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Review Article

Medicinal properties of milk thistle with special reference to silymarinñ An overview

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Abstract

Milk Thistle, ***Silybum marianum* Gaertn.** plant has been used for centuries as a natural remedy for several diseases. Its active constituent, silymarin displays several medicinal properties, viz. antioxidant, hepatoprotective, cytoprotective, amelioration of hepatic collagen accumulation in advanced fibrosis, immunomodulatory activity, etc. Present paper summarizes various research reports on the medicinal properties of the plant with special reference to silymarin.

Keywords: Antioxidant, Anti-fibrotic, Anti-inflammatory, Anti-tumourogenesis, Anti-carcinogenic, Hepatoprotection, Hepatotoxicity, Silybin, Silibinin, Silymarin, *Silybum marianum*, Milk Thistle.

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Introduction

In traditional systems of medicine, viz. Chinese Traditional Medicine, Japanese Herbal Medicine (Hozai and Kampo), Ayurvedic Medicine (Indian subcontinent), Traditional African Medicine, Traditional Medicines of Amazonian Basin (South America) and Arab Traditional Medicine herbal formulations are used and considered as safe and effective remedies for various diseases. Several plants have been evaluated for their therapeutic applications and many have emerged as clinically tested single or multi-drug formulations. However, still there is a long list of well-known as well as lesser known medicinal plants which need detailed pharmacological and clinical studies. ***Silybum marianum* Gaertn.**, commonly known as Milk Thistle, a member of the daisy family Asteraceae, is native to a narrow area of the Mediterranean but grown for centuries throughout Europe. In India it is found commonly in Jammu and Kashmir at an altitude of 1,800-2,400m and cultivated in other places for ornament on rocky or sandy soils. It is being used as a general medicinal herb from as early as 4th century B.C. and first reported by Theophrastus[1]. Dioscorides, a first century Greek physician who served the Roman army, gave the name *Silybum* to a number of edible thistles. The plant is erect, stout, 1-3m tall with large purple flowering heads and strongly spinescent stem and leaves. The leaves are characterized by distinct white milky veins, which give the plant its common name[2]. In Germany where the plant is often depicted as a religious symbol associated with the Virgin Mary, legend ascribes the white mottling to a drop of the Virgin Mary's milk. The species name *marianum* honours the symbolic association of the plant with the Virgin Mary[3].

Milk Thistle

The present paper is compilation of literature on pharmacological activities of the plant and its active constituents, silymarin. The chemical composition, adverse effects and efficacy analysis have also been discussed in brief.

Chemical composition

The active constituents of milk thistle are flavonolignans including silybin, silydianin and silychristin, collectively known as silymarin[4] with an empirical formula $C_{25}H_{22}O_{10}$ (Ref.5). Two pairs of diastereoisomeric flavonolignans, silybin A and B, isosilybin A and B, were isolated from ***S. marianum*** plant[6]. The structural similarity of silymarin to steroid hormones is believed to be responsible for its protein synthesis facilitatory actions[7]. Silybin or silibinin is the major constituent of silymarin with the greatest degree of biological activity, which accounts for 90% of the herb's component in most preparations[8,9]. Silymarin is found in the entire plant but is concentrated in the fruit and seeds[2]. Seeds contain

polyphenol (about 60%)[10], betaine and essential fatty acids, which may contribute to silymarin's anti-inflammatory and hepatoprotective effects[2].

Silymarin is not water-soluble and administered as an encapsulated standardized extract. The absorption with oral administration is low[11], about 20-40% of the administered dose of silymarin is excreted mainly through bile as sulphates and glucuronide conjugate in human beings[7] and to a lesser extent by the kidney[8],[12]. Silibinin when incubated with human liver microsomes produced one major metabolite, demethylated silibinin and at least two minor metabolites, mono-hydroxy and di-hydroxy silibinin[13]. Pharmacokinetic studies with silybin-phosphatidylcholine complex (silipide) have shown an increase in the oral bioavailability of silybin in healthy human subjects, probably by a facilitatory role of drug complex on the passage of the drug across the gastrointestinal tract[14, 15].

Medicinal properties

Antioxidant activity

Silymarin and its active constituent, silybin, have been reported to work as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. They protect against genomic injury, increase hepatocyte protein synthesis, decrease the activity of tumour promoters, stabilize mast cells, chelate iron and slow calcium metabolism[16]. It influences the enzyme systems associated with glutathione and superoxide dismutase[17]. A significant increase in the amount of the reduced glutathione (GSH) content was found in the liver, intestine and stomach after treatment with silibinin intravenously or silymarin intraperitoneally, whereas there was no change in the lungs, spleen and kidneys of rats[18]. It may protect the brain from oxidative damage for its ability to prevent lipid peroxidation and replenishing the GSH levels[19].

Silibinin displays cytoprotective properties[20] and it may protect blood constituents from oxidative damage[21]. The antioxidant properties were evaluated by studying the ability of this drug to react with relevant biological oxidants such as superoxide anion radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($HO^{\cdot}$) and hypochlorous acid (HOCl)[(Ref 22)]. Silibinin and silibinin dihemisuccinate (SDH) proved to be a strong scavenger of hypochlorous acid (HOCl)[(Refs 20)] but not of superoxide anion radical ($O_2^{\cdot-}$)[(Refs 20, 22)] produced by human granulocytes, and no reaction with H_2O_2 was detected[22]. However, SDH reacted rapidly with hydroxyl radical ($HO^{\cdot}$) and appears to be a weak iron ion chelator. The studies on rat liver microsome lipid peroxidation induced by Fe(III)/ ascorbate showed that SDH has an inhibitory effect, which is dependent on its concentration and the magnitude of lipid peroxidation[22].

Hepatoprotective activity

Use of the plant as a liver-protecting agent, dates at least to the first century. Antioxidant activity might be one of the important factors in the hepatoprotective action of silymarin[23]. It prevents carbon tetrachloride (CCl_4)-induced lipid peroxidation and hepatotoxicity in mice, by decreasing the metabolic activation of CCl_4 and by acting as a chain-breaking antioxidant[17]. It normalized elevated transaminases levels[24] protected against harmful increase in the membrane ratios of cholesterol: phospholipids and sphingomyelin: phosphatidylcholine[25] and prevented the cirrhotic changes[26] in CCl_4 treated rats. CCl_4 pre-treatment increased collagen content in livers of rats, and silymarin (50 mg/ kg administered for 5 days) treatment reduced it[26].

Iron overload is associated with liver damage, leading to fibrosis and eventually to hepatic cirrhosis[27]. The oxidative stress due to increased hepatic lipid peroxidation is the major cause of iron-induced hepatotoxicity. Silymarin pretreatment in rats reduced iron-induced elevated lipid peroxidation and levels of serum enzymes[28].

Rats with partial hepatectomy, when subjected to silymarin pretreatment showed increased synthesis of DNA, RNA, protein and cholesterol, suggesting the regeneration of liver[29]. Silymarin probably initiates a physiologic regulator, so the silybin fits in to a specific binding site on the polymerase, thus stimulating ribosome formation[30]. Owing to its structural similarity to steroids, it probably is able to enter the nucleus and specifically stimulate RNA polymerase I[(Ref 7)]. It increases the contents of cytochromes P-450, b5, the activity of amidopyrine-D-demethylase, hydroxylases of hexobarbital and aniline, improve the activity of the respiratory chain of microsomes, counteract inactivation of cytochrome P-450 into cytochrome P-420[(Ref 31)].

Silymarin is able to antagonise the toxin of mushroom poisoning from ***Amanita phalloides***[32, 33] and ***A. virosa***[34]. It showed anticholestatic effect in galactosamine toxicity associated inhibition of the synthesis of bile acids, their conjugation with proteins and

damage in the biliary system[35]. Silibinin significantly inhibited concanavalin A (Con-A)-induced liver disease[36]. It also provides hepatoprotection against poisoning by phalloidin[37], halothane[38], ischemic injury[39] and radiation[40].

Interaction with hepatotoxic drugs

Silymarin derivatives can protect liver from tetracycline toxicity; such as suppression of cholopoiesis, induction of lipid peroxidation, increased permeability of hepatocyte membranes, lowered stabilizing activity of bile, decreased detoxicating and absorbing-excretory capacity of the liver[41] and increased activities of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase in blood[42].

Approximately 900 medications have been identified as potentially hepatotoxic, many of them have interactions and cross reactivity and the severity of injury can range from asymptomatic or mild to fatal[43]. Hepatocellular injury is rarely due to the drug itself. The drug metabolizing enzymes activate chemically stable drugs to produce electrophilic metabolites. These potent agents bind covalently to molecules such as proteins and fatty acids in liver. This follows exhaustion of intracellular substances such as glutathione, which are capable of preferentially conjugating with toxic metabolites. In addition, free radicals produced by oxidative reactions of cytochrome P-450 can also bind covalently to proteins and to unsaturated fatty acids of cell membranes and results in lipid peroxidation and membrane damage. The end result is hepatocyte death related to failure to pump calcium from the cytosol and to depressed mitochondrial function[44].

Silymarin has a regulatory action on cellular and mitochondrial membrane permeability in association with an increase in membrane stability against xenobiotic injury[45]. It can prevent the absorption of toxins into the hepatocytes by occupying the binding sites as well as inhibiting many transport proteins at the membrane[46]. These actions along with antiperoxidative property make silymarin a suitable candidate for the treatment of iatrogenic and toxic liver diseases.

SDH, protected rats against liver glutathione depletion and lipid peroxidation induced by acetaminophen hepatotoxicity[47]. With relatively high doses (0.05 mmol/l), silymarin has been shown to reduce acetaminophen enhanced CYP 2E1 mediated cytotoxicity of methotrexate in human hepatocytes[48]. Silibinin has a strong affinity for the cytochrome P-450 enzymes[13]. It protects the exocrine pancreas from cyclosporin A (CiA) toxicity, inhibits lipid peroxidation on hepatic microsomes, mitochondria of rats and is also able to reduce the activity of various monooxygenases. It decreased cyclosporine-induced lipid peroxidation without a protective effect on GFR. The effect of silibinin on cyclosporine biotransformation in the liver is via cytochrome P-450(Ref 49). While, silymarin significantly reduced the activities of CYP3A4 and uridine diphosphoglucuronosyl transferase (UGT1A) enzymes as well as mitochondrial respiration during hepatic metabolism of paclitaxel (Taxol) in human hepatocyte cultures[50].

In vitro experiments with kidney cells damaged by paracetamol, cisplatin and vincristine have demonstrated that administration of silybin before and after the drug-induced injury can lessen or avoid the toxic effects[51].

Effect on alcoholic liver disease

Ethanol metabolism is directly involved in the production of reactive oxygen species and reactive nitrogen species. These form an environment favourable to oxidative stress[52]. The antioxidant silymarin successfully opposed alcoholic cirrhosis in baboons[53]. Silibin was found to be effective in alcoholic cirrhosis[7, 54] and was able to protect rats from ethanol-induced oxidative stress in the liver[55]. SDH showed beneficial effect on human hepatocytes when exposed to ethanol *in vitro*[56]. It is also reported that during silymarin treatment serum bilirubin, aspartate aminotransferase and alanine aminotransferase levels normalized in alcoholic liver disease patients, while gamma-glutamyl transferase activity and procollagen III peptide level decreased[57]. However, in a study conducted by Stickel *et al* (2003)the considerable efficacy of silymarin in alcoholic cirrhosis was not found[58] while in others it is noticed that silymarin had no effect on survival and the clinical course in alcoholics with liver cirrhosis[59,60].

Anti-inflammatory activity

Silymarin and its active constituent, silibinin showed anti-inflammatory effects[20, 61, 62], inhibition of neutrophil migration[63] and Kuppfer cell inhibition[62]. It has been found to inhibit the formation of leukotrienes and prostaglandin formation from polyunsaturated fatty acids in the liver, via

its inhibition of the enzyme lipoxygenase. These leukotrienes are known to be some of the most damaging chemicals found in man[64].

Immunomodulatory activity

Intraperitoneal injection of mice with silymarin with an endotoxin-free neutralizing anti-IL-12 antibody abrogated the protective effects of the silymarin against UVB-induced suppression of the contact hypersensitivity response. Furthermore, the treatment of silymarin did not prevent UVB-induced suppression of the contact hypersensitivity response in IL-12 knockout mice but prevented it in their wild-type mice. Moreover, i.p. injection of IL-12 to silymarin-treated or non-silymarin-treated IL-12 knockout mice resulted in an enhanced response to contact hypersensitivity compared with the response in mice that were exposed to either UVB alone or silymarin with UVB. These indicate that silymarin has the ability to protect mice from UVB-induced immunosuppression and that this protective effect is mediated, at least in part, through IL-12(Ref 65).

Silibinin significantly suppress the expression of CD80, CD86, MHC (Histocompatibility Complex Molecules) class I, and MHC class II in the murine bone marrow-derived dendritic cells (DCs), and was associated with impairments of lipopolysaccharide (LPS)-induced IL-12 expression in the DCs. Silibinin-treated DCs proved highly efficient with regard to Ag (antigens) capture via mannose receptor-mediated endocytosis. Silibinin is reported to inhibit the LPS-induced activation of MAPKs (Mitogen-activated protein kinases) and the nuclear translocation of the NF-kB p65 subunit[66]. Additionally, silibinin-treated DCs evidenced an impaired induction of Th1 response and a normal cell-mediated immune response.

In another study, silymarin significantly inhibited the LPS-induced activation of microglia and the production of inflammatory mediators, such as TNF-α and nitric oxide (NO) and reduced the damage to dopaminergic neurons. It significantly reduced the LPS-induced nitrite, inducible-nitric oxide synthase (iNOS) mRNA and protein levels in a dose-dependent manner[67].

Parenteral exposure to silymarin results in suppression of T-lymphocyte function and stimulates inflammatory processes[68]. Silymarin and its active constituent, silibinin inhibiting intrahepatic expression of TNF-α, interferon-gamma (γ-IFN), interleukin (IL)-4, IL-2, and iNOS; and augmenting synthesis of IL-10(Refs 67, 69, 70).

Silymarin may involve in suppression of TNF-induced activation of NF-κB, a nuclear transcription factor and NF-κB-dependent reporter gene transcription[71,72]. It blocked the translocation of p65 to the nucleus without affecting its ability to bind to the DNA. It also blocked NF-κB activation induced by phorbol ester, LPS, okadaic acid and ceramide, whereas H_2O_2-induced NF-κB activation was not significantly affected. Silymarin also inhibited the TNF-induced activation of mitogen-activated protein kinase and c-Jun N-terminal kinase and abrogated TNF-induced cytotoxicity and Caspase activation. It suppressed the TNF-induced production of reactive oxygen intermediates and lipid peroxidation. Overall, the inhibition of activation of NF-κB and the kinases may provide in part the molecular basis for the anticarcinogenic and anti-inflammatory effects, and its effects on caspases may explain its role in cytoprotection[72]. Silymarin may be useful in the development of therapeutic adjuvants[66] in which immunosuppression is required[69] including the immunity to infectious diseases[70].

Anti-viral activity

Though silymarin does not affect viral replication it may have beneficial role in viral hepatitis by its inhibitory action on inflammatory and cytotoxic cascade of events induced by the viral infection[7]. Silymarin exerts anti-inflammatory and antiviral effects by inhibited expression of tumour necrosis factor-alpha (TNF-α) in anti-CD3 stimulated human peripheral blood mononuclear cells and nuclear factor kappa B (NF-κB)-dependent transcription in human hepatoma Huh7 cells, and inhibited infection of Huh7 and Huh7.5.1 cells by JFH-1 virus, suggesting that it may assist in the management of patients with chronic hepatitis C[61].

Silybin and dehydrosylibin inhibited basal and dioxin-inducible CYP1A1 catalytic activity in both human keratinocytes (HaCaT) and human hepatoma cell (HepG2) lines used. The inhibitory effect of tested compounds was more pronounced in HaCaT cells than in HepG2 cells, and dehydrosilybin was a much stronger inhibitor than silybin[73].

Silibinin strongly inhibited growth of both HepG2 (hepatitis B virus negative; p53 intact) and Hep3B (hepatitis B virus positive; p53 mutated) cells with a relatively stronger cytotoxicity in Hep3B cells, which was associated with apoptosis induction. It also caused G1 arrest in

HepG2 and both G1 and G2-M arrests in Hep3B cells. Silibinin induced Kip1/p27 but decreased cyclin D1, cyclin D3, cyclin E, cyclin-dependent kinase (CDK-2) and CDK4 levels in both cell lines. In Hep3B cells, silibinin also reduced the protein levels of G2-M regulators. Furthermore, silibinin strongly inhibited CDK2, CDK4 and CDC2 kinase activity in this HCC cells[74].

Glycaemic and lipidaemic control

There is intriguing evidence that the beta subunit of the signalsome (IKKbeta), a crucial catalyst of NF-κB activation is an obligate mediator of the disruption of insulin signaling induced by excessive exposure of tissues to free fatty acids and by hypertrophy of adipocytes. IKKbeta plays a crucial role, not only in the induction of insulin resistance, but also atherogenesis, a host of inflammatory disorders and the survival and spread of cancer. Dietary silibinin can inhibit the growth of certain cancers in rodents, suggesting that this agent may indeed have clinical potential as an IKKbeta inhibitor. Silymarin has a favourable impact on glycaemic and lipidaemic control in type 2 diabetics with cirrhosis, may or may not be indicative of IKKbeta inhibition in skeletal muscle and adipocytes[75].

Impairments in the lipid spectrum of rat liver tissue, developed as a result of long-term simultaneous effect of ethanol and antituberculosis drugs isoniazid and rifampycin, were effectively corrected by silymarin[76]. Low-density lipoprotein (LDL) oxidation and smooth muscle cell growth represent key events in atherogenesis. Silibinin has inhibitory properties on LDL oxidation *in vitro* and might represent a novel tool in the prevention and therapy of atherosclerosis[77]. Silibinin-induced reduction of biliary cholesterol concentration both in humans and in rats might be, at least in part, due to a decreased synthesis of liver cholesterol[78]. A thermal burn which is associated with extensive oxidation of polyunsaturated fatty acids can be antagonized by silibinin[79].

Anti-fibrotic activity

Hepatic stellate cells and the derived myofibroblasts play a central pathogenic role in liver fibrogenesis. Silibinin at a concentration of 10^{-4}mol/l reduced the proliferation of freshly isolated rat hepatic stellate cells, but had no detectable effect on their viability, morphology and their cytoskeletal architecture. It also reduced the transformation towards myofibroblasts and down-regulated the gene expression of extracellular matrix components and the profibrogenic transforming growth beta (TGF-β)[80]. Alterations of TGFβ1 and c-myc expression in the liver may be involved in the hepatoprotective effects[81]. Inhibition of hepatic stellate cell proliferation and transformation might be the one important aspect of the potential antifibrotic properties[80].

Effect on growth factors

Milk thistle enhanced nerve growth factor-induced neurite outgrowth in PC-12 neural cells and prolonged their survival in culture. It also protected cultured rat hippocampal neurons against oxidative stress-induced cell death and can promote neuronal differentiation and survival[82].

Silibinin acts as an antiproliferative agent. At pharmacologically achievable concentrations (0.02-20 mM) it increased insulin-like growth factor-binding protein 3 (IGFBP-3) accumulation in PC-3 cell conditioned medium and a dose-dependent increase of IGFBP-3 mRNA abundance were also observed. An IGFBP-3 antisense oligodeoxynucleotide that attenuated silibinin-induced IGFBP-3 gene expression and protein accumulation reduced the antiproliferative action of silibinin. Silibinin reduced insulin receptor substrate 1 tyrosine phosphorylation, indicating an inhibitory effect on the insulin-like growth factor I receptor-mediated signaling pathway[83].

Anti-carcinogenic /anti-tumourigenesis activity

Silymarin feeding significantly inhibited tumour growth and also caused regression of established tumours[84], primarily targeted against stage I tumours and that the mechanism of such effects may involve inhibition of promoter-induced edema, hyperplasia, proliferation index and oxidant state[85]. It is associated with *in vivo* anti-proliferative, pro-apoptotic and anti-angiogenic efficacy in prostate tumour[86]. Feeding of silymarin during the promotion phase of 4-nitroquinoline 1-oxide (4-NQO)-induced rat tumourigenesis exerts chemopreventive ability against tongue squamous cell carcinoma through modification of enzymes activity, cell proliferation and/or PGE(2) content[87]. The cancer chemopreventive and anti-carcinogenic effects of silymarin in long-term tumourigenesis models and in human prostate, breast and cervical carcinoma cells were also reported. Treatment with

silibinin resulted in a highly significant inhibition of both cell growth and DNA synthesis in a time-dependent manner with large loss of cell viability only in case of cervical carcinoma cells[88].

It is well documented that ultraviolet (UV) light-induced immune suppression and oxidative stress play an important role in the induction of skin cancers. Topical treatment of silymarin to mouse skin prevents photocarcinogenesis. It was found to be associated with the inhibition of infiltrating leukocytes, particularly CD11b+ cell type, and myeloperoxidase activity[89]. Silymarin reduced the UVB-induced enhancement of the levels of the immunosuppressive cytokine, interleukin (IL)-10 and enhanced the levels of the immunostimulatory cytokine, IL-12 reduced number of UVB-induced H_2O_2 producing cells and iNOS expressing cells concomitant with decrease in H_2O_2 and nitric oxide production[65, 89]. Prevention of UVB-induced immuno-suppression and oxidative stress by silymarin may be associated with the prevention of photocarcinogenesis in mice[89].

Silibinin significantly induces growth inhibition, a moderate cell cycle arrest and a strong apoptotic death in both small cell and non-small cell human lung carcinoma cells. It inhibits cell growth via G1 arrest, leading to differentiation of androgen-dependent human prostate carcinoma LNCaP cells[90-92].

Phosphorylation status of retinoblastoma (Rb) and related proteins is important to drive cell cycle progression. In hyperphosphorylated state, they are growth stimulatory, but their hypophosphorylation is growth inhibitory. Cyclin-dependent kinases (CDKs), together with their catalytic subunit cyclins, phosphorylate Rb, which makes transcription factor E2Fs free from Rb-E2F complexes, resulting in cell growth and proliferation. Silibinin treatment resulted in decrease in CDK4 and CDK2 levels, respectively, but did not alter the protein levels of cyclin D1 and cyclin E. There is a strong decrease in protein levels of transcription factors E2F3, E2F4 and E2F5, respectively. Silibinin caused hypophosphorylation of Rb-related proteins may in part be responsible for its cancer preventive and anti-carcinogenic efficacy in different cancer models including PCA. This effect was mainly attributable to a large decrease in the amount of Rb phosphorylated at specific serine sites[93, 94].

Silybinin inhibits the growth of human prostate cancer cells (PCA) both *in vitro* and *in vivo* and effectively inhibits constitutive activation of NF-κB in advanced human prostate carcinoma DU145 cells[95]. Consistent with this, nuclear levels of p65 and p50 sub-units of NF-κB were also reduced. Silibinin treatment resulted in a significant increase in the level of IkappaBalpha (inhibitory κB-α)with a concomitant decrease in phospho-IkappaBalpha. Silibinin dose-dependently decreases IKKalpha kinase activity. Silibinin does not necessarily need an upstream event to bring about its inhibitory effect on IKKalpha and downstream effectors. Silibinin also inhibits TNF-α-induced activation of NF-κB via IkappaBalpha pathway and subsequently sensitizes DU145 cells to TNF-α-induced apoptosis[71].

Molecular modeling of silibinin showed that it is a highly lipophilic compound and interacts with lipid-rich plasma membrane, including binding with erbB1, thereby competing with the EGF-erbB1 interaction. Silymarin showed inhibitory effect on erbB1-Shc activation in prostate cancer (PCA) DU145 cells. Because the ligand-erbB1 autocrine-loop is causally involved in advanced and androgen-independent PCA, the observed effects of silibinin and its strong lipophilic nature could be useful in developing this agent for the prevention and therapy of PCA[96].

Silymarin and its major pure component silibinin has a strong anti-angiogenesis effect on the colon cancer cell line and it is effective in preventing N-butyl-N-(4-hydroxybutyl)nitrosamine-induced bladder carcinogenesis in mice and N-nitrosodiethylamine induced hepatocellular carcinoma in male Wistar albino rats[97-99]. Silibinin was found to suppress the growth and induce the apoptosis of ECV304 cells, at least partly, by inhibiting angiogenesis via modulation of NF-κB, Bcl-2 family and Caspases[100].

Adverse effects

Human studies have shown that silymarin is generally nontoxic and cause no side effects when administered to adults in a dose range of 240-900mg/day in two or three divided doses. A higher dose (>1500mg/day) may produce a laxative effect which may be due to increased bile secretion and bile flow[8]. Most commonly noted adverse effects such as bloating, dyspepsia, nausea, irregular stool and diarrhoea were observed in 2-10% of patients in clinical trials. It also produced pruritis, headache, exanthema, malaise, asthenia and vertigo[7]. Its effect in promotion of tissue regeneration and potential estrogen activity could promote

the growth of some tumours[101, 102].

In vitro studies showed that silymarin in higher concentrations have an inhibitory effect on both phase I and phase II drug metabolizing enzymes. The CYP3A4, CYP2D6 and CYP2C9 are the major enzymes inhibited by this flavonolignan. But the concentrations that obtained in plasma at pharmacological doses are comparatively very less (about 0.5 µmoles) compared to that needed for the inhibition of cytochrome enzymes (about 10 µmoles)[103, 104].

Efficacy analysis

The potential benefit of silymarin still remained a controversial issue. Researchers performed a systematic review on efficacy of silymarin for the treatment of chronic viral hepatitis B and C. The results revealed that out of many studies conducted by various workers, four trials included patients with hepatitis C, one included hepatitis B patients and two, unspecified chronic viral hepatitis. However, only one trial exclusively studied patients with hepatitis C, and none involved patients with only hepatitis B. Silymarin treatment resulted in a decrease in serum transaminases compared with baseline in four studies and compared with placebo in only one study. There is no evidence that silymarin affects viral load or improves liver histology in hepatitis B or C. Silymarin compounds likely decrease serum transaminases in patients with chronic viral hepatitis, but do not appear to affect viral load or liver histology[105]. Another report indicated that silymarin did not improve elevated aminotransferases in patients with chronic hepatitis C[106].

Conclusion

Herbal therapies sought and used encompass a wide range of approaches. Such approaches are often believed to be safer and better than standard medical practice because they are natural or are based on a religious, philosophical or a strongly felt concept of wellness and health. In recent years many researchers have examined the effects of plants used traditionally by indigenous healers and herbalists to treat diseases. ***S. marianum*** is a well-researched plant in the treatment of different diseases and silymarin is one of the favoured drugs. The protective effects of silymarin appear to rest on certain properties: activity against lipid peroxidation as a result of free radical scavenging, the ability to increase the cellular content of GSH; the ability to regulate membrane permeability and to increase membrane stability in the presence of xenobiotic damage; and capacity to regulate nuclear expression. It would be a superior herbal formulation if the potential benefits of silymarin observed in treating different experimental disease conditions is established in clinical trials.

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