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A REVIEW ON SILYMARIN AS A PROMINENT HETEROPROTECTIVE AGENT

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Abstract:

Widespread use of herbal drugs because of their protective effects on different organs toxicity has been shown in many studies. These protective effects have been illustrated in the fields of nephrotoxicity, hepatotoxicity, viral hepatitis, cancer, in vitro fertilization, neurotoxicity, depression, lung diseases, prostate diseases etc. Silymarin has cytoprotection activities due to its antioxidant activity and radical scavenging. The possible known mechanisms of action of silymarin protection are blockade and adjustment of cell transporters, p-glycoprotein, estrogenic and nuclear receptors. Moreover, silymarin anti-inflammatory effects through reduction of TNF-α, protective effects on erythrocyte lysis and cisplatin-induced acute nephrotoxicity have been indicated in some studies. Silymarin has also inhibited apoptosis and follicular development in patients undergoing IVF. Basis on such data, silymarin can be served as a novel medication in complementary medicine.

Keywords: Antioxidant, Cancer, Liver, Medicinal plant, Silymarin

Introduction:

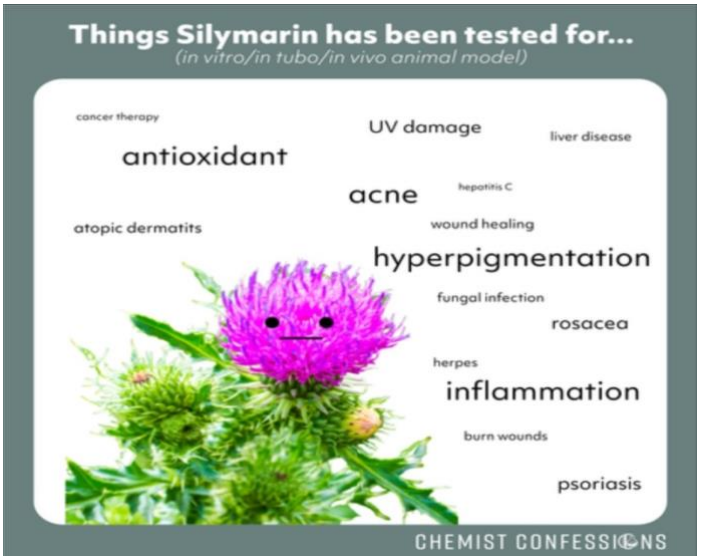

Figure:- Silybum marianum

Silybum marianum L. (Milk thistle), a member of Carduus marianum family, is an ancient medicinal plant which has been used for centuries for treatment of different diseases such as liver and gallbladder disorders, protecting liver against snake bite and insect stings, mushroom poisoning and alcohol abuse (1). This plant can be found in Kashmir, North America, Canada and Mexico with large leaves and a reddish-purple flower that are all thorny and the medicinal part of the plant is either the seeds or fruits (2).

Milk thistle was first grown in Europe and used as a liver tonic as it was said to be able to open the obstructions of the liver and spleen, and thereby was good for jaundice (Nicolas Culpepper, 1616-1654)(3). Moreover, this herb has been used for centuries as a natural treatment for upper gastrointestinal tract and digestive problems, liver and biliary tract diseases, menstrual disorders and varicose veins (4,5).

The very first usage of Milk thistle, however, was for its hepatoprotectant and antioxidant activities. Silymarin is the active component of this herb, which is a complex of other components, mainly silybin A, silybin B, isosilybin A, isosilybin B and also other flavonolignants such as silychristin, neosilyhermin, silyhermin and silydianin which exists in its fruit and seeds more than the other parts.

Silymarin effects have also been indicated in various illnesses of different organs such as prostate, lungs, CNS, kidneys, pancreas, and skin (9).

Silymarin has besides antifibrotic, immunomodulating, anti-inflammatory effects as well as antioxidant properties by scavenging free radicals and increasing the glutathione concentrations, so that it can be used in hepatitis and hepatic cirrhosis treatment and in mushroom poisoning (5, 7,10).

According to pharmacological studies, silymarin has been accepted as a safe herbal product, since using the physiological doses of silymarin is not toxic unless the improper administration of therapeutic dosages (10-12)

Mechanism of action:

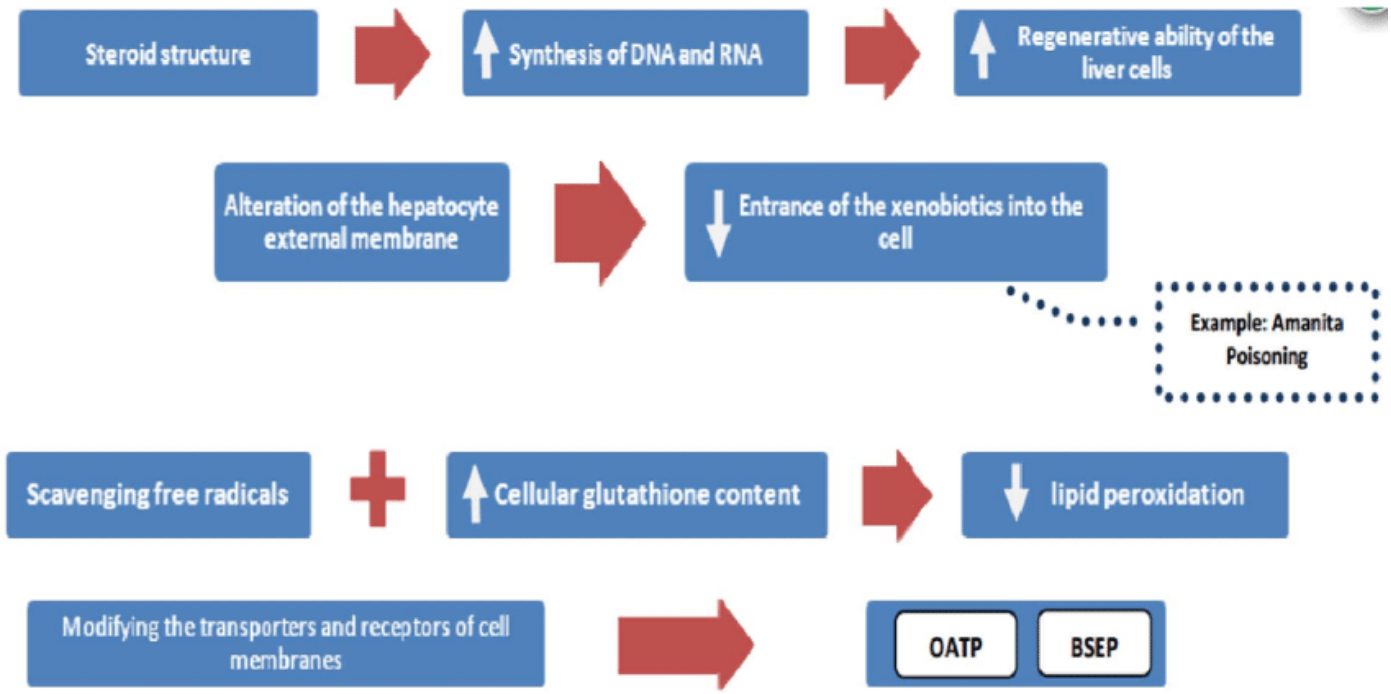

Figure:- Mechanism of action

Chemical nature of silymarin:

Flavonolignans are the common name of silymarin compounds. Even this basic name indicates that the molecular structure of this compound can be separated into two components, one is hybrid or the other is non-conventional lignans which are more suitable for the silymarin compounds group. Flavonolignans are naturally found in the form of stereoisomers because the basic structure contains several symmetrical centers. The chemical structure of milk thistle was described in Figure 1.The main silymarin compounds reported in the scientific literature are taxifolin, silybin A and B, silychristin, isosilychristin, silydianin, and silychristin. Naturally occurring iso- and trans-diastereoisomers of silibinin (silybin A and silybin B) and isosilibin (issilybin A and issilybin B).[13]

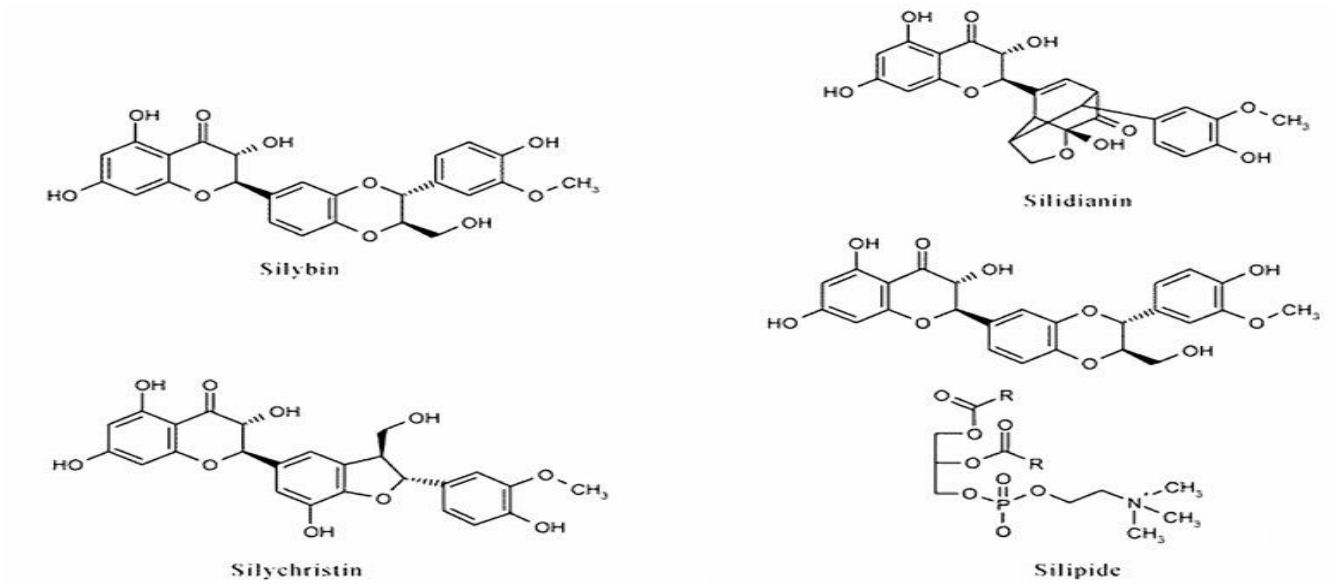

Figure:-. Chemical structure of the basic components of Silymarin.

EVIDENCE FROM STUDIES OF SILYMARIN AS A HEPATIC PROTECTOR AGAINST ETHANOL:

Silymarin has both hepatoprotective and regenerative actions. The mechanism of action is a reduction of the FR formed by toxins that damage the cell membranes (LPO) and competitive inhibition through hepatocyte external cell membrane modification. Silymarin forms a complex that impedes the entrance of toxins into the interior of liver cells. Additionally, silymarin metabolically stimulates hepatic cells and activates the RNA iosynthesis of ribosomes to stimulate protein formation[14]. In a study published by Sandoval et al, the authors observed a silymarin protection effect in rat hepatic cells when they used it as a comparison factor to measure liver weight/animal weight % (hepatomegaly). The hepatomegaly was reduced compared to other groups that were administered antioxidant substances. There was no significant difference observed between the silymarin group and the silymarin-alcohol group. This result suggests liver protection by silymarin. Silymarin enhances hepatic glutathione generation by elevating cysteine availability and inducing cysteine synthesis while inhibiting its catabolism to taurine. The regulation of cysteine synthesis may subsequently contribute to the antioxidant defense[15]. Silymarin reduced collagen accumulation by 30% in biliary fibrosis induced in rats. A study in humans reported a slight increase in the survival of patients with cirrhotic alcoholism compared with untreated controls. Silymarin is perhaps the most frequently used natural compound for the treatment of hepatic diseases worldwide due to its antioxidant, anti-inflammatory, and anti-fibrotic activities[16].

Study conducted with guinea pigs (Cavia porcellus) examining hepatic fibrosis induced through the administration of Et-OH (4/kg of weight/d) for 90 d revealed a significant reduction of lesion markers such as ALT, AST, and γ-glutamyl after silymarin treatment. The gene expressions of cytochrome 450 2E1 (CYP2E1), TNF-α, transforming growth factor beta-1 (TGF-β1), and nuclear factor kappa-light-chain-enhancer of activated B cells-1 were also reduced. There was also a reduction in FR and reduced markers of fibrosis such as alpha smooth muscle actin, collagen α 1(I), and in the caspase cytotoxicity marker. However, silymarin was less effective than vitamin C in this study. This result indicates that vitamin C is more effective in reducing the markers of damage and the production of ROS during Et-OH-induced lesions[33]. Another study evaluated the hepatoprotective effect by measuring the level of antioxidants and the effect of body weight (bw) in rats exposed to Et-OH (1.6 g/kg of bw for 4 wk)[16]. The results revealed that intoxication by Et-OH influences the bw of rats and the levels of thiobarbituric acid reactive substances (TBARS). The activity of the enzymes superoxide dismutase (SOD) and glutathione-S-transferase (GST) increased significantly. Conversely, glutathione (GSH), the activity of glutathione reductase (GR), glutathione peroxidase, and catalase (CAT) were reduced by exposure to Et-OH. The rats that received silybin and ascorbic acid had attenuated lesion markers, although the effect was greater in the group that received ascorbic acid than in the group treated with silybin. The study also concluded that stopping alcohol intake favors hepatic regeneration. Thus, it is more effective to take preventive measures than to implement curative treatment[17]. A mouse study examining the antioxidant, immunomodulatory activity and vascular function

of mice showed a significant increase in OS levels in animals that received ethanol (1.6 g/kg per bw/d during 12 wk). Ethanol increased the production of TBARS, nitrite levels, and the activity of GST. Ethanol also significantly diminished the content of GSH and the activity of SOD, CAT, GPX, and GR. Mice that received Et-OH plus silymarin (250 mg/kg of bw/d for 12 wk) normalized the altered parameters. In addition, the silymarin-treated mice had reduced levels of interleukin-10 (IL-10), TNF-α, interferon (IFN), IFN-γ, vascular endothelial growth factor-A, and TGF-1β. The treatment also reduced the levels of IL-4 in the blood. The results of silymarin treatment were similar to mice that received vitamin C treatment[18].

Hepatoprotection:

Liver is the key organ of metabolism and excretion is continuously and variedly exposed to xenobiotics because of its strategic placement in the body. Toxins absorb from the intestinal tract first enter the liver resulting in a variety of liver disorders. Thus, liver diseases remain one of the serious health problems. Liver damage ranges from acute hepatitis to hepatocellular carcinoma, being caused through apoptosis, necrosis, inflammation, immune response, fibrosis, ischemia, altered gene expression, and regeneration [19].

For many years, silymarin has been used as a "hepatoprotectant". Although the mechanism of action is not completely demonstrated, silymarin has been reported to have antioxidant, immunomodulatory, antifibrotic, antiproliferative, and antiviral properties. Silymarin has a short half-life and quick conjugation in the liver and principal excretion in bile. In means of controlling hepatic inflammation in vivo, it should be used with high or repeated oral doses [20].

Oral post-treatment with silymarin (50 mg/kg for 30 days) in rats extensively inverted the liver tissue changes induced by diethylnitrosamine and presented a relatively full protection [21].

HepG2 -cells death occurs via inhibition of Akt kinase stimulated by palmitate exposure and silymarin prevents this inhibition as it has hepatoprotective activity different from its antioxidant property.

In a clinical trial using silymarin in alcoholic patients with confirmed liver cirrhosis, silymarin (150 mg/three times per day) administered for two years and no influence of silymarin was seen in case of survival and clinical course of the disease in comparison to the sham group.

Prevention and treatment of Cancers:

Effects of silymarin or silybinin on breast cancer[27-28] ovarian cancer, lung cancer [29], skin cancer [30] prostate cancer [31-33], cervical cancer, bladder cancer, liver carcinoma[34], and colon cancer [35], have been reported [6].

Mechanism of cytoprotective activity of silybin related to antioxidative and radical-scavenging effects as well as the specific receptor interaction and modulation of a variety of cell-signaling pathways e.g. NF-kappa B, suppression of EGFR-MAPK/ERK1/2 signaling and IGF-receptor signaling [9]. In addition, Anti-apoptotic effect of silymarin against UV irradiation has been revealed by up-regulation of tumor-suppressor genes p53- and p21CIP1 [4,36].

Silymarin has been shown to have anti-angiogenic property in different kinds of cancers, which is one of the basic treatments of cancer. Moreover, previous studies have shown silymarin and silybin anti-angiogenic activity in human umbilical vein endothelial cells (HUVEC) dose-dependently by mechanism of decreasing of vascular endothelial growth factor (VEGF) and matrix metalloproteinase-2 (MMP-2) secretion Down-regulation of EGFR signaling by silymarin.

Pharmacological effect of silymarin:

Effect of silymarin on oxidative stress:

Various studies revealed that Silymarin could exert antioxidant properties in several mechanisms, which includes direct hindrance in free radical production, progression and enhancement of antioxidant enzyme activity by the transcription factor, and activation of an array of vitagenes which are ultimately responsible for protective molecule synthesis.[21] It is considered that the existence of hydroxyl groups in the molecular configuration of silymarin components is responsible for antioxidant and radical scavenging activity. Therefore, Silymarin can counteract the negative effects of the inflammatory process and oxidative stress by scavenging free radicals and controlling inflammatory cytokines. Silymarin used in vitro antioxidant activity by tackling the free radicals 1,1-diphenyl-2-picryl-hydrazyl (DPPH) and 2,2'-azino-bis (3-ethylbenzene-thiazoline-6- sulfonic acid diammonium salt) (ABTS).[22] The antioxidant properties of Silymarin may operate through a variety of methods. These comprise hindering the enzyme activity that produces reactive oxygen species, stopping free radicals production, intestinal ion chelation, encouraging the manufacture of protective molecules, and activating antioxidant enzymes.[Citation21] Silymarin's antioxidant effects have been shown to increase poly-(ADP-ribose)-polymerase function by maintaining NAD+ homeostasis, sirtuin 1 activity, and the AMP-activated protein kinase pathway (all significant regulatory processes associated with oxidative stress).[23] Furthermore, the radical scavenging properties of Silymarin enhance hepatic lipid homeostasis by reducing denovo lipogenesis through the down-regulation of acetyl-CoA carboxylase, fatty acid synthase, and peroxisome proliferator-activated receptor.[24]

Pharmacokinetics:

Crude silymarin extract is lipophilic and poorly soluble in water, so only about 20–50% is absorbed from the gastrointestinal tract after ingestion [18, 19]. For this reason, formulation scientists have endeavored to improve the oral bioavailability and solubility of silymarin preparations, but the commercially available silymarin-containing products differ significantly in their content, dissolution and oral bioavailability of the active ingredient silibinin [20]. In 1995, Rottapharm/Madaus invented a co-precipitation processing method that produced a high-quality silymarin (90–96% purity; approximately 60% of the content being silibinin) with an enhanced dissolution profile (> 90% of silibinin liberated by the co-precipitate); this advanced processing method was subsequently patented in 2014 under the trade name Eurosil 85® [20,21,22]. Most of the published clinical research on silymarin has used this standardized pharmaceutical preparation.

Pharmacodynamics:

Several pharmacologic actions of silibinin have been identified including antioxidant properties, anti-inflammatory properties, antifibrotic effects and insulin resistance modulation.[21]

Antioxidant Properties:

The production of reactive oxygen species (ROS) is a natural consequence of a variety of essential biochemical reactions in the liver, mostly related to the processes involved in detoxification. Exposure to high levels of toxins (e.g., alcohol, hepatotoxic drugs) or intensive oxidation of free fatty acids (i.e., insulin resistance) leads to abnormal production of ROS; the endogenous antioxidants may also become depleted. For example, it is widely acknowledged that ethanol promotes the formation of various free radicals in several cell types, including hepatocytes, Kupffer cells, endothelial cells and infiltrating inflammatory leukocytes [31]. The consequent imbalance, with persistent presence of ROS that are not neutralized by endogenous antioxidants, creates a condition called "oxidative stress", which is implicated in the pathogenesis of a variety of liver disorders including liver fibrosis [32].

In vitro, silibinin is found to be a potent scavenger of ROS, such as hydroxyl and peroxyl anions and hypochlorous acid, in various model systems, such as rat liver microsomes [6], as well as human platelets, leukocytes, endothelial cells [6], erythrocytes [7] and fibroblasts [5]. In addition, superoxide anion radicals and nitric oxide were inhibited in isolated Kupffer cells after treatment with silibinin (concentration at which 50% inhibition occurs of 80 μmol/l) [2].

Silymarin may augment the generation of glutathione in the liver via an increase in substrate availability (i.e. cysteine) for its biosynthesis, which subsequently contributes to the enhancement of its antioxidant capacity in liver tissues [3].

Silymarin protects liver cells by a number of mechanisms. First, it stabilizes membrane permeability through inhibition of lipid peroxidation, thereby helping the liver to maintain levels of its own protective antioxidant, glutathione [3]. Silymarin also protects against injury from various toxic chemicals such as carbon tetrachloride [32], for example, by inhibiting the production of tumor necrosis factor-alpha (TNF-α), interferon-gamma, interleukin (IL)-2 and IL-4 [16, 17] as a consequence of blocking hepatic nuclear factor kappa B (NFκB) activation [30, 31]. Silymarin is able to reduce the cellular uptake of xenobiotics, including mushroom poisons, by blocking organic ion uptake transporters on the surface of hepatocytes [31]. It also inhibits TNF-α expression, for example, when induced by α-amanitin toxin from poisonous mushrooms [40]. The hepatoprotective properties of silibinin are widely attributed to these antioxidant activities [11].

Anti-Inflammatory Properties:

Chronic inflammation has been associated with progressive hepatic fibrosis and the development of cirrhosis [12], and oxidative stress may be the common underlying mechanism in the initiation and progression of hepatic inflammation in various liver disorders [10]. NF-κB is an important transcriptional regulator of the inflammatory response and plays an essential role in regulating inflammatory signaling pathways in the liver [13]. Moreover, NF-κB is activated in virtually every chronic liver disease, including AFLD [44], NAFLD [25], viral hepatitis [26] and biliary liver disease [17, 18]. There is increasing evidence that demonstrates the overall inhibition by silymarin of inflammatory mediators such as NF-κB and inflammatory metabolites (e.g., prostaglandin E2 [PGE2] and leukotriene B4 [LTB4]) [19].

Kupffer cells are resident liver macrophages that appear to be involved in innate immune responses and host defense through the expression and secretion of inflammatory mediators [20]. In isolated rat Kupffer cells, silymarin weakly inhibited PGE2 formation but strongly inhibited LTB4 formation, even at low concentrations (15 μmol/l) [2]. This selective inhibition of LTB4 formation by Kupffer cells and possibly other cell types may account for the anti-inflammatory potential of silymarin.

Antifibrotic Effects:

Silibinin has demonstrated antifibrogenic effects in animal and in vitro models [21,23]. Hepatic fibrogenesis, which results from chronic liver tissue damage, is characterized by activation of hepatic stellate cells (HSCs), a liver-specific type of pericyte. Activated HSCs develop into myofibroblasts, which are responsible for the deposition of collagen fibers leading to liver cirrhosis. In an in vitro model of human hepatic fibrogenesis, silibinin demonstrated antifibrogenic properties by dose-dependently inhibiting the growth factor-induced production of pro-collagen in activated human HSC [18].

The antifibrogenic effect of silymarin has also been confirmed in an animal model of alcohol-induced hepatic fibrosis in non-human primates receiving chronic treatment with alcohol [4]. In this study, baboons were fed alcohol (50% of daily calories) for 3 years with a nutritionally adequate diet, which resulted in an increase of collagen type I in hepatic biopsy samples. Results showed that concomitant administration of silymarin significantly reduced the alcohol-induced increase in hepatic collagen type I.

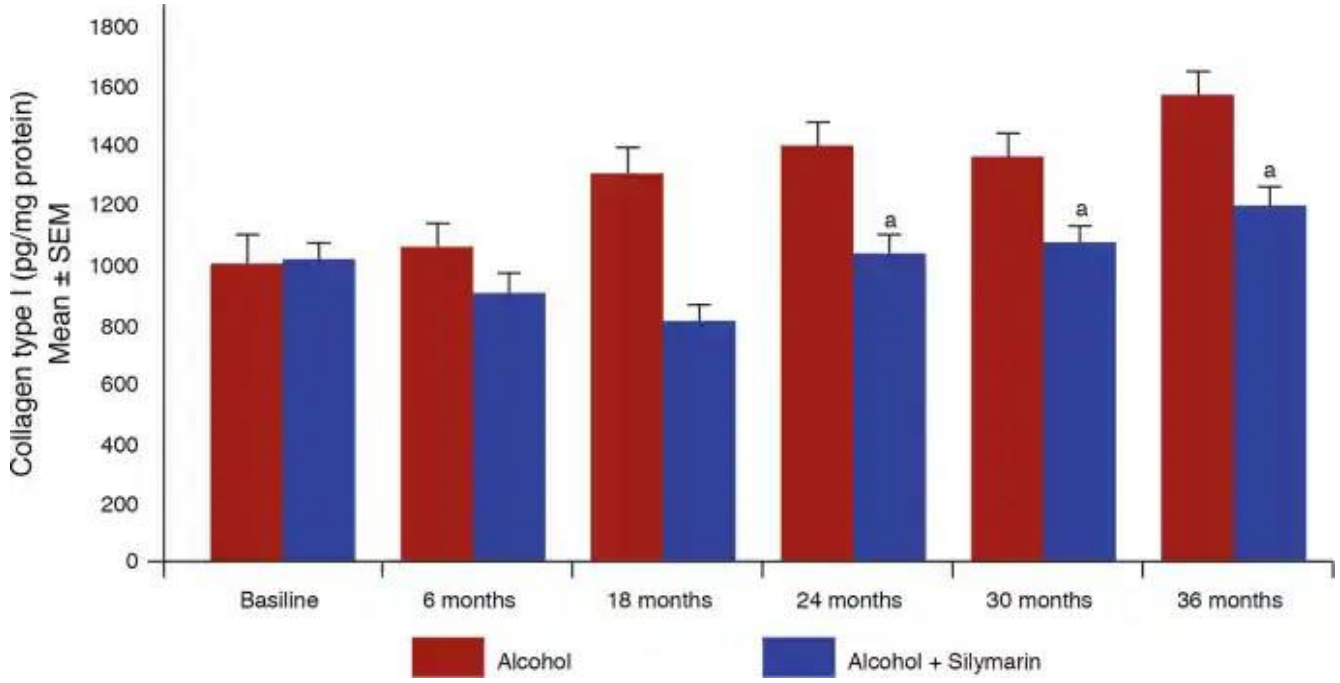

Figure:- Diff. b/w alcohol and alcohol+silymarin Vs collagent ype 1

Clinical Effects of Silymarin::

Liver Cirrhosis/Alcohol-Related Liver Disease:
Fatty liver disease (FLD) is caused by the accumulation of excess fat in the liver, which can lead to serious liver disease for many people. In individuals who consume too much alcohol, alcoholic fatty liver disease (AFLD) is the earliest stage of alcoholic-related liver disease [18]. Silymarin has been investigated in a number of clinical studies in patients with liver cirrhosis and/or alcohol-related liver disease Six of these clinical trials were conducted in patients affected by liver cirrhosis (mainly alcohol-related) Four studies examined the impact of silymarin on clinical outcomes such as mortality and two of these trials had survival as the primary clinical endpoint . The impact of silymarin in these studies is shown, with the study by Ferenci et al. showing a significant impact on mortality [25]. This was a double-blind, prospective, randomized study that was performed to determine the effect of silymarin (Eurosil 85®-derived formulation) on the outcome of patients with cirrhosis [29]. Of the 170 patients with cirrhosis, 87 were treated with silymarin 420 mg/day (alcoholic: 47, non-alcoholic: 40), and 83 received placebo (alcoholic: 45, non-alcoholic: 38) for at least 24 months, with a median observation period of 41 months. In the placebo group, there were 32/39 liver-related deaths, whereas in the silymarin group 16/28 patient deaths were related to liver disease. In this study, the 4-year survival rate was significantly higher (58% vs. 39%) in silymarin recipients than placebo recipients ($P = 0.036$) [31]. Subgroup analyses found that treatment reduced mortality in patients with alcoholic cirrhosis ($P = 0.01$) and in patients with less severe cirrhosis (class A disease according to the Child-Turcotte criteria [24]) ($P = 0.03$).

Amatoxin-Induced Liver Failure:

The ingestion of amatoxin-containing mushrooms may result in hyperacute liver failure, depending on the ingested dose [17]. Amatoxin is known to inhibit RNA polymerase II [15], which is essential for hepatocyte function. Therefore, amatoxin is used experimentally as a toxic model for liver failure. Although no prospective studies on the use of silymarin for amatoxin-induced liver failure in mushroom poisoning can be designed, abundant clinical evidence shows that parenteral use of a silibinin-based formulation may be considered as the treatment of choice in this setting [24, 26]. Early diagnosis and prompt initiation of intravenous therapy are crucial.

Antifibrotic Effects:

Silibinin has demonstrated antifibrogenic effects in animal and in vitro models [29, 30, 32]. Hepatic fibrogenesis, which results from chronic liver tissue damage, is characterized by activation of hepatic stellate cells (HSCs), a liver-specific type of pericyte. Activated HSCs develop into myofibroblasts, which are responsible for the deposition of collagen fibers leading to liver cirrhosis. In an in vitro model of human

hepatic fibrogenesis, silibinin demonstrated antifibrogenic properties by dose-dependently inhibiting the growth factor-induced production of pro-collagen in activated human HSC [32].

Toxicity and Safety:

In clinical trials, silymarin has been used for up to 4 years at doses of up to 420 mg/day (recommended dose) and for up to 48 weeks at 2100 mg/day [30]. Overall, silymarin and silibinin are well tolerated with only minor adverse events reported [13]. Results of systematic reviews of clinical trials of silymarin show a low incidence of adverse events (< 4%, slightly lower than with placebo) and no treatment-related serious adverse events [13] or deaths [13]. In placebo-controlled trials in a total of almost 600 patients, the proportion of patients discontinuing treatment because of adverse events was very low (0.68%) and similar to placebo (0.67%); the most commonly reported (≥ 1% of patients) adverse events in these trials were headaches and pruritus, both of which occurred in < 1.5% of patients [10]. In open-label trials in a total of > 3500 patients, gastrointestinal adverse events (diarrhea, dyspepsia, irregular stools and nausea) were among the most commonly reported; however, all occurred in < 0.25% of patient

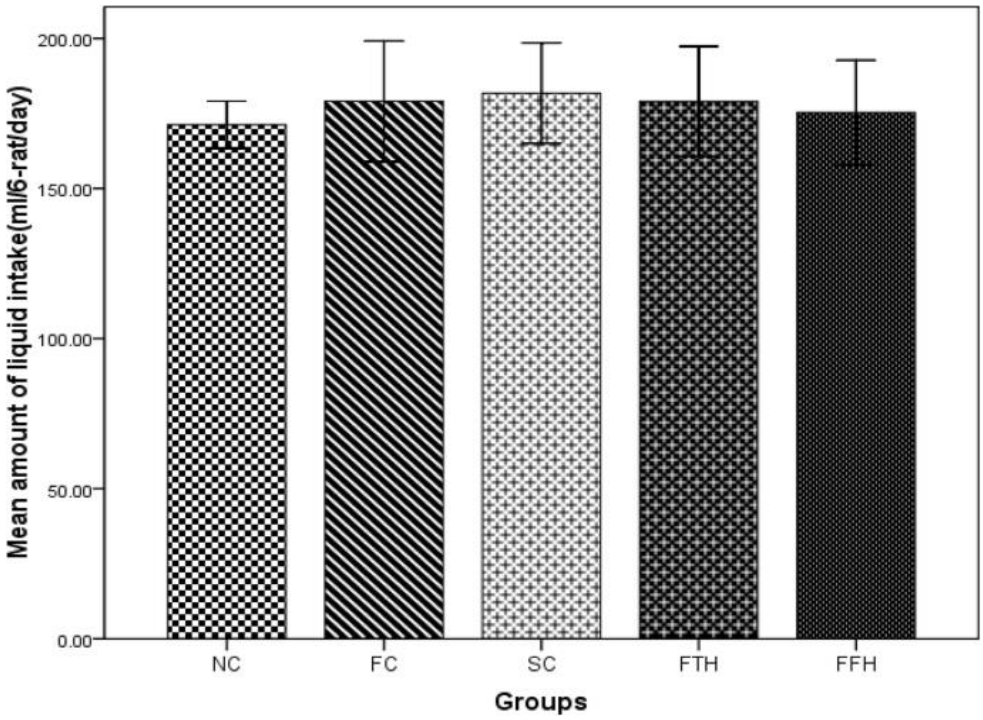

Figure:-groups Vs mean amount of liquid intake

Conclusions:

Silymarin has shown positive effects as supportive treatment in most forms of liver disease including cirrhosis and liver damage due to alcohol abuse. In clinical trials that included patients with cirrhosis, there was a significant reduction of liver-related deaths with silymarin treatment [13]. The mechanism of action by which silymarin produces these clinical effects is attributed to its antioxidant activity. It exerts an antioxidant effect by acting as a scavenger of the free radicals that induce lipid peroxidation as well as influencing the enzyme systems associated with the cellular damage that leads to fibrosis and cirrhosis.

By reducing oxidative stress and the consequent cytotoxicity, silymarin protects intact liver cells or cells not yet irreversibly damaged and thus may be considered hepatoprotective. This effect was evident in a study of diabetic patients with mild cirrhosis, in which silymarin reduced signs of hepatic dysfunction and improved glycemic control. Therefore, while silymarin can support liver functionality, even in the more advanced stages of fatty liver disease, for maximum benefit, treatment with silymarin should be initiated as early as possible in patients with fatty liver disease (AFLD or NAFLD) or DILI when the regenerative potential of the liver is still high and when removal of oxidative stress, the cause of cytotoxicity, can achieve the best results[33].

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