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Review In The Flavonolignan Analysis Evaluation Of A Dry Milk Thistle (Silybum Marianum) Extract For Potential Liver Interference.

Miss.Poorva Arunkumar Kamble, Dr. Vijay R. Salunkhe, Suraj Hanmant Kolekar.

Department of Pharmaceutical Quality Assurance, Rajarambapu College of Pharmacy Kasegaon, Taluka - Walwa, Sangli, Maharashtra 415409, Maharashtra, India

ABSTRACT:-A powerful medical herb, milk thistle (Silybum marianum) has long been used to enhance liver, spleen, and kidney functions, promote milk production, alleviate period cramps, reduce depression, and diminish gallstones and jaundice. Milk thistle may greatly enhance carcass components, body weight, and feed intake in quail diets, according to studies. When added to Japanese quail diets, milk thistle powder enhanced carcass components, body weight, and feed intake. Along with a drop in HDL, ALT, and AST, blood components including albumin and total protein also improved. Plasma's antioxidant total was likewise markedly enhanced by the addition of milk thistle levels. Silymarin consumption in quail diets raised albumin, vitamin D3, and white blood cell counts.

Even in poor conditions, milk thistle is still a crop that may be utilized for a variety of reasons, despite the increased interest in natural medicine, herbal food supplements, and livestock feeding. Common agronomic procedures are difficult to use because of a number of unresolved difficulties, including the species' physiological and morphological characteristics that are similar to those of non-domesticated plants. Another significant barrier to the dissemination of this crop among farmers is the absence of trustworthy field data needed to establish appropriate planting practices.

The purpose of this study is to provide current knowledge on the primary morphological and phytochemical properties, agronomic aspects, and new applications of milk thistle. In order to assist farmers in growing this difficult and resource-rich crop, it also fills in technical knowledge gaps and specifies additional objectives for experimental activities.

KEYWORDS:- Alternative Crops, Bioactive Compounds, Low-Input Management, Medicinal Plants, Milk Thistle, Silymarin.

INTRODUCTION:- Humans are exposed to various toxins and poisons through air, food, and water, causing dangerous effects related to exposure time. Currently, focus is on drug discovery from herbal medicines, which play a crucial role in preventing diseases and preventing non-organ or organ toxicity.[1]

For more than 2,000 years, milk thistle, a spiky plant belonging to the Asteraceae family, has been used medicinally, mostly to cure liver illness and shield the liver from harmful toxins. The presence of a flavonoid complex termed silymarin, which is made up of a combination of silybin, is associated with the plant's medicinal

properties.[2] Recent studies have broadened the application of silymarin to include the possibility of treating more diseases and conditions. Silymarin stimulates protein biosynthesis, increases breastfeeding, has immune-modulatory action, and is an antioxidant, anti-inflammatory, and antifibrotic substance. Additionally, it suppresses mitogenic signals, DNA synthesis, and cell proliferation in human cervical, breast, and prostate cancer cells. The plant's achenes have the greatest concentration of silymarin.[3]

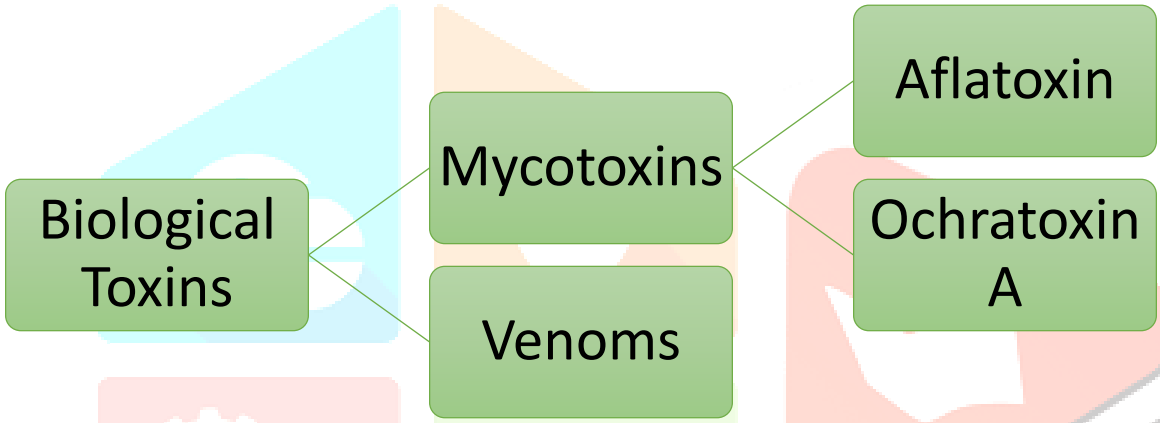
The morphological and phytochemical traits of milk thistle, a plant with possible use in Mediterranean climates, are covered in this paper. It also draws attention to the fact that S. marianum is a noxious plant in some places, including Pakistan, where infestations can reduce wheat output by 7% to 37%. The plant's massive rosette, which may reach a diameter of one meter, can dispense with other grassland plants and make it more difficult for cattle to roam about and graze. Furthermore, cattle may become intoxicated after consuming the plant due to its capacity to absorb nitrogen, particularly in the early stages of wilting. In order to guarantee the plant's widespread cultivation and possible advantages, the review highlights the necessity of addressing these limitations.[4,5]

METHODS:- This study of the literature examines the antidotal effects of milk thistle and its constituents, classifying them as chemical and biological toxic agents. The review was carried out by using pertinent keywords from databases such as Science Direct, Web of ScienceVR, SciVerse ScopusVR, and PubMedVR. There was no time restriction on the inclusion of both in vitro and in vivo investigations.[6]

MILK THISTLE'S FLAVONOID CHARACTERISTICS:- Among the many flavonoids found in milk thistle fruits, silymarin, a combination of flavonolignans with potent antioxidant properties, makes up the majority of the fruit. 50% of silymarin is made up of silybin, the main flavonolignan, which is followed by isosilibine, silydianin, and sily chrysanthemum. Plant stems and seeds contain larger amounts of silydianin, which conjugates dangerous free radicals and inhibits pre-inflammatory reactions. Seed extract absorbs 20% to 50% after oral treatment, with phosphatidylcholine complexes absorbing more.[7]

It has been demonstrated that milk thistle, a plant high in flavonoids and antioxidants, strengthens the body's defenses against illness. It is useful in treating conditions like high blood lipids, vascular blockage, atherosclerosis plaque formation, toxicity, kidney disorders, drug poisoning, liver disorders, feed poisoning, chemical toxicity, viral diseases, and neurological disorders because its vitamin and iron content boosts hematopoiesis. Special substances included in milk thistle seeds, such as histamine and resin, aid to fortify the body and ease persistent constipation. Antinutritional chemicals like tannin, which may attach to extracellular enzymes and alter materials like hemicellulose, are also present in the plant. Milk thistle tannins can impact how proteins are digested, reducing feed intake and perhaps boosting lamb's microbial digestion. Tannin's detrimental impact on protein digestibility, however, can result from the breakdown of tannin protein linkages during the enzymatic digestion stage. The nitrate content of milk thistle may potentially be harmful to animals that eat the plant.[8,9]

SOURCE AND DISPERSAL:- Native to the Mediterranean basin, milk thistle is a species of the Mediterranean-Turanic chorotype that has spread to other continents. With the exception of Friuli, the majority of the Po Valley, and the Alps, it is found all throughout Italy between 0 and 1100 meters above sea level. For more than 2,000 years, milk thistle has been used medicinally, mostly to treat liver conditions. Dioscorides and Plinius the Elder later made reference to the plant, although Theophrastus was the first to describe it. Today, the plant is found all over the world, both as a crop and in wild populations. It is mostly grown for its silymarin. Natural habitats for milk thistle include highly disturbed, productive areas as well as anthropogenic locations such as roadside ditches. Because of its exceptional seed production, quick wind distribution, and vitality, it spreads readily across cultivated areas. For three to four years, or even up to nine years, seeds buried in soil can continue to grow. In warmer and colder regions, milk thistle is a harmful pest on agricultural land because it is hostile and competitive with crops in many farmed areas.[10,11]



(Figure 1)

BIOLOGICAL TOXINS:- Studies have demonstrated the antidotal or protective properties of milk thistle and its secondary metabolites against biological toxins such as bacterial toxins, snake venoms, and mycotoxins. These effects include decreasing TNF-a release, raising Bcl-2 protein levels, inhibiting caspase-3 activation, neutralizing phospholipase A2 and proteases, and having anti-oxidative, anti-inflammatory, and anti-apoptotic qualities.(fig 1)[12]

Mycotoxins:-

- Aflatoxin:- Aspergillus parasiticus and A. flavus generate the secondary fungal metabolites known as aflatoxins B1, B2, G1, and G2, which are dangerous food pollutants. The most powerful kind, aflatoxin B1 (AFB), has hepatotoxic, hepatocarcinogenic, and genomic consequences on humans and several animal species. In adult male albino rats, silymarin (20 mg/kg/day) demonstrated antioxidant efficacy against lipid peroxidation and associated enzymes produced by AFB. Additionally, the silymarin phytosome, commonly known as the silymarin-phospholipid complex, showed protective properties against aflatoxicosis. Administration of silymarin phytosomes reduced the negative effects of AFB1 in male broiler chickens. When AFB is present in the diet, milk thistle may boost immune function and growth performance whereas AFB might cause immunosuppression and growth retardation.[13]

- Ochratoxin A:- A naturally occurring fungal mycotoxin, ochratoxin A (OTA) is generated by Aspergillus and Penicillium species. OTA possesses immunotoxic, hepatotoxic, nephrotoxic, and carcinogenic properties. Reduced antibody responses, decreased natural killer (NK) cell activity, and decreased macrophage bacteriolytic potential were the mechanisms by which OTA immunosuppressive effects were achieved. The preventive benefits of silibinin (12.5 lg/mL) against OTA-induced hepatotoxicity (2.5 lmol/L) have been established. This action was accomplished by reducing the cytotoxicity of OTA and inhibiting the production of TNF-a from isolated rat Kupffer cells and perfused rat livers. In a different study, researchers created an OTA-induced immunotoxic model in white Leghorn cockerels to assess the protective benefits of silymarin. They demonstrated that silymarin supplements (10 g/kg) might lessen the immunotoxic impact of OTA (1 mg/kg).[14]

Venoms:- According to research, phospholipase A2, hyaluronidases, and Zn2þ metalloproteases are crucial for the development and progression of snake venom toxicity. Agents having anti-myotoxic, anti-hemorrhagic, and anti-edematogenic properties are examples of venom antidotes. The venom of Bothrops jararaca snakes can be avoided by using natural products. By preventing the production of snake venom PLA2, silymarin (100 mg/kg) given orally an hour before to envenomation can shield mice against jararaca venom. A cocktail of N,N,N',N'-tetrakis (2-pyridylmethyl) ethane-1,2-diamine and silymarin was tested for its ability to reduce the increasing toxicity caused by the venom of Echis carinatus. Furthermore, silymarin (200 mg/kg) taken orally has demonstrated protective properties against the venom of Hemiscorpius lepturus scorpions.[15,16]

GENETICS AND BREEDING:- There are two species in the Silybum genus: S. marianum (L.) Gaertn. and S. eburneum Coss. and Durieu. Given their ease of interfertility and cross-pollination, these two forms are probably variations of the same species. Under field circumstances, the average outcrossing rate for the diploid species S. marianum is 2%. Although the plant is becoming more and more popular as a multifunctional crop and is economically significant in the herbal market, it has not been extensively bred. Since the early 2000s, there has been little genetic research done, mostly to create high-yielding cultivars with higher silymarin content. Because of this, farmed plants continue to exhibit characteristics of undomesticated species, like asynchronous blooming, prickly leaves, fruit dispersion at maturity, and variable yield quality and stability. These characteristics are widespread in medicinal and aromatic plants (MAPs) and are frequently evolved by the plant to guarantee the best possible reproductive outcomes and environmental adaptability. As a result, a simple breeding process is required to overcome these limitations and enhance the plant's stability and yield quality.[17,18]

CHEMICAL COMPOUNDS:- Silybin, silibinin A and B, silicristin, silidianin, apigenin, dehydrosilybin, deoxysilyn cristin, and deoxysilyn dianin are among the chemicals found in the seeds of this plant. Up to 4% silymarin, a mixture of flavonoids including silibinin A and B, silidianin, silicristin, and dihydroxysilibin, is present in the dried seed extract. Myristic, palmitic, and stearic acids, as well as sylandrin, silybinom, and silyhermin, are additional flavonolignans. Additionally, the dried seeds include up to 20% oil that has little therapeutic use. Silymarin is readily absorbed from the digestive system and takes two to four hours to reach its

peak blood concentration. Eighty percent of it is eliminated from the bile during its six-hour half-life. The most potent hepatoprotective and antioxidant component of silymarin is sylibin.[19]

PHARMACOLOGY AND THERAPEUTIC EFFECTS:- Silybum marianum or its derivatives have numerous health benefits, including hepatoprotection, renal protection, hypolipidemia, anti-atherosclerosis, cardiovascular protection, insulin resistance prevention, cancer prevention, and Alzheimer's prevention. Traditional medicine in Europe uses silymarin for treating various diseases and liver disorders.[20]

Liver Conditions:- For more than 2000 years, Silybum marianum has been used as a hepatoprotective. Numerous clinical and laboratory investigations have shown how well it protects the liver against poisons including acetaminophen, carbon tetrachloride, and tetrachloromethane. Through a number of processes, such as antioxidant activity, free radical scavenging, elevated cellular glutathione concentration, DNA polymerase activation, and hepatocellular membrane stability, silymarin produces the hepatoprotective action.[21]

The primary causes of silymarin's hepatoprotective effects are its antioxidant activity and capacity to scavenge free radicals. Glutathione modulation and the resulting membrane stability reflect this action. Silymarin increases ribosomal RNA production and liver cell regeneration by stimulating DNA polymerase. By blocking the 5-lipoxygenase cycle and preventing the liver's Kupffer cells from producing leukotrienes and free radicals, it also reduces the size of the enlarged liver.[22]

Silymarin's impact on cellular permeability is linked to changes in membrane lipids, such as phospholipids and cholesterol, and it also affects other lipid compartments in the liver that may have an impact on lipoprotein absorption and secretion. It has been proposed that silymarin may reduce triglyceride production in the liver, however there is little information on how silymarin affects triglyceride metabolism in the liver.[23]

Live animals have demonstrated that silymarin shields liver cells from a range of illnesses, such as those caused by chemicals, viruses, and naturally occurring toxins. By preventing liver poisoning and the formation of peroxidation lipids brought on by the injection of halothane, thallium tetrachloride, carbon tetrachloride, and acetaminophen, silymarin pretreatment shields lab animals from Amanitamuscaria toxicity.[24]

According to clinical studies, people with liver problems have lower levels of aspartate transaminase and alanine transaminase in their blood serum after taking 120 mg of silybin twice a week for two months. When silymarin extract is administered for eight weeks, 88% of patients have a substantial drop in liver enzyme levels, with fewer than 1% experiencing mild side effects.

Silymarin can reduce morality in patients by up to 80% when administered to treat intoxication brought on by Amanita muscaria. Up to 48 hours after Amanita muscaria intoxication, intravenous silybin (20–50 mg/kg/day for 3–4 days) totally prevents liver damage.[25]

However, there are conflicting findings when silymarin is used to treat alcohol-induced liver damage. After four weeks, silymarin (420 mg/day) significantly decreased enzyme levels and liver histology evaluation in 300 individuals with alcohol-induced liver damage, according to a multiple controlled double-blind trial. Conversely, when administered three times a day at dosages of 280 and 150 mg, silymarin did not lower mortality as compared to the control group in a double-blind research.[26]

To sum up, silymarin functions as an antioxidant, lowering carbon tetrachloride-induced metabolic activation and preventing chain rupture.

In hepatitis patients, silymarin therapy has been demonstrated to provide inconsistent outcomes. Treatment with 240 mg silipide twice daily for a week dramatically decreased γ-glutamyl transpeptidase levels in comparison to the control group, according to a double-blind trial conducted on 20 patients with active chronic hepatitis. Another research of 157 individuals with viral hepatitis revealed that the treatment group's levels of aspartate transaminase, alanine transaminase, and bilirubin were significantly lower than those of the control group. However, 151 individuals with viral hepatitis were examined, and silymarin did not improve their conditions.[27]

By promoting the repair of liver tissue through enhanced protein synthesis, silymarin prevents liver damage. Additionally, it promotes DNA synthesis and ribosome production, which are exclusively triggered in liver damage. Silibinin may have hepatoprotective effects against Amanitaphalloides poisoning because it suppresses the liver cytochrome P450 (CYP) detoxification pathway. In addition to limiting the harmful effects of the toxin, this suppression of toxin bioactivation guards against free radicals produced by CYP system enzymes.[28]

Inhibiting cellular permeability, which is linked to changes in membrane lipids, is one of silymarin's most potent characteristics. This implies that silymarin could affect the absorption and secretion of lipoproteins. It has been demonstrated that silymarin and silibinin decrease phospholipid synthesis and turnover in the rat liver, decrease the incorporation of labeled glycerol into the lipids of isolated hepatocytes, promote phosphatidylcholine synthesis, and raise cholinephosphate cytidylyltransferase activity in the rat liver.[29]

Silymarin may reduce triglyceride production and partially counteract the rise in triglycerides and total lipids caused by carbon tetrachloride in the liver. Additionally, it offers defense against lipid peroxidation and carbon tetrachloride's hepatotoxicity.[30]

HYPOGLYCEMIC ACTIVITY:- In rats with hyperlipidemia, silymarin has been shown to lower levels of phospholipids, especially those carried by low-density lipoprotein, as well as cholesterol and low-density lipoprotein. According to laboratory research, silymarin prevents the consequences of high cholesterol and lessens the formation of atherosclerotic plaque in rats and rabbits with hypercholesterolemia by improving the excretion of low-density lipoproteins and lowering the production of cholesterol in the liver cells. Silymarin can counteract the decrease in serum-free fatty acids brought on by thioacetamide and correct the rise in plasma lipids after carbon tetrachloride injection. Silymarin reduces low-density lipoprotein in plasma and enhances low-density lipoprotein binding to hepatocytes in hepatic damage brought on by paracetamol. According to clinical studies, silymarin can help people with hypercholesterolemia lower their blood cholesterol levels. Patients who took 420 mg doses of silymarin daily saw a rise in high-density lipoprotein cholesterol and a decrease in gallbladder cholesterol.[31]

RENAL DISEASES:- In lab mice, silymarin, a substance present in many foods, has been shown to prevent kidney damage and abnormalities. Additionally, it promotes 30% more cell replication and improves the production of proteins and nucleic acids, both of which support kidney function. It has been demonstrated that silymarin helps diabetic patients with nephropathy, keeping them from dying too soon as a result of the condition.

After three months of silymarin use, a 50% reduction in the urine albumin-creatinine ratio was seen in 60 diabetic individuals whose urinary albumin excretion exceeded 300 mg/day. Silymarin's potential benefits for diabetic nephropathy and proteinuria in people with type 2 diabetes who have overt nephropathy have been connected to its anti-inflammatory and antioxidant properties. In individuals with type 2 diabetes who have proteinuria and overt nephropathy, silymarin may be added to renin-angiotensin system inhibitors to lower malondialdehyde, albumin excretion in the urine, and tumor necrosis factor-α.[32]

NERVOUS SYSTEM:- Rat pups that consume alcohol may have a decreased capacity for learning; however, this impact is avoided when silymarin is given concurrently. Silymarin can enhance nerve transmission in diabetic individuals and prevent brain damage brought on by blockages in brain arteries. Diabetes mellitus impairs cognitive, memory, and learning abilities. In diabetic rats, silymarin at a dosage of 100 mg/kg improves memory recall and storage but not short-term spatial memory. The reduction of lipid peroxidation in hippocampal tissue is thought to be the cause of silymarin's beneficial effects.[33]

ENDOCRINE GLAND:- According to an animal research, silymarin shields the pancreas against substances like cyclosporine and alloxan. Over a 6-month period, treatment of 60 individuals with insulin-resistant diabetes resulted in notable decreases in insulin demand, glycosuria, daily mean glucose levels, and fasting blood glucose.[34]

HEMATOLOGIC EFFECTS:- The main characteristic of silymarin is that it has antioxidant effects on blood molecules, which are important since oxidation of blood chemicals can exacerbate chronic disorders like cardiovascular disease. Additionally, it helps stop copper and other free radicals created from oxygen from hemolyzing red blood cells.[35]

IMMUNE SYSTEM:- According to lab studies, silymarin has no effect on chemotactic or phagocytic activities or non-stimulated neutrophils. On the other hand, it prevents myeloperoxidase release when neutrophils are stimulated, and leukocyte mobility inhibitors may not work as well when neutrophils are cultured with silymarin. In 40 patients with alcoholic liver cancer, silymarin treatment decreased the number of T8þ cells, inhibited lymphocytotoxicity, and boosted lectin as a stimulator of lymphoblast deformation.[36]

ANTICANCER EFFECTS:- It has been discovered that silymarin and silybin have chemopreventive effects on a number of cancer types, including animal breast, prostate, and epidermal cancer. Additionally, they have cytoprotective properties on human breast and prostate cancer cells. The Adriamycin effect of inhibiting cell growth can be enhanced by pre-inoculation with silybin. However, there is worry that this plant may interact with chemotherapy medications through biochemical peroxidative pathways because of its potent antioxidant activities. There is no proof that silybin interacts with the cytotoxic effects of doxorubicin or other cytotoxic drugs, although it can enhance cytotoxic interactions with them. According to research on animals, silymarin can stop the development of cancer in rat models of epithelial tumors and stimulate hepatic DNA in noncancerous cells. In people After taking 450 mg of silymarin daily, a man with hepatocellular cancer exhibited improvement.[37,38]

OSTEOPOROSIS:- Silybum marianum contains taxifolin, which has significant estro-genic qualities. Furthermore, silymarin's flavonoid molecules can influence femur metaphysis independently of with B estrogenic receptors by acting on the uterus as an estrogenic agonist.[39]

PSORIASIS:- Psoriasis has long been treated with silymarin. By eliminating undesirable metabolites from bodily cells, particularly the liver, and by blocking the cAMP cycle and leukotriene formation, it may help treat psoriasis. Patients with psoriasis may have an elevated cAMP cycle and increased leukotriene production, which silymarin may suppress to have positive results.[40]

SIDE EFFECTS AND TOXICITIES:- In individuals with documented kiwi fruit allergies, Silybum marianum, a plant with anti-inflammatory qualities, has been connected to allergic responses including anaphylaxis. Even when given in large quantities to animals, it has been shown to have no discernible adverse effects. According to some specialists, the plant's stimulatory actions on the liver and gallbladder may cause a slight laxative effect in the early days of ingestion. But in a randomized controlled experiment, silymarin's adverse effects hardly outweighed those of the placebo. The herb is safe to use for an extended period of time and does not cause abnormalities.[41]

There is no research on silymarin's impact on glucose metabolism changes in persons without liver disease, although it can reduce insulin demand in diabetic patients with alcohol-related liver cirrhosis. Taking 400 mg silymarin twice a day for 90 days reduced lipoperoxidase and liver damage in comparison to the control group, according to a double-blind study conducted on six female patients who were frequent users of psychoactive substances.[42]

Silymarin can lessen the negative effects of chemical medications, including blood lipid-lowering, anticancer, and psychotropic medications. However, there is no proof that people with organ-specific illnesses or those who are ill may experience negative herb responses.[43]

CONSUMPTION DURING BREASTFEEDING AND PREGNANCY:- Silybum marianum can be used by youngsters, pregnant women, and nursing mothers; however, there is no evidence of long-term adverse effects. It is recommended for preventing liver damage and treating pruritus in pregnant women linked to bile duct blockage. For pregnant women who have been poisoned by Amanita mushrooms, administration is crucial. Long-term impacts, however, have not been established.[44]

DOSE:- The suggested dosages of plant silymarin should be modified when used in conjunction with other therapies because they are based on dosages that are often given. The kind and severity of the ailment, as well as the unique qualities of each patient, influence the dosage. Herb experts recommend a variety of dosages for people; the majority of research uses concentrated standard formulations that contain 70% to 80% silymarin. 100–200 mg of standardized plant extract should be taken orally twice daily with meals. Because of its greater reabsorption, silybin has been introduced in combination with phosphatidylcholine. In order to treat acute hepatotoxicity brought on by Amanita poison, silybin was administered intravenously in Europe at a dose of 20 to 50 mg/kg of body weight. The inability of silymarin to dissolve in water makes tea an undesirable administration route. The inability of silymarin to dissolve in water makes tea an undesirable administration

route. However, if the seeds are crushed and fried, silymarin can be consumed as herbal tea. Three times a day with meals, 12 to 15 g of fried and pulverized grains is the typical dosage.[45,46]

DISCUSSION:- Silybum marianum, another name for silymarin, is a strong antioxidant that scavenges free radicals and inhibits lipid peroxidation. By raising cellular glutathione, controlling the permeability of the liver cells' membranes, and preventing stellate hepatocytes from transforming into myofibrills—which causes collagen fiber deposition that results in cirrhosis—it has been demonstrated to protect the liver.[47]

Strong antioxidants and free radical scavengers, silymarin and silybin replenish internal antioxidants and guard against oxidative stress. Many pathological illnesses, including chronic inflammation, neurological disorders, diabetes, atherosclerosis, cardiovascular diseases, cancer, gastrointestinal disorders, infectious diseases, and wound complications, are linked to oxidative stress. Antioxidants have the capacity to reverse unfavorable circumstances, and both clinical and experimental studies have shown encouraging outcomes for the use of plant-based antioxidants in the prevention and treatment of serious illnesses.[48]

Silymarin provides protection against chemically induced lipid peroxidation by acting as an antioxidant in human plasma and in human liver and pulmonary microsomes. Studies on animals have demonstrated that oxidative stress and liver damage are caused by increasing chronic iron overload; silymarin's antioxidant activity can prevent this toxicity. According to human research, silymarin may increase the antioxidant effects of alcoholic cirrhosis by boosting superoxide dismutase in red blood cells and lymphocytes.[49]

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