platelet activation factor have also been observed (Nose et al., 1993).

Blessed Thistle/Herb/Supplement Interactions

- **Antacids**: Traditionally, blessed thistle is believed to stimulate gastric acid secretion, and may reduce the efficacy of antacids.
- **Antibacterials**: Blessed thistle may have antibacterial effects (Vanhaelen-Fastre, 1972; Vanhaelen-Fastre, 1973; Vanhaelen-Fastre & Vanhaelen, 1976).
- **Anticoagulants and antiplatelets**: Blessed thistle has been shown to possess PAF antagonist properties, which in theory may reduce PAF-stimulated platelet aggregation, increasing bleeding risk (Nose et al., 1993). Clinical effects in humans have not been assessed.
- **Anti-inflammatory herbs**: In the standard rat paw model of inflammation, cnicin had mild anti-inflammatory effects (Mascolo et al., 1987). Lignans such as arctigenin and trachelogenin appear to exert inhibitory effects on cyclic AMP, phosphodiesterase, and histamine release in rat mast cells (Nose et al., 1993). Antagonist activities against calcium ions and platelet activation factor have also been observed (Nose et al., 1993).
- **Antineoplastics**: Cnicin and arctigenin have exhibited cytotoxic activity against some tumor cell lines including leukemia (HL-60), hepatomas, and sarcomas via inhibition of cellular DNA, RNA or protein synthesis (Barrero et al., 1997; Cobb, 1973; Eich et al., 1996;

Hirano et al., 1994; Moritani et al., 1996; Ryu et al., 1995; Vanhaelen-Fastre & Vanhaelen, 1976). Arctigenin has been noted to induce differentiation in mouse myeloid leukemia cell lines (Umehara et al., 1993). Blessed thistle is included in some brands of the unproven anticancer herbal remedy, Essiac®.

- **Antiviral agents**: Lignans in blessed thistle may have antiviral activity (particularly anti-HIV) and may theoretically interact with other antiviral agents (Pfeiffer et al., 1999).

Blessed Thistle/Lab Interactions

- Insufficient available evidence.

Blessed Thistle/Food Interactions

- **Coagulation panel**: Blessed thistle has been shown to possess PAF antagonist properties, which in theory may reduce PAF-stimulated platelet aggregation, increasing bleeding risk (Nose et al., 1993). Clinical effects in humans have not been assessed.

MECHANISM OF ACTION

Pharmacology

- **Constituents**: The chemical constituents of blessed thistle include sesquiterpene lactone glycosides such as cnicin (0.2–0.7%), polyacetylen (Vanhaelen-Fastre, 1974), and absinthin (Kataria, 1995); triterpenoids such as a-amyrenone, a-amyrin acetate, a-amyrine, and multiflorenol acetate (Kataria, 1995; Ulbelen & Berkan, 1977); lignans such as trachelogenin, arctigenin, and nortracheloside (Vanhaelen & Vanhaelen-Fastre, 1975); flavonoids; polyenes; tannins (8%); and essential/volatile oils (0.3%) such as p-cymene, fenchon, citral, and cinnamaldehyde (Vanhaelen-Fastre, 1973). Salonitenolide has also been found to be present (Vanhaelen-Fastre, 1974). Lignans such as trachelogenin may contribute to the bitter characteristics of blessed thistle. Cnicin has also been identified as a principal bitter ingredient in blessed thistle (Schneider & Lachner, 1987).
- **Antimicrobial effects**: Antimicrobial activity of blessed thistle has been attributed to cnicin and polyacetylene constituents

(Vanhaelen-Fastre, 1972; Vanhaelen-Fastre, 1973; Vanhaelen-Fastre & Vanhaelen, 1976). Antibacterial activity of cnicin and the essential oil of blessed thistle herb have been observed in vitro against *Bacillus subtilis*, *Brucella* species, *Escherichia coli*, *Proteus* species, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus faecalis* (Vanhaelen-Fastre, 1972; Vanhaelen-Fastre, 1973; Vanhaelen-Fastre & Vanhaelen, 1976). Other studies have demonstrated no activity against *Klebsiella*, *Pseudomonas*, *S. aureus*, *S. tyhpi*, or yeast (Perez & Anesini, 1994; Perez & Anesini, 1994a; Recio, Rios, & Villar, 1989). Several lignans have also been under investigation as antiviral (particularly anti-HIV) and anticancer agents (Eich et al., 1996; Hirano et al., 1994; Maeda & Mitsuya, 1995; Yang et al., 1996).

- **Anti-inflammatory effects**: In the standard rat paw model of inflammation, cnicin had mild anti-inflammatory effects (Mascolo et al., 1987). Lignans such as arctigenin and trachelogenin appear to exert inhibitory effects on cyclic AMP, phosphodiesterase, and histamine release in rat mast cells (Nose et al., 1993). Antagonist activities against calcium ions and platelet activation factor have also been observed (Nose et al., 1993).
- **Antiproliferative effects**: Cnicin and arctigenin have exhibited cytotoxic activity against some tumor cell lines including leukemia (HL-60), hepatomas, and sarcomas via inhibition of cellular DNA, RNA, or protein synthesis (Barrero et al., 1997; Cobb, 1973; Eich et al., 1996; Hirano et al., 1994; Moritani et al., 1996; Ryu et al., 1995; Vanhaelen-Fastre & Vanhaelen, 1976). Arctigenin has been noted to induce differentiation in mouse myeloid leukemia cell lines (Umehara et al., 1993). Blessed thistle is included in some brands of the unproven anticancer herbal remedy, Essiac®.

Pharmacodynamics/Kinetics

- Following oral ingestion of blessed thistle by rats, the lignans arctiin and tracheloside are metabolized to their genins, arctigenin, and trachelogein. Peak serum levels are reached at 4 hr for arctigenin and at 8 hr for trachelogenin (Nose et al., 1993).

HISTORY

- The blessed thistle plant grows 30–50 cm high. The stems are heavily branched, fuzzy and sticky; the leaves are thorny and dentate, and

the upper leaves form a cup around a flower (which is pale yellow and daisy-like). The leaves, flowering tops, and seeds have been used medicinally. Blessed thistle is native to the Mediterranean region of Europe, and has been naturalized throughout the United States and Europe.

- Blessed or "holy" thistle has been used for more than 2000 years as a "bitter" to stimulate appetite, enhance bile secretion, strengthen the liver, diminish jaundice, decrease flatulence, and aid digestion. Preparations of blessed thistle have also been used historically as a diuretic, diaphoretic, emmenagogue, contraceptive, antipyretic, as a cure for bubonic plague sores and malaria, and as a general tonic/cure-all. Currently, blessed thistle is most often recommended as a bitter tonic to treat dyspepsia, flatulence, and indigestion. It is also sometimes used as a treatment for diarrhea or hemorrhage, wound healing, lactation stimulation, or dysmenorrhea. Blessed thistle is sometimes added as a fifth ingredient to the unproven anticancer herbal remedy, Essiac®.
- Blessed thistle is also used as a flavoring agent in Benedictine liqueur.

EVIDENCE TABLE

- No available studies qualify for inclusion in the evidence table.

EVIDENCE DISCUSSION

Abortifacient

- **Summary**: Blessed thistle has sometimes been used traditionally as an abortifacient. There is limited human study in this area. Safety and efficacy have not been established.

Dyspepsia/Indigestion/Flatulence

- **Summary**: Blessed thistle is sometimes recommended as a treatment for dyspepsia, indigestion, and flatulence (although historically, blessed thistle is believed to stimulate gastric acid secretion). There is limited scientific study in this area, and the extent of these gastrointestinal effects remains unclear.

Viral Infections

- **Summary**: In vitro studies suggest a broad spectrum of antimicrobial activity of blessed thistle. Lignans in blessed thistle have been investigated as anti-HIV agents (Pfeiffer et al., 1999). However, blessed thistle has exhibited no antiviral activity against herpes, influenza, or polioviruses (May & Willuhn, 1978. There are no reliable human trials of blessed thistle as a treatment for viral infections. There is insufficient scientific evidence to recommend for or against the use of blessed thistle for this indication.
- **Evidence**: There is one case report of an HIV infected woman who used an herbal mixture including blessed thistle (Duke, 1997). Although she reportedly felt symptomatic improvement with the use of this preparation, she subsequently died of pneumonia. Additional details, such as viral load or CD4+ counts are not available. The potential effects of other herbs in the preparation are not known.

PRODUCTS STUDIED

Brands used in Statistically Significant Clinical Trials

- Not applicable.

Brands Shown to Contain Claimed Ingredients Through Third-Party Testing

- **Consumer Lab**: NA. Last accessed 8/10/07.
- **Consumer Reports**: NA. Last accessed 8/10/07.
- **Natural Products Association**: NA. Last accessed 8/10/07.
- **NSF International: NA.** Last accessed 8/10/07.
- **U.S. Pharmacopeia: NA.** Last accessed 8/10/07.

European Trade Names (Herbal Mixtures Containing Blessed Thistle)

- Asgocholan, Bilisan forte, Bomgall forte S, Carvomin, Cheiranthol, Chola-Dolan, Digestivum Hetterich, Esberigal, Frisoman, Gallexier, Gallitophen, Gastritol, Gastrosan, Gladlax, Hepaticum-Divinal, Hevert-Gall S, Losapan, Mag Kottas, Leber-Gallentee, Mariazeller,

Rasyana, Tisane Antibiliaire et Stomachique, Tisane pour le coeur et la circulation H, Ventrodigest.

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