Milk Thistle Drugs
Hollow promises or real benefit?

A review of the latest findings

PHYTOPHARM 2015 – Bonn, 23th July 2015

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Acknowledgments

The author of this presentation was employed as Head of Research & Development of Madaus GmbH (2007 – 2014) and involved in international cooperation including but not limited to projects with the US SyNCH Team partly financed by various NIH grants.

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Silymarin drug development

Milk thistle extracts

Silymarin drugs

Silibinin formulation
Milk Thistle:
Flower – Pappus – Seeds
Silymarin

History

&

Basic Research
Milk Thistle: Initial description in Europe

Theophrastus (371 – ca. 287 BC)
• Mentioned first time as „Pternix“ – the upright growing stem of the plant

Pedanius Dioscorides (ca. 40 – ca. 90)
• *Materia medica* – Used a mixture of root extract and mead (fermented honey) as emetic after various *intoxications*.
    Silybum: Sillybon (Greek) = tassel, appendix

Caius Plinius Secundus (Pliny the Elder) (23 – 79)
• Described in *Naturalis Historiae* several thistle species (Carduus)

Hildegard of Bingen (1098 – 1179)
• Explicitly mentioned milk thistle with its popular name as cultivated medicinal plant

Hieronymus Bock (1498 – 1554)
• *Das Kreütter Buch*, 1539, contains a description of milk thistle
Milk Thistle: History in European medicine

Pietro Andrea Mattioli (Pierandrea) (1501 – 1577)
• Translated Dioscorides’ *Materia medica*, (commented issue in 1554)
  Mentioned Carduus marianus against stitches in the side and jaundice.

Adam Lonitzer (Lonicerus) (1528 – 1586)
• Milk thistle – good to use for the inflamed liver

Albrecht von Haller (1708 – 1777)
• First use of milk thistle comparable to modern phytotherapy

Johann Gottfried Rademacher (1772-1850)
• Propagated the idea of medicinal use of the milk thistle.
• Prepared Tincture Rademacher (*Tinctura Cardui mariae*)
• Treated liver, spleen and gall bladder.
„The Biological Treatment of Disease“
Gerhard Madaus, 1938
Practical use of Carduus Marianus (milk thistle) for the treatment of:
Hepato- & -cholangiopathy
... treatment of ikterus, cholangitis, spleen diseases...
Silymarin: Basic Research 1

Aus dem Institut für Pharmakologie und experimentelle Therapie der früheren Universität Breslau (Direktor: Prof. Dr. O. Eichler).

Versuche zum Schutz gegen leberschädigende Gifte.

Von

O. Eichler und M. Hahn.

(Eingegangen am 11. Oktober 1948.)

Naunyn-Schmiedebergs Arch. 206 (1949)
Silymarin: Basic Research 1

Experiments on the protection against liver toxic poisons

Animal testing with carbon tetrachloride.
Silymarin: Basic Research 2

Professor Dr. Dr. h.c. mult. Hildebert Wagner

Study of pharmacy 1950 - 1953
Doctoral studies 1954 - 1956
Postdoctoral qualification (habilitation) 1960
Tenured professor (chair of pharmacognosy) 1965
Director, Institute of pharmaceutical biology, Munich till 1999

• Visiting professor, Columbus University, Ohio 1970/71
• Dean of the faculty of chemistry & pharmacy, university Munich, Germany 1981 - 83
• Ph.D. honoris causa, universities of Budapest & Debrecen, Hungary 1989
• Ph.D. honoris causa, university of Dijon, France 1997
• Ph.D. honoris causa, university of Helsinki, Finland 1997
• Professor honoris causa, medicinal faculty university Beijing, China 1990
• Professor honoris causa, university of Arequipa, Peru 1992
Silymarin: Basic Research 2

Sonderdruck aus:
» ARZNEIMITTEL-FORSCHUNG «
» DRUG RESEARCH «
Arzneim.-Forsch. (Drug Res.) 18, 688—696 (1968)
Editio Cantor KG / Aulendorf i. Württ.

Aus dem Institut für Pharmazeutische Arzneimittellehre der Universität München
Zur Chemie des Silymarins*) (Silybin), des Wirkprinzips der Früchte von Silybum marianum (L.) Gaertn. (Carduus marianus L.)
Herrn Professor Dr. H. Böhme zum 60. Geburtstag gewidmet
Von H. Wagner, L. Hörhammer und R. Münster**)
Silymarin: Basic Research 2

From the Institute for Pharmaceutical Instruction, University of Munich

The chemistry of silymarin (silybin), the active principle of the fruits of *Silybum marianum* (L.) Gaertn. (*Carduus marianus* L.)

Dedicated to Professor Dr. H. Böhme on his 60th birthday

H. Wagner, L. Hörhammer and R. Münster
Silymarin: Main components (Flavonolignans)

Silibinin A (25-30%)

Silibinin B (25-30%)

Isosilibinin A (ca.5%)

Isosilibinin B (ca.5%)

Silicristin (ca.20%)

Silidianin (ca.15%)

**Chemical Structure:**

- **Silibinin A**
  - C_{25}H_{22}O_{10}
  - MW = 482.4 g/mol

- **Silibinin B**

- **Isosilibinin A**
  - C_{25}H_{22}O_{10}

- **Isosilibinin B**

- **Silicristin**
  - C_{25}H_{22}O_{10}

- **Silidianin**
  - C_{25}H_{22}O_{10}
Silymarin: Basic Research 3

Sonderdruck aus

» ARZNEIMITTEL-FORSCHUNG «
» DRUG RESEARCH «
Arznei.-Forsch. (Drug Res.) 18, 698–704 (1968)
Editio Cantor KG / Aulendorf i. Württ.

Aus dem Biologischen Institut Madaus, Köln-Merheim

Zur Pharmakologie und Toxikologie von Silymarin, des antihepatotoxischen Wirkprinzipes aus Silybum marianum (L.) Gaertn.

Von

G. Hahn, H. D. Lehmann, M. Kürten, H. Uebel und G. Vogel
unter Mitarbeit von I. Baumann, I. Dobberstein, E. Eisen, A. Ersfeld,
S. Krüger, E. Meier und H. Walther
The pharmacology and toxicology of Silymarin, the antihepatotoxic principle of Silybum marianum (L.) Gaertn. 1968; Drug Res. 18 (6) 698-704.

As silymarin is evidently capable of exerting protective and curative effects of various degrees under various experimental conditions and against various hepatic poisons, it may be concluded that it is in fact the active principle of Silybum marianum, a plant which has long been claimed to possess liver-protective properties.
Buformin (1-butylbiguanide) oral antidiabetic marketed by Gruenenthal as **Silubin**
Silymarin: Nomenclature 2

Supplement to WHO Chronicle, 1977, Vol. 31, No. 10

International Nonproprietary Names for Pharmaceutical Substances

**silibinin**

- **Latin**: silibininum
- **French**: silibinine
- **Spanish**: silibinina
- **Russian**: силибинин
- **Arabic**: سيليبينين
- **Chinese**: 水飞蓟宾
- **Phonetic**: silibinin
- **Molecular formula**: C$_{25}$H$_{22}$O$_{10}$
- **ATC Codes**: DCF

No alternate national name found.

**National commission(s) using same name**

DCF

**silicristin**

- **Latin**: silicristinum
- **French**: silicristine
- **Spanish**: silicristina
- **Russian**: силикристин
- **Arabic**: سيليكرستين
- **Chinese**: 水飞蓟丁
- **Phonetic**: silicristin
- **Molecular formula**: C$_{25}$H$_{22}$O$_{10}$
- **ATC Codes**: 

No alternate national name found.

**National commission(s) using same name**

No data found on use of name by national commission(s).

**silidianin**

- **Latin**: silidianinum
- **French**: silidianine
- **Spanish**: silidianina
- **Russian**: силидидианин
- **Arabic**: سيليديدانيين
- **Chinese**: 水飞蓟宁
- **Phonetic**: silidianin
- **Molecular formula**: C$_{25}$H$_{22}$O$_{10}$
- **ATC Codes**: 

No alternate national name found.

**National commission(s) using same name**

No data found on use of name by national commission(s).
Silymarin

Clinical Research
Scientific papers around Silymarin/Silibinin

(PubMed)
Pharmacodynamic properties

Pharmacologic properties of silymarin:

• Anti-oxidative
• Influence on DNA expression
• Anti-inflammatory activity
• Regenerative effects
• Anti-angionetic effects
• Regulation of apoptosis
• Modulation of steroid hormone receptors
• Modulation of drug transporters
• Antiviral effect
Pharmacodynamic properties & therapeutic target

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Therapeutic approach:

**Gastroenterology**
• Hepatoprotectant / choleric
• Pancreoprotectant
• Antidote (Amanita poisoning)
• Virostatic (Hepatitis C)

**Cardiovascular**
• Hypcholesterolemic agent

**Urology**
• Treatment of nephropathy

**CNS**
• Use in neurodegenerative processes

**Skin protection**
• X-Ray-, UVB-Protection

**Cancer**
• Anticancer agent
• Adjuvant treatment of cancer
Pharmacodynamic properties & therapeutic target

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**Skin protection**
- X-Ray-, UVB-Protection

**Cancer**
- Anticancer agent
- Adjunct therapy of cancer
Silymarin

Hepatoprotective?

Origin of liver disease?

Parameters of liver damage?

Endpoints of clinical trials?
Silymarin: Liver cirrhosis

Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver

P. Ferenci¹, B. Dragosics¹, H. Dittrich², H. Frank³, L. Benda⁴, H. Lochs¹, S. Meryn¹, W. Base¹ and B. Schneider⁵

1 Ist Department of Gastroenterology and Hepatology, University of Vienna, 2 Ambulatorium Süd der Wiener Gebietskrankenkasse, 3 Department of Internal Medicine, Sophienspital and 4 Department of Internal Medicine, Krankenhaus Floridsdorf, Vienna (Austria) and 5 Institute of Biometry, Medical University Hannover, Hannover (F.R.G.)

(Received 26 July 1988)
(Accepted 22 December 1988)
Double blind, placebo controlled trial:
170 patients with cirrhosis of various origin.
2 years treatment with 140mg silymarin TID.

The results of the study suggest that mortality of patients with cirrhosis was reduced by treatment with silymarin. This effect was more pronounced in alcoholic cirrhosis.

(Accepted 22 December 1988)
Silymarin: Liver cirrhosis

1. Survival curves for 170 patients with cirrhosis of the liver treated with silymarin or placebo (Kaplan-Meier Life-Table analysis, Wilcoxon-Breslow test \( P = 0.036 \); Mantel-Cox test \( P = 0.058 \)).
Silymarin: Hepatitis C

Effect of Silymarin (Milk Thistle) on Liver Disease in Patients With Chronic Hepatitis C Unsuccessfully Treated With Interferon Therapy

A Randomized Controlled Trial


Michael W. Fried, MD
Victor J. Navarro, MD
Nezam Afzhal, MD
Steven H. Belle, PhD
Abdus S. Wahid, PhD
Roy L. Hawke, PharmD, PhD
Edward Doo, MD
Catherine M. Meyers, MD
K. Rajender Reddy, MD
for the Silymarin in NASH and C Hepatitis (SyNCH) Study Group

Context The botanical product silymarin, an extract of milk thistle, is commonly used by patients to treat chronic liver disease, despite scant and conflicting evidence of its efficacy.

Objective To determine the effect of silymarin on liver disease activity in patients with chronic hepatitis C virus (HCV) infection unsuccessfully treated with interferon-based therapy.

Design, Setting, and Participants Multicenter, double-blind, placebo-controlled trial conducted at 4 medical centers in the United States. Participants included 154 persons with chronic HCV infection and serum alanine aminotransferase (ALT) levels of 65 U/L or greater who were previously unsuccessfully treated with interferon-based therapy. Enrollment began in May 2008 and was completed in May 2010, with the last follow-up visit completed in March 2011.

Intervention Participants were randomly assigned to receive 420-mg silymarin, 700-mg silymarin, or matching placebo administered 3 times per day for 24 weeks.
Effect of Silymarin (Milk Thistle) on Liver Disease in Patients With Chronic Hepatitis C Unsuccessfully Treated

After 24 weeks of treatment the mean decline in serum ALT activity at the end of treatment did not differ significantly between placebo and treatment group. There was no significant change in HCV RNA levels.

Abdus S. Wahed, PhD
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Yubelkis Matias, 19, a student at Bronx Community College, lives with fatty liver disease.
Yubelkis Matias, 19, a student at Bronx Community College, lives with fatty liver disease.
In the hepatocyte, FFA may be oxidized at mitochondrial and extramitochondrial sites, or incorporated in triglycerides.

Increased levels of lipoipopolysaccaride (LPS) lead to activation of Kupffer cells, which release chemotactic factors and proinflammatory cytokines, and generate oxidative stress-related products including reactive oxygen species (ROS).

NASH – Rationale for the use of silymarin

Possible silymarin targets

Prerequisites:
- High daily dose > 2g silymarin/day
- Bioavailable formulation (e.g. nanoparticles)
- Suitable clinical endpoints for trials
Silibinin i.v.

Treatment of live threatening diseases:

Amanita poisoning
Experiments on liver protection by silymarin
Dogs treated with Amanita phalloides

- Excessively pre-treated (100%)
- Untreated (100%)
Silibinin-C-2’, 3 - dihydrogen succinate, disodium salt
Silibinin-C-2', 3 - dihydrogen succinate, disodium salt
α-Silibinin docking at OATP sites
α-Amanitin docking at OATP sites
α-Amanitin competing with silibinin
Complete receptor blocking
NCT00915681 – US Study

Prevention and treatment of Amatoxin induced hepatic failure with intravenous silibinin:
An open multicenter clinical trial (Phase II/III)

**Study Objective:**
The study aims to assess the efficacy and safety of intravenous silibinin in the prevention of severe morbidity (defined as liver transplant) and death in amatoxin poisoned patients.

**Primary Endpoint:**
Proportion of enrolled patients without liver transplant or death.

**Secondary Assessments:**
AST, ALT, bilirubin, PT/INR, and creatinine as indicators of liver and renal function, adverse events and vital signs.
NCT00915681 – Main limitations of the study

- Placebo control impossible
- Power insufficient for showing differences in survival
- Analytical data about amatoxin concentration (severity of intoxication) missing
- Different time between intoxication and start of treatment
- Intensive care treatment different (site effect)
- No comparable historical subgroup data available
Silibinin i.v.

Treatment of live threatening diseases:

Chronic Hepatitis C
HCV kinetics – 14 days silibinin infusion

Silibinin:
Host cell modulator
or
Direct-acting antiviral
Participants in “Silibinin & HCV”

University of Washington, Seattle, USA

Hôpital Henri Mondor, Créteil, France

Université de Lyon, France

Universität Heidelberg, Germany

Los Alamos National Laboratory, USA

University of Illinois, Chicago, USA

Hiroshima University, Japan
1. Receptor binding
2. Endocytosis
3. Fusion and uncoating
4. Translation and polyprotein processing
5. RNA replication
6. Virion assembly
7. Transport and release
HCV – Reproduction cycle

1. Receptor binding
2. Endocytosis
3. Fusion and uncoating
4. Translation and polyprotein processing
5. RNA replication
6. Virion assembly
7. Transport and release
Silibinin inhibits viral entry

- Silibinin inhibits HCV early steps of infection by affecting endosomal trafficking of virions

- Silibinin inhibits HCV infection and hinders HCV entry by slowing down trafficking through clathrin-coated pits and vesicles into early endosomes

- Silibinin interacts with membranes which could lead to an alteration of clathrin coat disassembly
Silibinin is a DAA against HCV in vitro

- Silibinin inhibits HCV replication in cell culture
- This inhibition is at least partly mediated by direct inhibition of HCV RdRp
- Thus, silibinin and related compounds are non-nucleoside inhibitors (NNIs) of HCV RdRp
- The observed \textit{in vitro} IC50s are in keeping with the antiviral effect of IV, but not oral silymarin
Silibinin mode of action keeps to be controversially discussed

- Effect on HCV entry and cell-to-cell spread in vitro with only marginally suppression of HCV RNA replication.

- Pronounced inhibition of HCV RNA replication by inhibiting the viral replication complex interacting with NS5B (RdRp) and NS4B (influencing the membranous web morphology)
Milk Thistle Drugs: Hollow promises or real benefit?
Conclusion

Hollow promises:

• Underdosed use of a poor formulated silymarin extract in patients with serious liver damage.

• Curative use of oral silymarin in patients with chronic hepatitis C.

Real benefit:

• Immediate intravenous infusion of silibinin in patients with amatoxin poisoning in line with aggressive hydration.

• Development of an oral silibinin formulation for long term use in patients with HCV infection.
Thank you!

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