A general introduction to medicinal plants and *silybum marianum*

[1]Farhat Ali Khan, [2]Muhammad Zahoor, [1]Naseem Ullah, [4]Shazeb Khan, [3]Muhammad Khurram, [5]Sartaj Khan, [6]Javid Ali

[1]Department of Pharmacy, Sarhad university of Science and Information Technology, KpK, Pakistan.
[2]Department of chemistry, university of Malakand, Lower Dir, Chakdara, Pakistan.
[3]Department of Microbiology and Biotectnology, Sarhad university of science and information technology, KpK, Pakistan.
[4]Department of Pharmacy, university of Malakand, Lower Dir, Chakdara, Pakistan
[5]Community Medicine, Bannu Medical College Bannu.
[6]PCSIR Laboratories complex, peshawar

Abstract: Use of plants based drugs for curing various ailments is as old as human civilization and is used in all cultures through out history. The primitive man started to distinguish between useful and harmful are poisonous plants by trail and errors. A well defined herbal pharmacopoeia was developed by tribal people, which was based on information collected from local flora, religion and culture. The knowledge of medicinal plants was gradually developed and passed on from one individual to other, which foundation for traditional medicine through out the world. Recently, a variety of liver diseases are spreading very rapidly in our society and different herbal remedies are used by the local practitioners as a therapeutic agent. Among these herbal formulations, *Silybum marianum* is found to be highly effective for liver disorders.
[Farhat Ali Khan, Muhammad Zahoor, Naseem Ullah, Shazeb Khan, Muhammad Khurram, Sartaj Khan, Javid Ali. **A general introduction to medicinal plants and *silybum marianum*.** *Life Sci J* 2014;11(09s):471-481]. (ISSN:1097-8135). http://www.lifesciencesite.com. 94

Key wards: Natural products, Milk thistle, Silymarin, Liver ailment

Introduction

1.1. Medicinal plants

Plants are used for variety of purposes. The history of natural product is relatively old and dates back to the time when the early man became conscious of his environment. Cultured and civilized man is said to have been on earth for some two or three million years and he has struggled for his life during the greater portion of the era. Thousands of years' effort, by examination much has thought him to differentiate between useful and harmful plants. Since then herbs have been used in all cultures as an important source of medicine [1].

The history of human culture and civilization of Egypt, Assyrian, China, and Indies valley, knows that the elders and wise man of those times used medicinal plants to treat many diseases. Information about these medicinal plants is present in the old literature, mythological stories, folklore, medicinal treaties, epic poems and thousand years' old manuscripts, copper plates and palm leaves and other information on these cultures which are preserved even today. The unearth of Shanidar cave in Iraq in 1963 opened the grave of Neanderthal man buried sixty thousand year ago along with so many flowers of his time. The plants present in the grave were later known to have many medicinal properties.

The earliest records of the use of medicinal plants are that of Chaulmoogra oil from *Hydnocarpus gaertn*, which was identified to be effective in the treatment of leprosy. Such a use of medicinal plants for the treatment of leprosy was written in the pharmacopoeia of the Emperor of China between 2730 and 3000 B.C. In the same way, the castor seeds and seeds of opium were found from ancient Egyptian tombs, which confirm their use in that part of Africa as for back as 1500 B.C. The written records existing in "Ebers papyrus" also show the use of medicinal plants at that time in Egypt [2]. According to the history of medicinal plants, the Materia Medica of Hippocrates, who is currently known as the father of medicine, composed of herbal formulations, nearly 400 simple formulations having been compiled and explain by him. Plin was a Theophrastus of Ethan's (370-287B.C) a well-known botanist who wrote a number of manuscripts including the famous Historia planetarium. Just about 500 plants, mostly cultivated, were marked out in this manuscript [3]. However, the significant pharmacological collection of the Greeks was the authoritative text of Dioscoridies [3]. Later than him Pliny the elder (23-79 AD) wrote "Natural History" in 37 volumes. Galen compiled some 30 books on pharmacology beside "Galanicals" his medical formulae [4].

Chinese medicine, with its use of pharmaceutical preparation Known as fangs, also utilized a variety of plants. The written document of Chinese traditional medicine can be marked out to

Shen Nong Ben Cao Jin (22-250 AD). Later Li Shizhens, a great physician and naturalist, wrote "Ben Cao Gang Mu" published in 1596 that has been regarded as complete pharmacopoeia having a total of 1894 entries.

Many western personalities described herbal medicines including Discoridies and Galen in the first and second centuries to Culpeper in the 17th century. The first chemical isolated from plant was benzoic acid, discovered in 1560. Some simple compounds like glycerol, oxalic acid, lactic acid, citric acid and tartaric acid were extracted from various organic sources, both plants and animals by a German chemist Karl Wilhelm Scheele (1742-1786).

Rig Vedas and Ayuvedas are the main source of Indian medicines. They are mainly based on the use of drugs of plant origin. The Ayurvedic system of medicine is mainly credited to Charaka [5] and Sushruta [6], who described about 700 medicinal plants. The Muslim rulers introduced their traditional system of medicine in India and included in the native Ayurvedic medicine.

In the last five decades the development and introduction of immuno-stimulants, antibiotics and antitumer agents isolated from plants have led a dramatic success in control of many diseases. During the last decade the use of traditional medicines has expended globally and has gained attractiveness. These are used not only for primary health care of poor people in the developing countries, but are also used in the countries where conventional medicine is predominant in the National Health Care System [7]. According to WHO herbal medicines serve the health needs of about 80% of the world's population, especially for million of people in the vast rural areas of developing countries [5].

More than 50% of all the medicines in clinical use have a natural product origin [8]. Of the worlds 25 best selling pharmaceutical agent, 12 are natural products derived [9]. More than 600 botanical items have been recognized in various edition of the United State Pharmacopoeia [10].

The most important factors for the continued use of the traditional medicines are its ready accessibility, cheapness and socio-cultural reasons. A long tradition of the use of herbal remedies exists in some countries and the people especially of the rural areas have more faith in the traditional medicines. The fact that most of the medicinal plants have been used over the ages for treatment of diseases is believable evidence that many of the medicinal plants prescription are realistically safe but scientific toxicological trials are still necessary [11].

Medicinal plants were the major basis of products used to maintain health until the nineteenth century, when the German chemist Friedrich Wohler, attempting to get ready ammonium cyanate from silver cyanide and ammonium chloride, by chance synthesized urea. This was the first organic synthesis in history and heralded the period of the synthetic compound. With this discovery, the Western science rewarded no good attention to the phytomedicines; they started to use their energy on synthetic lines. But before long they bounced reverse to the herbal medicines when they observed comparatively more ill-effects of the synthetic drugs as compared to the herbal medicines. Though the herbal medicines are very different from well-defined synthetic drugs, for example, the accessibility and value of the raw materials are often problematic; the active principles are frequently unidentified; and standardization, stability, and quality control are possible but not simple. In contrast with modern medicine, herbal medicines price less, are more often used to treat chronic diseases, and the incident of undesirable side effects seems to be less common. A vast number of plants have medicinal properties; in fact, many pharmaceutical drugs were originally derived from plants. Ethno-pharmacology – the scientific study of indigenous medicines – is an interdisciplinary science practiced all over the world. Phototherapeutic agents or herbal medicines are standardized herbal preparations that contain, as active ingredients, complex mixtures of plant materials in the crude or processed state. One basic characteristic of phototherapeutic agents is the fact that they normally do not have a direct or strong pharmacological action. For this reason, these agents are not suitable for emergency treatment.

Nowadays, the use of medicinal plants and their bioactive phytocompounds and our scientific information about them comprises the modern field of the phytosciences. This is a science created from the incorporation of a range of disciplines that have never been connected before, combining some different areas of economic, social, and political fields, chemistry, biochemistry, physiology, microbiology, medicine, and agriculture.

In short, the medicinal plants are reliable sources for the treatment of many health problems. Man has depended a lot on the herb in the past, and even at present the use of plants as medicine is popular. For the future health challenges the plants are reasonably prepared to serve the man. The only need is to develop the isolation and purification techniques. At the same time it is important to pay good attention to minimize the pollution, as the polluted materials are always of the little use or simply useless.

1.2. *Silybum marianum*

Silybum marianum commonly known as Milk thistle,Ladys thistle, Holly thistle, Marian thistle,Blessed thistle, Mary's thistle, Carduus

marianus thistle, Mariana mariana, Carthamus maculatum [12, 13] is native of southern Europe, mainly the Mediterranean regions, indigenous to North Africa, Asia Minor, and Southern Russian Fedrations. *S marianum* is now naturalized through out Europe, in North and South America, Australia [14]. The plant thrives in dry, stony or rocky areas, harsh atmosphere fields. Being a hostile shelter, *S. marianum* was once seen as an indication of poor husbandry and a threat to farm lands. Nowadays, it is retrieval its magnetism as an ornamental plant and is also grown commercially in countries like Argentina, Australia, Russia, China, Germany, Romania and Hungary [12, 13].

Silybum marianum is an annual or biennial tubby, rigid herb that is also wide and jagged. Bulky rosette basal leaves grow up in its first season, which lies close to the ground. It rises to a height of 2.5 meter and a width of 0.9 meter. Each plant produces up to four stems which are hollow, spherical and be full of a milky white sap [15-17].

It has large leaves that are broad and shiny green. They are distinct with white vein like marking, having spiny boundaries. The grown-up leaves have deeper lobes with a wavier margin, while the young leaves are shallowly lobed with spin [15-17].

The flowers of *Silybum marianum* are blue or white in color, thislle like and single. They have many tubular florets that are about 6 cm in diameter and are bordered by rigid bracts that end in sharp spines. After flowering, white, thick feathery thistledown develops and spread the seeds [15, 17, 18].

Seeds are obliquely obovoid and are 6-7 millimeter long and 3 millimeter wide. Color of the seeds is brown and has a yellowish extrapolative enlarged ring at its tip and a canaliculated hilum at other end [16, 19].

1.3. Cultivation

Silybum marianum is most frequently propagated through seed which need light to germinate The ordinary growing season is early spring to summer, with flower maturation taking place from June to July [12,13].

1.4. Harvesting

In early summer the flower heads are collected and the seeds are gathered in late summer.The harvesting time for seeds is very important. The seeds heads are due for collection when they form a perfusion of thick, white, fluffy thistledown, containing the ripest seeds. If harvesting is belated, the wind may take away as much as half of the crops [16, 12].

1.5. Medicinal Importance of *Silybum marianum*

Based on the widespread folk use of *Silybum marianum* in cases of jaundice, European medical researchers began to investigate its medicinal effects. It is presently used to treat alcoholic hepatitis, liver cirrhosis, liver poisoning, and viral hepatitis, and to protect the liver in general from the effects of liver-toxic medications. However, on the other hand of this wide usage, there is no ultimate confirmation that it is useful.

Standardized *S. marianum* extract is known as silymarin. Silymarin itself is a combination of at least seven chemicals. The very most active of these chemicals is commonly known as silibinin. But, silibinin too is, in fact, a mixture, comprising the two linked substances silibinin A and silibinin B [20]. When inject intravenously, silibinin is thought to work as an antidote to poisoning by the death cap mushroom, *Amanita phalloides*. The animal studies propose that *S. marianum* extracts can also defend against many other poisonous substances, from toluene to the drug acetaminophen [21-26]. One animal study suggests that *S. marianum* can also save fetal damage caused by alcohol [27].

Silibinin is hypothesized to work by displacing toxins trying to bind to the liver and by causing the liver to regenerate more speedily. It may also be active as an antioxidant and as well stabilize liver cell membranes [28, 29].

In Europe, *S. marianum* is regularly supplementary as extra defense when patients are given medications known to cause liver problems. On the other hand, *S. marianum* failed to confirm useful for preventing liver inflammation caused by the Alzheimer's drug Cognex (terrine) [30].

Silybum marianum is also used in a vague state known as minor hepatic insufficiency, or sluggish liver [31]. This term is often used by European physicians and American naturopathic practitioners, conventional physicians in the united state don't be well-known with it. Symptoms are said to include aching in the ribs, fatigue, unhealthy skin appearance, general malaise, constipation, premenstrual syndrome, chemical sensitivities, and allergies.

One small, but actually well-conducted, double-blind trial established proof that *Silybum marianum* might get improved blood sugar control in type 2 diabetes [32]. *S. marianum* may also suggest a number of protections to the kidney [33]. A highly preliminary proof hints that *S. marianum* may help decrease breast cancer threat [34]. *S. marianum* is occasionally recommended for gallstones and psoriasis, but there is slight to no evidence as up till now that it really helps these conditions.

In one small, placebo-controlled trial, the topical application of *S. marianum* by means of methylsulfonylmethane for one month seen to be effective in the treatment of forty six subjects with the skin condition rosaceous [35].

1.6. Scientific Evidence for *Silybum marianum*

As noted above, there is most important evidence from studies in animals that *Silybum marianum* can keep the liver from many toxins. Though, human studies of people suffering from a variety of liver diseases have often yielded mixed results. A 2007 review of published and unpublished studies on *S. marianum* as a treatment for liver disease caused by alcohol or viral hepatitis accomplished that benefits were seen only in low-quality trials, and, even in those, *S. marianum* did not show more than a negligible benefit [36].

1.7. Acute Viral Hepatitis

A twenty one day, double-blind, placebo-controlled study of fifty seven people with acute viral hepatitis found important improvements in the group receiving *Silybum marianum* [37]. A thirty five day study of one hundred fifty one individuals are thought-out to have acute hepatitis showed no advantage with *S. marianum*, but this study has been criticized for weakening to document that the participants in reality had acute hepatitis [38, 39].

1.8. Chronic Viral Hepatitis

Inconsistent facts exist in relation to whether *Silybum marianum* is helpful for chronic viral hepatitis B or C [40-45]. The *S. marianum* does not appear to affect levels of virus in the body, but might help protect the liver from damage and recover some symptoms.

1.9. Alcoholic Hepatitis

A double-blind, placebo-controlled study performed in 1981 followed one hundred six Finnish soldiers with alcoholic liver disease over a period of four weeks [46]. The treated group showed a significant decrease in high liver enzymes and development in liver histology, as evaluated by biopsy in twenty nine subjects.

Two similar studies provided on the whole equivalent results [47, 48]. However, a three month, randomized, double-blind study of one hundred sixteen people showed little to no additional benefit, probably because most participants reduced their alcohol use and approximately half stopped drinking totally [49]. One more study found no advantage in seventy two patients followed for fifteen months [50]. It is definitely more effective for people with alcoholism to stop drinking than to carry on drinking and take *Silybum marianum*.

1.10. Liver Cirrhosis

A double-blind, placebo-controlled study of one hundred seventy peoples with alcoholic or non-alcoholic cirrhosis found that in the group treated by *Silybum marianum* the four year survival rate was 58% as compared to only 38% in the placebo group [51]. This difference was statistically significant.

A double-blind, placebo-controlled trial that enrolled one hundred seventy two peoples with cirrhosis for four years also found reductions in death, but they just missed the predictable cutoff for statistical importance [52]. A two year, double-blind, placebo-controlled study of two hundred individuals with alcoholic cirrhosis found no reduction in mortality attributable to the use of *S. marianum* [53]. Though, in an analysis of nineteen randomized trials, researchers concluded that *S. marianum* was notably more effective at reducing mortality from liver cirrhosis compared to placebo, but no more effective at reducing mortality from any cause [54].

Other double-blind studies of people with a variety of cirrhosis have looked at changes in tests of liver function rather than mortality. Some found benefit, while others did not [55, 56].

1.11. Dosage

The standard dosage of *Silybum marianum* is 200 mg two to three times a day of an extract standardized to contain 70% silymarin.

There is some evidence that silymarin bound to phosphatidylcholine may be better absorbed [57, 58] this form should be taken at a dosage of 100 mg to 200 mg twice a day.

Warning: Considering the severe nature of liver disease, a doctor's supervision is necessary. Also, do not inject *S. marianum* preparations that are intended for oral use!

1.12. Side Effects

Silybum marianum is thought to have very little toxicity. Animal studies have not shown any negative effects even when high doses were administered more than a long period of time [59].

A study of 2,637 participants reported in 1992 showed a low rate of side effects, limited mostly to mild gastrointestinal disturbance. However, on rare occasions severe abdominal pain may occur [60].

On the basis of its widespread use as a food, *S. marianum* is thought to be safe for pregnant or nursing women and researchers have enrolled pregnant women in studies [60] However, safety in young children, pregnant or nursing women, and individuals with severe renal disease has not been formally well-known.

1.13. Drug Interaction

No drug interactions are known. Though, one report has noted that silibinin can inhibit a bacterial enzyme called beta-glucuronidase, which plays a part in the activity of certain drugs, such as oral contraceptives [61]. This could theoretically reduce their usefulness.

S. marianum contains a variety of active constituents; mostly the flavonoids in nature and a variety of compounds have so far been isolated from it.

Table 1. A list of compounds reported from *Silybum marianum*

Sr/no.	Name of Compound	M.Formula	M.Weight	Melting Point (˚C)	Ref.
1	4,7-Epoxy-3,8-bilign-7-ene-3,4,5,9,9-pentol	$C_2OH_{22}O_6$	358	Not reported	[62]
2	1,8,15-Hepta decatriene-11,13-diyne	$C_{17}H_{22}$	226	Not reported	[63]
3	1,8,15-Hepadecatriene-11,13-diyne	$C_{17}H_{22}$	226	Not reported	[63]
4	2,9,16-Heptadecatriene-4,6diyn-8-ol	$C_{17}H_{22}O$	242	Not reported	[63]
5	Isosilybin	$C_{25}H_{22}O_{10}$	482	239-240	[64]
6	Isosilychristin	$C_{25}H_{22}O_{10}$	482	155-157	[65]
7	Neosilyhermin A	$C_{25}H_{22}O_9$	466	Not reported	[66]
8	Neosilyhermin B	$C_{25}H_{22}O_9$	466	Not reported	[67]
9	Kaempferol3,7diglycoside	$C_{27}H_{28}O_{16}$	608	Not reported	[67]
10	Silandrin	$C_{25}H_{22}O_9$	466	234-236	[68]
11	Silychristin	$C_{25}H_{22}O_{10}$	482	174-176	[69]
12	Silybin	$C_{25}H_{20}O_{10}$	480	168-170	[64]
13	2,3-Dehydrosilybin	$C_{25}H_{20}O_{10}$	480	174-176	[63, 65]
14	2,3-dehydrosilychristin	$C_{25}H_{20}O_{10}$	480	Not reported	[70]
15	Silymonin	$C_{25}H_{24}O_9$	468	258-260	[71]
16	Silydianin	$C_{25}H_{24}O_{10}$	484	190-192	[71]
17	Silyhermin	$C_{25}H_{22}O_9$	466	93-95	[67]
18	2-(1-Undecen-3,5,7,9-tetraynyl) oxirane	$C_{13}H_8O$	180	95-97	[67]
19	12-Tridecene4,6,8,10-tetraynal	$C_{13}H_8O$	180	N0treported	[63]
20	4,5-Dihydroxy flavon 7-0[rhamnopyranosyl-(12)-D-galacturonopyranoside	$C_{27}H_{28}O_{15}$	592	N0t reported	[66]

A standardized extract of the seed of *S. marianum* contains about 70-80% of silymarin and 20-30% chemically undefined fraction, comprising generally polymeric and oxidized polyphenolic compounds [71].

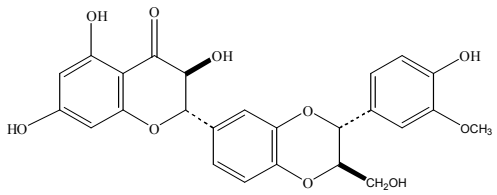
1.14. Silymarin

Silymarin is an active extract of the seeds of *Silybum marianum* [73]. It is used for the treatment of many liver disorders characterized by degenerative necrosis and functional impairment [74]. In addition, it is capable to antagonize the toxin of *Amanita phalloides* [75, 76] and provides hepatoprotection against poisoning by paladin, [77] galactosamine, [78] thioacetamide, [79] halothane [80] and carbon tetrachloride [81]. The compound too protects hepatocytes from injury caused through ischemia, radiation, iron overload and viral hepatitis [82]. Silymarin is incorporated in the pharmacopoeia of many countries and is often used as encouraging therapy in food poisoning due to fungi and in chronic liver disorders, for example statuses [83] and alcohol associated liver disease [84].

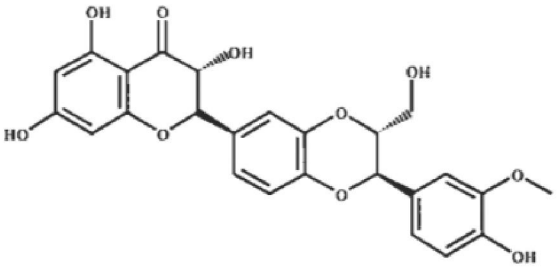
Formerly, it was thinking to be a single large, complex molecule but in 1974 it was exposed that silymarin is a mixture of several flavonolignans [85]. Flavonolignans are produced by the free radical oxidative coupling of the coniferyl alcohol 'a component of lignin' and falconoid dihydroquercetin 'also called taxifolin' [86, 87]. This reaction gives Silybum, which is found to be the most bioactive component of silymarin, and a mixture of regioisomers diasteromers [87]. The three most important flavonolignans in *S.marianum* are silybin, also called as silybin, silychristin and silydianin. Moreover, diastereomers of silybin i.e. silybin A and silybin B have been isolated, and the regioisomers silybin, isosilybin A and B [87]. A disteriomers of silychristin now known as silychristin A was discovered and referred to as silychristin B [88].

Other minor compounds consist of isosilychristin, desoxysilydianin, desoxysilychristin, dehydrosilybin, silybinone, silandrin, silymonin, silyhermin, and neosilyhermin A and B. These compounds are present in all parts of plant, but are more concentrated in the seeds.

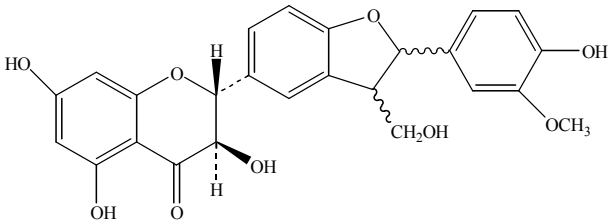
1.15. Structure of silymarin isomers and other reported compounds.



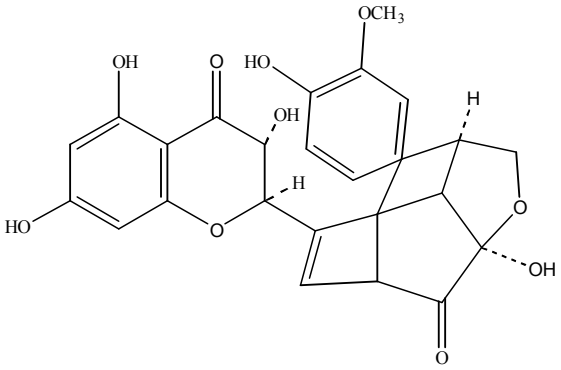
Silybin



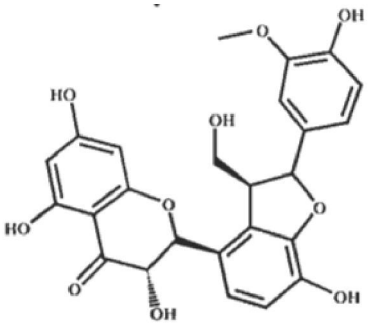
Isosilybin



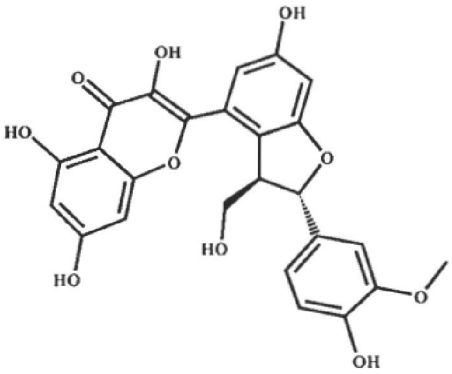
Silychristin



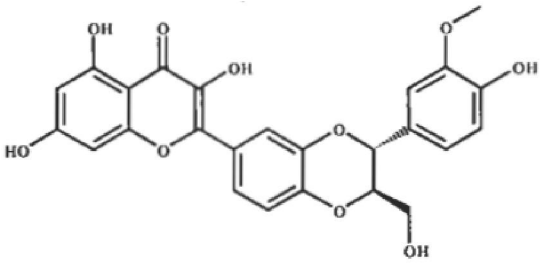
Silydianin



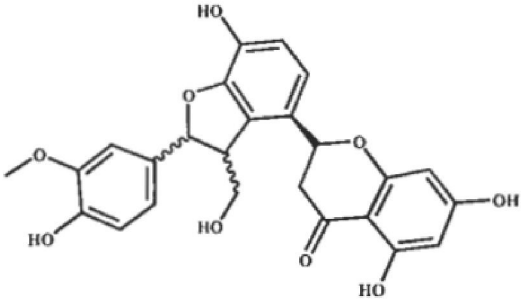
Isosilychristin



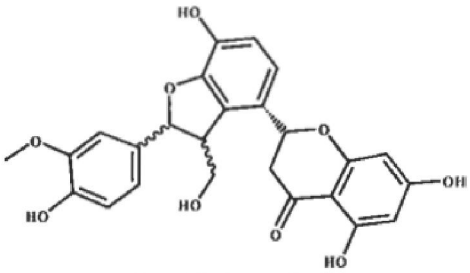
2,3-Dehydrosilychristin



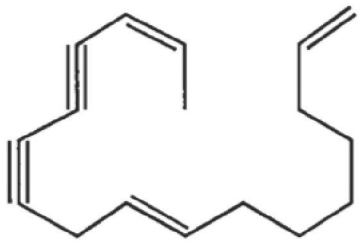
2,3-Dehydrosilybin



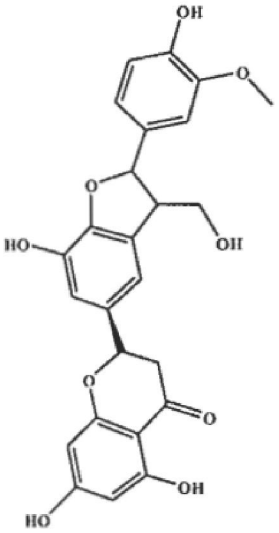
Neosilyhermin A



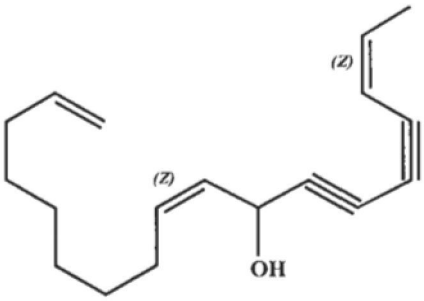
Neosilyhermin B



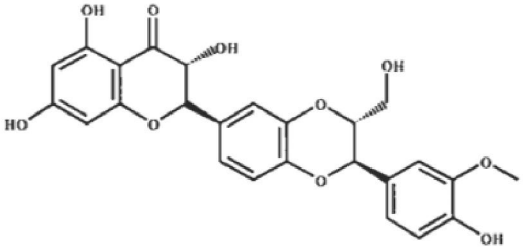
1,8(*Z*),15(*Z*)-Heptadecatriene-11,13-diyne



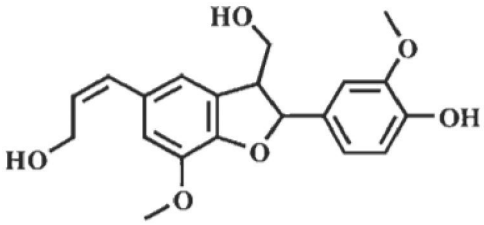
Silyhermin



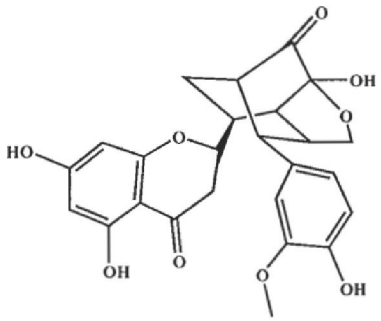
2(*Z*),9(*Z*),16-Heptadecatriene-4,6-diyn-8-ol



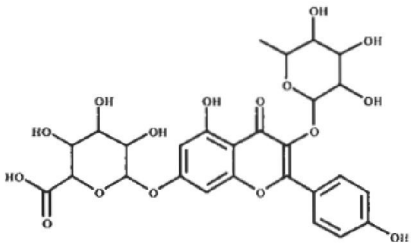
Isosilybin



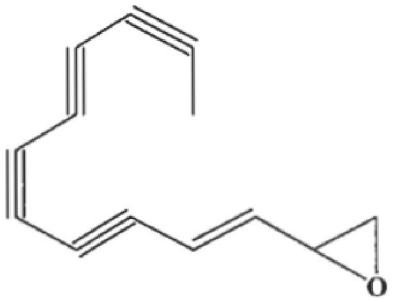
4,7'-Epoxy-3,8'-bilign-7-ene-3',4',5,9,9'-pentol



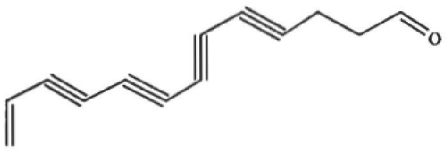
Silymonin



Kaempferol 3-O-α-L-rhamnopyranoside, 7-O-β-D-galacturonopyranoside



2-(1-Undecen-3,5,7,9-tetraynyl) oxirane



12-Tridecene-4,6,8,10-tetraynal

1.16. Mechanism of Action

Silymarins hepativoprotective effects accomplished by a number of mechanism including antioxidation [89], inhibition of lipid per oxidation[90], increase liver detoxification by inhibition of phase one detoxification and enhanced glucoronidation [91, 92] and defense of glutathione depletion [93]. Studies have also shown silymarin shows several ant-inflammatory effects, inhibition of leukotriene as will as prostaglandin synthesis, kupffer cell inhibition, mast cell stabilization, and inhibition of neutrophil migration [94-98]. In addition, silymarin has been known to increase hepatocyte protein synthesis, thus enhancing hepatic tissue regeneration [99]. Animal studies have also established silymarin reduces the transfer of hepatic stellate cells into myofibroblasts, slowing or even reversing fibrosis [100]. Clinical studies conducted in Hungary also established silymarin to have immunomodulatory effects on the diseased liver [101, 102]

1.17. Pharmacokinetics

Silymarin is not water soluble, making tea preparations unproductive, for that reason it is usually administered orally in capsul form. Because absorption of silymarin from the gastrointestinal tract is only moderate (23-47%), it is best administered as a standardized extract of 70-80% silymarin. In animal and humans, peak plasma levels are achieved in four to six hours after an oral dose. Silymarin is extracted chiefly by means of bile but some clearance is too achieved through the kidneys. The clearance half-life of silymarin is six to eight hours [103].

Keeping in view the wide application of *Silybum marianum* as a medicinal plant and its active constituent silymarin which is a strong hepatoprotective agent used for different types of liver ailments, the present information is therefore, an initiative for the awareness of the local peoples using such types of either crude phytochemicals or the whole plant for liver diseases. This study is also providing a scientific database for the study of these compounds.

References

1. Baquar, S. R 1995. The Role of Traditional Medicine in Rural Environment, In: Traditional Medicine in Africa, Issaq, S. (Editor), East Africa Educational Publishers Ltd., Nairobi, pp. 141-142.
2. Lanfranco 1999. GInvited Review Article on Traditional Medicine, EJB, 2(2): 1-3.
3. Evans, W. C 2000. Trease and Evans Pharmacognosy, 15thEdition, W. B. Sounders, London, pp. 3-4,488-491.
4. Tyler, V. E., Brady, L. E., and Robbers, J. E. 1976. Pharmacognosy, 7th Edition, Lea and Febiger, Philadelphia, pp. 1-3.
5. General Guidelines for Methodologies on Research and Evaluation of Traditional MedicineWorld Health Organization (WHO) 2001. Geneva, p. 1.
6. Kunja Lal, B.M1912. Work of Susruta, Calcata.
7. Vickers, A., and Zollman 1999. C ABC of Contemporary Medicine, Herbal Medicine, BMJ, 319(16): 1050-1053.
8. Balandrin M. F, Kinghorn A. D and Farnsworth N. R 2005. Human Medicinal Agents from Plants., (A. D. Kinghorn and M. F. Balandrin, eds), ACS Symposium Series 534, Washington, DC.
9. Neill M. O, and. Lewis J. A 2006. Human Medicinal Agents from Plants., (A. D. Kinghorn and M. F. Balandrin, Eds.) ACS Symposium Series 534, Washington, DC.

10. Tyler V 2006. E. Human Medicinal agents from Plants., (A. D. Kinghorn and M. F. Balandrin, Eds.) ACS Symposium Series 534, Washington, DC.
11. Rehman A. U J 1985. of Science and Medicine., 28, 3.
12. Keville K 1991. The Illustrated Herbal Encyclopedia: A Complete Culinary, Cosmetic, Medicinal and Ornamental Guide to Herbs. Simon and Schuster Australia, East Roseville, New South Wales.
13. Crygan FC , Frohne D,Holtzel C,Nagell A,Pfander HJ, Willuhn G,Buff W 1994. Herbal Drugs and Phytopharmaceuticals :A Hand Book for Practice on a Scientific Basis. Medpharm Scientific Publishers, Stutlgart.
14. Fletcher K A 1991. Moderen Australasian Herbal.Penguin Books Australia,Ringwood , Victtoria.
15. Mars B 1997. The Herbal Pharmacy. Hale Software , inc.Boulder,Colorado.
16. Chevallier A 1996. Encyclopedia of Medicinal Plants. Dorling Pty Limited, St leonards, New South Wales.
17. Bisset NG 1994. Herbal drugs and phytopharmaceuticals. Boca Raton,FL,CRC Press.
18. Nice J 2000.Milk Thistle. Element Book Limited, Shaflesbury,Dorset.
19. Kroll DJ, Shaw HS, Oberlies NH 2007. Milk thistle nomenclature: why it matters in cancer research and pharmacokinetic studies. Integr Cancer Ther.;6:110-119.
20. Muriel P, Garciapina T, Perez-Alvarez V, 1992. Silymarin protects against paracetamol-induced lipid peroxidation and liver damage. J Appl-induced lipid peroxidation and liver damage. J Appl Toxicol.;12:439-442 Toxicol.;12:439-442.
21. Paulova J, Dvorak M, Kolouch F, 1990. Verification of the hepatoprotective and therapeutic effect of silymarin in experimental liver injury with tetrachloromethane in dogs [in Czech]. Vet Med (Praha).;35:629-635.
22. Skakun NP, Moseichuk IP 1988. Clinical pharmacology of legalon [in Russian]. Vrach Delo.;5:5-10.
23. Tuchweber B, Sieck R, Trost W 1979. Prevention of silybin of phalloidin-induced acute hepatotoxicity. Toxicol Appl Pharmacol.; 51:265-275.
24. Boari C, Montanari FM, Galletti GP, 1981. Toxic occupational liver diseases. Therapeutic effects of silymarin [in Italian]. Minerva Med.;72:2679-2688.
25. Szilard S, Szentogyorgyi D, Demeter I 1988. Protective effect of Legalon in workers exposed to organic solvents. Acta Med Hung.;45:249-256.
26. La Grange L, Wang M, Watkins R, 1999. Protective effects of the flavonoid mixture, silymarin, on fetal rat brain and liver. J Ethnopharmacol.;65:53-61.
27. Schulz V, Hansel R, Tyler VE 1998. Rational Phytotherapy: A Physicians' Guide to Herbal Medicine, 3rd ed. Berlin, Germany: Springer-Verlag;:216.
28. Hikino H, Kiso Y 1988. Natural products for liver disease. Econ Med Plant Res.;2:39-72.
29. Muzes G, Deak G, Lang I, 1990. Effects of silymarin (Legalon) therapy on the antioxidant defense mechanism and lipid peroxidation in alcoholic liver disease [in Hungarian]. Orv Hetil.;131:863-866.
30. Allain H, Schuck S, Lebreton S, 1999. Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer's disease. Dement Geriatr Cogn Disord.;10:181-185.
31. Giannola C, Buogo F, Forestiere G, 1985. A two-center study on the effects of silymarin in pregnant women and adult patients with so-called minor hepatic insufficiency [in Italian]. Clin Ther.;114:129-135.
32. Huseini HF, Larijani B, Heshmat R 2006. The efficacy of Silybum marianum (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled, clinical trial. Phytother Res.. [Epub ahead of print].
33. Sonnenbichler J, Scalera F, Sonnenbichler I, 1999. Stimulatory effects of silibinin and silicristin from the milk thistle Silybum marianum on kidney cells. J Pharmacol Exp Ther;290:1375-1383.
34. Zi X, Feyes DK, and Agarwal R 1998. Anticarcinogenic effect of a flavonoid antioxidant, silymarin, in human breast cancer cells MDA-MB 468. Clin Cancer Res. 1998;4:1055-106415. Zi X, Feyes DK, and Agarwal R. Anticarcinogenic effect of a flavonoid antioxidant, silymarin, in human breast cancer cells MDA- MB 468. Clin Cancer Res.;4:1055-1064.
35. Berardesca E, Cameli N, Cavallotti C, 2008. Combined effects of silymarin and methylsulfonylmethane in the management of rosacea: clinical and instrumental evaluation. J Cosmet Dermatol.;7:8-14.
36. Rambaldi A, Jacobs B, Gluud C 2008. Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. Cochrane Database Syst Rev. 2007;CD003620. J Cosmet Dermatol.; 7:8-14.

37. Magliulo E, Gagliardi B, Fiori GP 1978. Results of a double blind study on the effect of silymarin in the treatment of acute viral hepatitis, carried out at two medical centres [translated from German]. Med Klin.;73:1060-1065.
38. Bode JC, Schmidt U, Durr HK 1977. Silymarin for the treatment of acute viral hepatitis? Report of a controlled trial [translated from German]. Med Klin;72:513-518.
39. Magliulo E, Gagliardi B, Fiori GP 1978. Results of a double blind study on the effect of silymarin in the treatment of acute viral hepatitis, carried out at two medical centres [translated from German]. Med Klin.;73:1060-1065.
40. Berenguer J, Carrasco D 1977. Double-blind trial of silymarin vs. placebo in the tresatment of chronic hepatitis. Munch Med Wochenschr;119:240-260.
41. Buzzelli G, Moscarella S, Giusti A, 1993. A pilot study on the liver protective effect of silybin-phosphatidylcholine complex (IdB 1016) in chronic active hepatitis. Int J Clin Pharmacol Ther Toxicol.;31:456-460.
42. Lirussi F, Okolicsanyi L 1992. Cytoprotection in the nineties: Experience with ursodeoxycholic acid and silymarin in chronic liver disease. Acta Physiol Hung. 80:363-367.
43. Gordon A, Hobbs DA, Bowden DS 2006. Effects of Silybum marianum on serum hepatitis C virus RNA, alanine aminotransferase levels and well-being in patients with chronic hepatitis C. J Gastroenterol Hepatol. 21:275-80.
44. Torres M, Rodriguez-Serrano F, Rosario DJ 2006. Does Silybum marianum play a role in the treatment of chronic hepatitis C? P R Health Sci J;23:69-74.
45. Saller R, Brignoli R, Melzer J, 2008. An updated systematic review with meta-analysis for the clinical evidence of silymarin. Forsch Komplement Med.;15:9-20.
46. Salmi HA, Sarna S 1982. Effect of silymarin on chemical, functional and morphological alterations of the liver. A double-blind controlled study. Scand J Gastroenterol. 17:517-521.
47. Feher J, Desk G, Muzes G, 1989. Liver protective action of silymarin therapy in chronic alcoholic liver diseases [in Hungarian]. Orv Hetil.;130:2723-2727.
48. Fintelmann V, Albert A 1980. Proof of the therapeutic efficacy of LegalonŴ for toxic liver illnesses in a double-blind trial [translated from German]. Therapiewoche; 30:5589-5594.
49. Trinchet JC, Coste T, Levy VG, 1989. Treatment of alcoholic hepatitis with silymarin. A double-blind comparative study in 116 patients [translated from French]. Gastroenterol Clin Biol.;13:120-124.
50. Bunout D, Hirsch SB, Petermann MT, 1992. Controlled study of the effect of silymarin on alcoholic liver disease [translated from Spanish]. Rev Med Chil.;120:1370-1375.
51. Ferenci P, Dragosics B, Dittrich H, 1989. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. J Hepatol;9:105-113.
52. Benda L, Dittrich H, Ferenzi P, 1980. The influence of therapy with silymarin on the survival rate of patients with liver cirrhosis [translated from German]. Wien Klin Wochenschr.;92:678-683.
53. Pares A, Planas R, Torres M, 1998. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. J Hepatol.;28:615-621.
54. Lucena MI, Andrade RJ, de la Cruz JP, 2002. Effects of silymarin MZ-80 on oxidative stress in patients with alcoholic cirrhosis. Results of a randomized, double-blind, placebo-controlled clinical study. Int J Clin Pharmacol Thers;40:2-8.
55. Angulo P, Patel T, Jorgensen RA 2000. Silymarin in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. Hepatology. 32:897-900.
56. Schandalik R, Gatti G, Perucca E 1992. Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. Arzneimittelforschung42:964-968.
57. Barzaghi N, Crema F, Gatti G, 1990. Pharmacokinetic studies on IdB 1016, a silybin-phosphatidylcholine complex in healthy human subjects. Eur J Drug Metab Pharmacokinet15:333-338.
58. Awang D 1993. Milk thistle. Can Pharm J126:403-404.
59. Adverse Drug Reactions Advisory Committee 1999. An adverse reaction to the herbal medication milk thistle (Silybum marianum). Med J Aust. 170:218-19.
60. Giannola C, Buogo F, Forestiere G, 1985. A two-center study on the effects of silymarin in pregnant women and adult patients with so-called minor hepatic insufficiency [in Italian]. Clin Ther 114:129-135.
61. Kim DH, Jin YH, Park JB, 1994. Silymarin and its components are inhibitors of beta-glucuronidase. Biol Pharm Bull17:443445.
62. Ralph J 1994. Perkin J.C.s. I,3485.

63. Schutle K.E, Rucker G, Stigler H 1970. Arch.Pharma. 303, 7.
64. Mericili A.H 1988. Planta Medica,44,45.
65. Kalonga M 1981. Naturforch Z. B, 36,262.
66. Ahmad A.A 1989. Phytochemistry, 28,1751.
67. Fiebig M, Wagner H 1984. Planta Medica,51,310.
68. zila I, Tetenyi P, Antus S, Selignann O, chari V.M 1981. Planta Medica,43,121.
69. Arnove A., Merlini L 1979. Chem J. Soc. Chem Comm. 696.
70. Wagner H, Seligmann,L O, Horhammer M.s, Sonnenbichler 1971.Tet.Lett,1895.
71. Wagner H 1976. Naturforsch Z. B,31, 876.
72. Morazzoni P , Bombardelli E 1995. Silybum marianum (Carduus marianus). Fitoterapia; VI: 3-42.
73. Lecomte J 1975. Les propriétés pharmacologiques de la silybine et de la silymarine.Rev Med Liege; XXX: 110-4.
74. Desplaces A, Choppin J, Vogel G, 1975. The effects of silymarin on experimental phalloidine poisoning. Arzneimittelforschung 25: 89-96.
75. Choppin J, Desplaces A 1978. The effects of silybin on experimental phalloidine poisoning. Arzneimittelforschung; 28: 636-41.
76. Vogel G, Trost W. Zur 1975 anti-phalloidinaktivität der silymarine silybin und disilybin. Arzneimittelforschung; 25: 392-3.
77. Barbarino F, Neumann E, Deaciuc J, 1981. Effect of silymarin on experimental liver lesions. Rev Roum Med Intern; 19: 347-57.
78. Schriewer H, Badde R, Roth G, 1973. Die antihepatotoxische wirkung dessilymarins bei der leberschädigung durch thioacetamid. Arzneimittelforschung 23: 160-1.
79. Siegers CP, Frühling A, Younes M 1983. Influence of dithiocarb, (+)catechin and silybine on halothane hepatotoxicity in the hypoxic rat model. Acta Pharmacol Toxicol (Copenh) 53: 125-9.
80. Mourelle M, Muriel P, Favari L, 1989. Prevention of CCl4-induced liver cirrhosis by silymarin. Fundam Clin Pharmacol; 3: 183-91.
81. Luper S 1998. A review of plants used in the treatment of liver disease: part I. Altern Med Rev; 3: 410-21.
82. Skottova N, Kreeman V 1998. Silymarin as a potential hypocholesterolaemic drug. Physiol Res 47: 1-7.
83. Ferenci P, Dragosics B, Dittrich H, 1989. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. J Hepatol; 9: 10513 105-13.
84. Wagner, H., P. Diesel, and M. Seitz 1974. Chemistry and analysis of silymarin from Silybum marianum. Arzneim. Forsch. 24: 466-471.
85. Kim, N.C., T.N. Graf, C.M. Sparacino, M.C. Wani, and M.E. Wall 2003. Complete isolation and characterization of silybins and isosilybins from milk thistle (Silybum marianum). Org. Biomol. Chem. 1: 1684-1689.
86. Lee, D.Y.W.and Y.Z. Liu 2003. Molecular structure and stereochemistry of silybin A, silybin B, isosilybin A, and isosilybin B, isolated from Silybum marianum (milk thistle). J. Nat. Prod. 66: 1171-1174.
87. Martin, R.J., D.R. Lauren, W.A. Smith, D.J. Jensen, B. Deo, and J.A 2006. Douglas. Factors influencing silymarin content and composition in variegated thistle (Silybum marianum). New Zeal. J. Crop Hort. 34: 239-245.
88. Wagner H. Plant constituents with antihepatotoxic activity. In: Beal JL, Reinhard E eds 1981. Natural Products as Medicinal Agents.Stuttgart: Hippokrates-Verlag.

7/5/2014