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REVIEW ON HEPATOPROTECTIVE MEDICINAL PLANTS

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ABSTRACT

Liver is a vital body organ which play important role in metabolic activities also helps in biosynthesis, storage and digestion. Different types of liver diseases such as Hepatitis, cirrhosis, fibrosis and hepatosis. Several herbal formulations, which remain mixtures of different herbal extracts, are used for the treatment of liver infections. Hepatoprotective herbal drug containing various chemical constituents such as Alkaloids, glycosides, flavonoids, monoterpenes. Hepatoprotective medicinal drug are *Azadirachta indica* (Neem) having different parts of plant treatment and containing active constituents like Azadirechtin, Nimbin, and Nimbidinine. *Emblica officinalis* (Amla) a vital role in lipogenesis, formation of lipoproteins, and catabolism of cholesterol and having active constituents Vitamin C, tannins. *Curcuma longa* (Turmeric) having active constituents such as Volatile oils, curcuminoids. *Eclipta-alba* (Bhringraj) in Ayurveda has remained widely used as a traditional medicine for its mult-therapeutic properties and active constituents Wedilo-lactone, Wedelic acid, nicotine. *Silybus marianum* (Milk thistle) is having active constituents are silybin Silycrystin, Silydianin. The medical administration plans have been proposed to report liver diseases but the search for novel methods and formulations for treating hepatic disorders continues. Hepatoprotective herbal drugs containing extraction and isolation of the drug.

KEYWORDS: Hepatoprotective, *Emblica officinalis*, *Azadirachta indica*, *Eclipta-Alba*, *Curcuma longa*, *Silybus marianum*, Liver, Herbal drugs.

INTRODUCTION

Liver is one of the essential organs of human body which play important role in the metabolism of proteins, lipids and carbohydrates. Liver have two major hepatic disorders which have high death rate.[1] Liver is the largest internal organ in the human body and having playing important role in digestion, biosynthesis, metabolism and detoxification.[2] Liver diseases which classified as acute or chronic hepatitis (inflammatory liver diseases), hepatosis (Non inflammatory liver diseases) and cirrhosis (degenerative disorder resulting in liver fibrosis).The treatments of choice for liver diseases are conventional or synthetic drugs for the treatment of these diseases are insufficient and irregularly cause serious side effect.[3] Chronic hepatic injury may progress to liver fibrosis resulting in clinical problems and injury of the organ.[4]

The liver having as a process blood filter, by converting ammonia into urea, and by removing and emitting substances from the blood that otherwise be toxic. In addition, the liver makes proteins that control blood clotting and influence the immune system, between others.[5] Some compound holding inorganic producing hepatotoxicity are arsenic, phosphorus, copper and iron. The organic agents include certain naturally taking place plant toxins such as pyrrolizidine alkaloids, mycotoxins and bacterial toxins.[6]

In India, about 40 poly herbal commercial formulations are reputed to have hepatoprotective action it has been reported that 160 phytoconstituents from 101 plants have hepatoprotective activity. Hepatoprotective herbal drugs containing various types of chemical constituents such as phenols, coumarins, lignans, essential oil, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids, and xanthines.[7]

Herbal drugs are prescribed commonly even when their biologically active components are unknown because of their effectiveness, less side effects moderately low cost.[8] The medicinal herbs (MHs) have been widely used to prevent liver diseases and have been reported as a highly main source for the development of likely hepatic-protectants. Some known mitochondria-targeted hepatic-protectants originated from natural constituents, such as salvianolate, daidzin, and silybin.[9]

Pyllanthus niruri highly valued in the treatment of liver ailments and has remained shown to have anti-hepatitis B virus surface antigen activity in both in vivo and in vitro studies.[10]

HEPATOPROTECTIVE MEDICINAL PLANTS

Table 1: Hepatoprotective Medicinal plants.

Sr.No	Name of drug and synonym	Biological Source	Active Constituents	Uses
1	Neem (Margosa)	Aerial parts of *Azadirachta indica* (Meliaceae)	Azadirechtin, Nimbin, Nimbidinine, stigmasterol,	Insecticide, antifeedant, nematicide, Antimicrobial
2	Amla (Indian goose berry)	Dried as well as fresh fruits of *Emblica officinalis* (Euphorbiaceae)	Vitamin C, phyllemblin, tannins	Diuretics, laxative, ingredient of Triphala and Chyavanprash
3	Turmeric(Curcuma)	*Curcuma* longa (Zingiberaceae)	Volatile oil, curcuminoids, DL- ar Turmerone	Anti-inflammatory, condiment, spice,
4	Bhringraj (Eclipta) maka	Entire herb *Eclipta-alba* (Asteraceae)	Wedilo-lactone, Wedelic acid, nicotine, Alkaloid cliptine,epigenin	Brain tonic, improves complexion, hepatoprotective
5	Milk-Thistle(Silymarin)	*Silybus marianum* (Asteraceae)	Silybin Silycrystin, silydianin, neosilyhermin	Liver disorders

1) *Azadirachta indica* (Neem)

Azadirachta indica (Neem) (*Azadiracta indica* A. Juss) tree belongs to the family of (Meliaceae). Neem is one of the most versatile medicinal plants having a broad spectrum of biological activity in India and its neighboring countries subsequently immemorial. Neem seed oil and extract are proved effective against some fungi that cause infection to human body. It is used as anthelmintic, antileprotic (prevents leprosy), antibacterial, antidermatophytic activity. Neem seed spent (cake) is an active ingredient in preparation of mosquito repellent coil.[11] Azadiracta indica also has major role in traditional medicine, and leaves and fruits are the vital parts with therapeutic potential. Its active phytochemical constituents are Nimbidin, margosic acid, Nimbin, and polysaccharides.[12]

Fig. 1: Neem (*Azadirachta indica*).

Geographical Source

It is found in India, Pakistan, Bangladesh, Sri- Lanka, Thailand, Malaysia and South Africa.

Extraction

The powdered sample is (140 g) was extracted with a methanol solvent is (260 ml) by using a maceration method for 3 days. Subsequently the extraction, the sample was filtered by using a Bruckner funnel. The methanol solvent remained evaporated by using a rotary evaporator under reduced pressure at 20 C for 1 h. The crude extract became a semi solid mass (11.15 g). The methanol semi solid mass (0.53 g) was shifted into a plastic tube for antioxidant activity, total phenols and biochemical screening tests. The remaining methanol semi solid mass (10.62 g) was dissolved in distilled water (120 ml) and was stirring until the crude extract dissolved. The water solution was transferred into a separator funnel and fractionation by 20 ml and 30 ml of hexane, butanol, ethyl acetate and chloroform. After extraction, all portion were kept inside the fume hood for evaporation of the mother solvents to give hexane (0.22 g), chloroform (1.28 g), ethyl acetate (0.24 g) and butanol crude extract (2.34 g). Finally, the remaining water part was evaporated to give a water crude extract (1.35 g).[13]

Extraction for tablets

The extracts of L52 and L38 tablets were prepared by soxhlation process with ethanol and water. The shade dried whole tablet powder was packed in thimble kept in the Soxhlet apparatus and extraction was allowed to run separately using ethanol and water. Finally, the Marc was dried. Ethanol and aqueous extract were concentrated by evaporating the solvent and the obtained extracts were weighed. The physical characteristics and percentage yield of

the various extracts were reported. The dried extracts of all solvents were kept in desiccator prior to analysis.[14]

Isolation of Azadirechtin from Neem Seed Kernel

The ground Neem seed kernels (500 g) were extracted with n-hexane (4 × 500 mL) at room temperature 25 °C to separate Neem oil. The defatted need seed cake was then extracted with methanol 4 of the volume. It partition with n-hexane (250 mL) and 95% 500 mL), and the combined extract was concentrated to one-fourth aqueous methanol (250 mL) to remove the residual oil and other nonpolar constituents. The methanol extract after concentration under vacuum was again partitioned with water (250 mL) and ethyl acetate (250 mL), and the organic phase was decolorized with activated charcoal (5 g), filtered, and evaporated under vacuum to obtain a viscous concentrate (6 g). The concentrate was dissolved in ethyl acetate (10 mL) and precipitated in excess of hexane to obtain a powder enriched in Azadirechtin (20%, 5.0 g). The process was repeated again twice to further enrich Azadirechtin and yielded a powdered concentrate containing 60% Azadirechtin (2.6 g).[15]

Animal study

Animal study of Margosa oil (Neem oil) ingestion indicate that the injury sequence inductees with the rapid development of mitoses and binucleated cells, followed by mitochondrial injury, swelling, and pleomorphic with in the nuclei of hepatocytes. Propagation and hypertrophy of the endoplasmic reticulum and subsequent micro vesicular steatosis have also remained noted. It has been suggested that Margosa oil is a mitochondrial uncouples, increasing mitochondrial respiration and decreasing in mitochondrial ATP. These effects may be due to changes in fatty acid metabolism that result in a change in the proportion of acid-soluble and acid-insoluble coenzyme A esters. Uniform though some advice that supplementary therapy with L-carnitine and coenzyme A may be useful in the management of Margosa oil-induced Reye's syndrome, avoidance of oral use of this herbal product is clearly prudent.[16]

Chemical Constituents

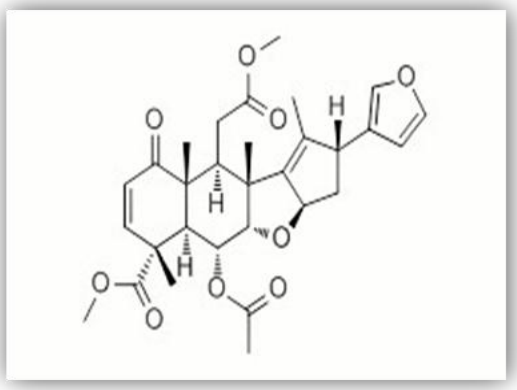

Fig. 2: Nimbin

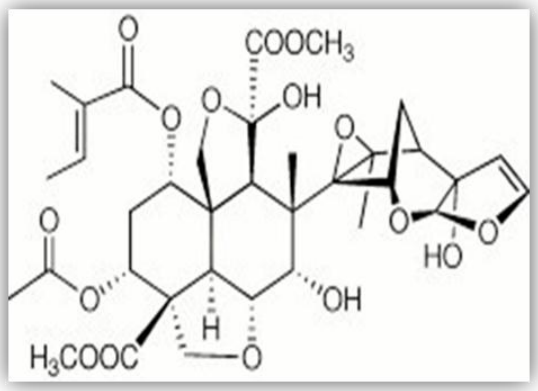

Fig. 3: Azadirechtin

Herbal Formulation

Neem Liquid Cream

The advantages of the liquid cream as against solid creams are applied easily and uniformly over large surface of the skin and they are more easily absorbed and they spread very thin layers. Formula

Amino glycol	----------	1-5/4gm
Glycerin	----------	20.00gm
Neem oil	----------	45.00gm
Sesame oil	----------	20.00gm
Cetyl alcohol	----------	4.00gm
Stearic acid	----------	3-5/4gm
Rose water	----------	115.00gm

Fig. 4: Neem Cream.

2) *Emblica officinalis* (Amla)

Phyllanthus emblica (syn. *Emblica officinalis*), commonly known as the Indian gooseberry in English, is arguably the most important medicinal agent in the traditional Indian system of Ayurvedic medicine.[17] The fruits are yellowish- green in color, globular in shape, fleshy, and smooth striated with an obviate-obtusely triangular six-celled nut. The fruits are widely used to make pickle, chutneys, and as a vegetable in various dishes.[18]

Fig. 5: Amla (*Emblica officinalis*).

Geographical Source

It is a small or medium size tree found in all deciduous forests of India. It is also found in Sri-Lanka and Myanmar.

Experimental animals and treatment protocol

Sprague-Dawley rats (150–200 g) of either sex were obtained from Central Drug Research Institute, Lucknow, and were kept in the departmental animal house, Integral University. The rats were housed separately in cages for adjustment at standard laboratory conditions (relative humidity of 50% ± 15% and temperature of 22°C±2°C with 12h light/dark cycle) for one week before and during the start of the experiment. Rats were kept on a standard pellet diet with free access throughout the housing period and were providing with drinking water ad libitum. The experiment was conducted in accordance with the guidelines of the Committee for the Resolve of Control and Supervision of Experiments on Animals. They were divided into six groups, each consisting of five rats.

Experimental procedure

Animals were divided into six groups of five animals each (n=5) Animals of Groups I, II, III, IV, and V remained pretreated orally with 1 mL/kg body weight of 1% carboxyl methyl cellulose (CMC), 1 mL/kg body weight of 1% CMC, 250 mg/kg body weight of *Emblica*

officinalis suspended in CMC, 500 mg/kg body weight of *Emblica officinalis* suspended in CMC, and 3 mg/kg body weight of on dansetron (standard drug), respectively for five repeated days. CMC was used as a suspending agent and 1% CMC as a diluent for the preparation of each EEEO or on dansetron suspensions as per the treatment protocol. After 30 minutes of this procedure, the animals were euthanized with thiopental sodium (40 mg/kg body weight, in traperitoneally), and the guts were removed. Stomachs were homogenized in 100 mL of 0.1 N sodium hydroxide. The supernatant was mixed with 4 mL of 0.5 N sodium hydroxide and the absorbance was read at the wavelength of 560nm Phenol red recovered from stomachs of Group VI rats lost immediately after administration of test meal served as standard stomach.[19]

Isolation procedure

The extract fraction of emblica fruit hull remained subjected to silica gel column chromatography, giving 12 fractions. Fractions EA-3, EA- 4, EA-5, EA-8 and EA-11 were previously known fraction EA-10 (dark brown powder 5 g), which exhibit the highest DPPH radical searching among the remaining fractions, was chromatographed on a Sephadex LH-20 column (2.4 100 cm, 25 to100 ml), and then equilibrated with 100% water. Elution was performed in sequence with 0%, 10%, 30%, 50%, 70%, 90% and 100% methanol in water. Each fraction (50 ml) was collected and subjected to TLC and HPLC analyses.[20]

Chemical test

1. Alcoholic or aqueous extract of the drug gives blue colour with ferric chloride solution.
2. Adding gelatin and sodium chloride in aqueous extract produces milky white colour.
3. In the aqueous extract of Amla add lead acetate to remove precipitate by filtration. To filtrate add solution of 2:6 dichlorophenol – indophenols the colour disappear.[21]

Chemical Constituent

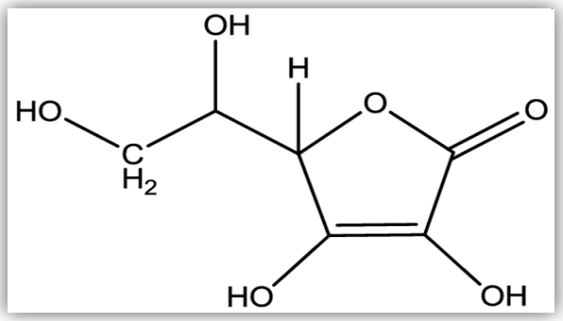

Fig. 6: Vitamin C.

Herbal Formulation

Lavender Shampoo

Formula.

Amla	----------	105.00gm
Shikakai	----------	180.00gm
Henna	----------	105.00gm
Khus	----------	105.00gm
Char	----------	100.00gm
Charilla	----------	100.00gm
Reetha	----------	200.00gm
Sodium Benzoate	----------	2.50gm
Lavender oil	----------	160.00gm
Water purified Q.S. to Make	----------	2.50 litre

Fig. 7: Lavender Shampoo.

3) *Curcuma longa* (Turmeric)

Turmeric (*Curcuma longa*) is a perennial herb belonging to ginger family (Zingiberaceae). The main biological activity of turmeric is related to Curcumin which has commonly used as curry powder. Curcumin has a polyphenol structure and has been traditional used as everyday treatment for various diseases.

It having studies suggested that Curcumin has antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, Reno protective, anti- cancer, hepatoprotective, hypoglycemic properties which are turns through pathways and regulating gene expression. Although a large body of in vitro and animal studies have supported hepatoprotective activity of Curcumin, results from single human study have remained inconclusive.[22]

Fig. 8: Turmeric (*Curcuma longa*).

Geographical Source

In India 90 percent of total output of the world. Tamil Nadu, Andhra Pradesh, Kerala. 70 species of rhizomatous herbs distributed in South East Asia and especially India, China, Thailand, Italy, Malaysia and Australia.

TP capsule preparation

The dried turmeric powder was capsulated with 500 mg in each capsule. The TP capsules were kindly provided by Korea INS Pharmaceuticals. The Curcumin content of the TP was tested using high-performance liquid chromatography at the Korea Health Supplement Institute and was found to be approximately 0.79 mg/g.[23]

Chemical test

1 Powdered drug with sulphuric acid gives crimson colour.

2 The aqueous solution of turmeric with boric acid reddish- brown colour which on addition of alkali changes to greenish-blue.

3 With acetic anhydride and concentrated sulphuric acid, it gives violet colour. When this test is observed under ultraviolet light, red fluorescence is seen.[21]

Chemical Constituent

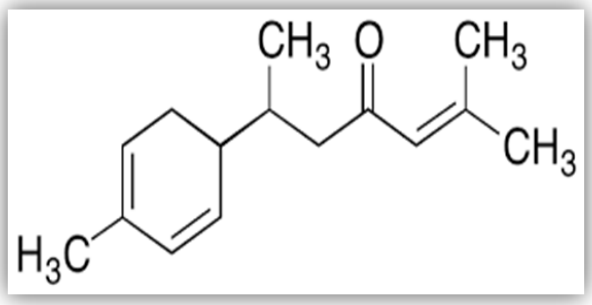

Fig. 9: DL-ar Turmerone.

HERBAL FORMULATION

Turmeric Skin freshener (astringent) Lotion

It is generally used to freshener the skin and to remove the residual traces of creams

Formula

Henna paste 3%	----------	9.50gm
Turmeric	----------	0.50gm
Tincture of benzoin	----------	1.00ml
Perfume	----------	0.30ml
Rose water Q.S. to make	--------	100.00ml

Fig. 10 Turmeric Lotion.

4) *Eclipta Alba* (Bhringraj)

Medicinal herb *Eclipta Alba*, (of the family Asteraceae) also known as "Bhringraj" in Ayurveda has been widely used as a traditional medicine for its multiple therapeutic

properties mainly leprosy, asthma, bronchitis, inflammatory diseases, hepatoprotective agent, anti-viral and anti-venom purposes (usually snake venom) and hair growth promoting activity for days. It is the best Ayurvedic option for liver cirrhosis and infective hepatitis.[24]

Fig. 11: Bhringraj (*Eclipta Alba*).

Geographical Source

In tropical parts of world and all over India, abundant in marshy places and available in all seasons.

Extraction and Purification

The freshly collected complete plants (40Kg) remained thoroughly washed, cut into small pieces, and crushed into mash in deionized water. The pulp take a diluted in 4 folding and boiled for 1 hour. The suspension was filtered complete four layers of cheese cloth and concentrated by evaporation. Take 250g of concentrate aqueous extract was homogenized in methanol: water (30:70 v/v) (0.6 L4) and incubated instant at room temperature with stirring. This mixture was extracted by ethyl acetate (0.5 L4) and dichloromethane (0.5 L3). After eliminating water from the organic layers on sodium sulfate, it remained dried to obtain (9g) dark-brown viscous material. The solvent extracted substance remained mixed with silica gel, dried under vacuum and overloaded on the top of silica gel (50g) gravity column. Elution was carried out in dichloromethane solvent with a gradient of methanol from 0% to 50%.[25]

Chemical Constituent

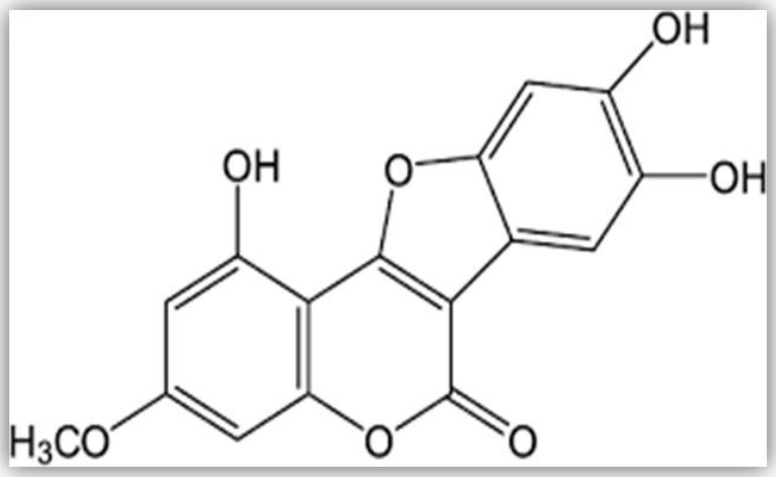

Fig. 12: Wedilo-lactone.

HERBAL FORMULATION

Bhringraj Powder

Formula

Each 100gm Powder Contain

Bhringraj Powder (*Eclipta alba*) 100%

Fig. 13: Bhringraj powder.

5) *Silybum marianum* (Milk thistle)

Silybum marianum (L.) Gaertn is herbaceous stout thistle of the family (Compositae), regarded generally as Milk Thistle. The plant growing up to 3 meter in length in rocky soils bearing large purple flowering at heads. The leaves are marked by distinct white "milky"

veins that give the plant its common name. *Silybum marianum* was used medicinally to treat disorders of the gallbladder, spleen and liver, but the most important medicinal application of *S. marianum* is its use as a hepatoprotective herbal treatment and as supportive treatment for chronic inflammatory liver disorders such as hepatitis, cirrhosis, fatty infiltration, and some other forms of liver damages due to toxic chemicals, poisonous mushrooms, and alcohol.[26]

The active constituents of thistle are flavonolignans, including silybin, silydianin and silychristin, collectively known as Silymarin. Silymarin have to protect liver cells from variety of toxins, including acetaminophen, ethanol, CCl4 and D-galactosamine. The leaves having characterized by distinct white "milky" veins that give the plant its common name. Silybin is the component with the greater biologically active and milk thistle extracts are usually standardized to contain 70–80 percent silybin. The mechanisms that provide Silymarin their hepatoprotective effects and include anti-oxidation, anti-lipids peroxidation enhanced detoxification and protection against glutathione depletion.[27]

Fig. 14: Milk Thistle (*Silybum marianum*).

Geographical Source

It found in Europe, Canada and S. America, it is known to be indigenous to Kashmir.

Animal Study

The protecting effects of the polyphenolic extracts of *Silybum marianum* and *Cichorium intybus* on the thioacetamide- induced hepatotoxicity in rat was investigated. The extracts was injected to the rats, at a dose of 25 mg kg-1(one) body weight composed with thioacetamide at a dose of 50 mg kg body weight. Expressively decrease in the activity of the rats and aminotransferase, alkaline phosphatase and bilirubin was observed in the groups

treated with extracts and thioacetamide compared with the group that treated only with thioacetamide. The level of Na+, K+ and liver weight between different groups was not significant. This find out that suggest the hepatoprotective effect of *Silybum marianum* and *Cichorium intybus* of the extracts on liver cells give in the presence of flavonoids and their antioxidant effects.[28]

Experimental animals

Male Wistar albino rats of 200-230 g were acclimatized for 7 days under standard husbandry conditions, i.e., room temperature of, relative humidity of 45%-55% and light: dark cycle of 12:12 h. All the experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC) of Krupanidhi College of Pharmacy, Bangalore, and conducted according to the Committee for the Purpose of the Control and Supervision of Experiments on Animals (CPCSEA) guidelines.[29]

Chemical Constituent

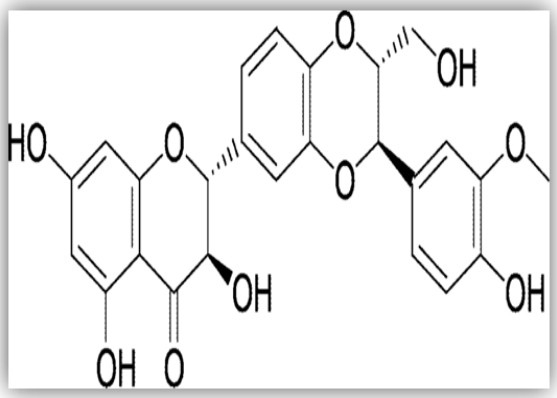

Fig. 14 Silybin.

Formulation

Silymarin Milk Thistle Capsules

Supplement Facts

Serving Sizes 1 Capsules	Serving per contain 60
Extract Dry Powder Milk Thistle	400mg

Other Ingredients

Lactose

Magnesium Stearate

Fig. 16: Silymarin Milk Thistle Capsules.

CONCLUSION

The hepatoprotective medicinal plants are used to treatment of liver disease and treat hepatic disorders such as hepatitis A, hepatitis B. *Azadirachta indica*, *Emblica officinalis*, *Curcuma longa*, *Eclipta Alba*, *Silybus marianum* are medicinal plants having effective formulation for pharmacological experiments and clinical trials. This review helpful and give the idea about the various biological activities such as hepatoprotective activity and overview of biological sources, chemical constituents and structures, geographical sources, extraction process, experimental animals and experimental procedure. Medicinal plants containing chemical testing, commercial production and herbal formulation such as Shampoo, Cream and Lotion. It also containing various dosage forms such as tablets, Capsule, powder.

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