Silymarin in the Prevention and Treatment of Liver Diseases and Primary Liver Cancer†

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Abstract: In chronic liver diseases caused by oxidative stress (alcoholic and non-alcoholic fatty liver diseases, drug- and chemical-induced hepatic toxicity), the antioxidant medicines such as silymarin can have beneficial effect. Liver cirrhosis, non-alcoholic fatty liver and steatohepatitis are risk factors for hepatocellular carcinoma (HCC). Insulin resistance and oxidative stress are the major pathogenetic mechanisms leading the hepatic cell injury in these patients. The silymarin exerts membrane-stabilizing and antioxidant activity, it promotes hepatocyte regeneration; furthermore it reduces the inflammatory reaction, and inhibits the fibrogenesis in the liver. These results have been established by experimental and clinical trials. According to open studies the long-term administration of silymarin significantly increased survival time of patients with alcohol induced liver cirrhosis. Based on the results of studies using methods of molecular biology, silymarin can significantly reduce tumor cell proliferation, angiogenesis as well as insulin resistance. Furthermore, it exerts an anti-atherosclerotic effect, and suppresses tumor necrosis factor-alpha-induced protein production and mRNA expression due to adhesion molecules. The chemopreventive effect of silymarin on HCC has been established in several studies using in vitro and in vivo methods; it can exert a beneficial effect on the balance of cell survival and apoptosis by interfering cytokines. In addition to this, anti-inflammatory activity and inhibitory effect of silymarin on the development of metastases have also been detected. In some neoplastic diseases silymarin can be administered as adjuvant therapy as well.

Keywords: Cancer prevention, chronic liver diseases, hepatitis B virus, hepatitis C virus, hepatocellular carcinoma, silymarin, steatohepatitis.

INTRODUCTION

Silymarin is an extract of the milk thistle (Silybum marianum). The tea made of milk thistle was used for the treatment of liver diseases already in the ancient world. Dating back to the time of the ancient Greeks (Theophrastus, 4th century B.C.) and Romans (Pliny the Elder, 1st century A.D.), the seeds of milk thistle (also known as St. Mary’s thistle and lady’s thistle), have been used to protect liver health [1]. In the 1st century A.D., Dioskurides used this plant as an emetic as well as a general medicinal herb. It became a favored medicine for hepatobiliary diseases in 16th century and the drug was revived again in 1960 in central Europe [2,3]. Milk thistle grows up to 6 feet tall, particularly well on sunny slopes in Mediterranean countries, particularly Spain and Greece. The plant of the milk thistle blooms from June through August, and the shiny black seeds are harvested after the end of the summer to be used for medicinal purposes [1].

Silymarin is a mixture of flavonoids and polyphenols. The commercial silymarin preparations contain several different flavonoids, like silibinin (silybin A and B), isosilibinin (isosilybin A and B), silichristin and silidianin Fig. (1). Silibinin is the major bioactive component of this material. The most prevalent forms are the diastereoisomers silybin A and silybin B. Silymarin has membrane-stabilizing and antioxidant activity, it promotes hepatocyte regeneration, reduces inflammatory reaction, and inhibits fibrogenesis. These results have been established in experimental and clinical trials [4-13].

The pharmacological data [1, 14] show that silymarin possesses fairly specific effects on cell-regulating mechanisms, beyond the well known reactive oxygen species (ROS) scavenging properties confirmed in new studies, indicating a potential to reduce toxic effects of other drugs (e.g. cisplatin, amiodarone). This scavenging effect has been proved by atomic force microscopic examinations [15]. In some models, silymarin already at low dose was shown to reduce the inducible nitric oxide synthase-mediated production of nitric oxide and to modulate the inflammatory immune response [1, 14].

In liver diseases caused by oxidative stress (alcoholic and non-alcoholic fatty liver and steatohepatitis, drug- and chemically-induced hepatic toxicity) the antioxidant medicines such as silymarin is the primary therapeutic modality of choice [4, 16, 17]. This can be realized in part by proper composition of food, in part by application of free radical scavengers such as the marketed silymarin products [18-21]. Recently several reports have dealt with the beneficial effect of silymarin not only in chronic liver diseases caused by oxidative stress, but also in viral-induced chronic hepatitis and in primary liver cancer. Chronic hepatitis and liver cirrhosis are the risk factors of hepatocellular carcinoma (HCC). In several studies the chemopreventive and adjuvant effect of silymarin has been also established in different kind of tumours.

SILYMARIN AND LIVER DISEASES

Silymarin and Experimental Liver Damage

Hepatoprotective activity of silymarin has been demonstrated by various researchers from all over the world against partial hepatectomy models and toxic models in experimental animals by using acetaminophen [22], carbon tetrachloride [23, 24], ethanol, D-galactosamine and Amanita phalloides toxin [25]. Silymarin has also been found to protect liver cells from injury caused by ischemia, radiation and viral hepatitis [25]. In these experiments the biochemical markers of hepatocyte damage namely, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and \( \gamma \)-glutamyl transpeptidase, caused by the toxic effects were decreased. The signs of lipid peroxidation (malondialdehyde content) and the parameters of antioxidant capacity (activities of superoxide dismutase, catalase, and glutathione peroxidase) beneficially changed after silymarin treatment [25-27]. Additional demonstrations of silimaryn effects include up regulation of low-density lipoprotein receptor and peroxisome proliferators-activated alpha gene expression [27]. Newer novel findings suggest that silymarin and garlic have a synergistic effect, and could be used as hepatoprotective agents [28].

Silymarin and Micronodular Liver Cirrhosis

In our own earlier clinical pharmacological studies [7, 11, 12] we have demonstrated in a prospective multicentre controlled trial, treatment with silymarin (Legalon 140, Madaus, Cologne, Germany) for 6 months in 36 human patients (biopsy confirmed) with micronodular hepatic cirrhosis (Child A). The treatment had a beneficial effect on immune response of the body and on parameters of the antioxidant protective mechanism [11, 12]. Serum procollagen III levels also decreased significantly in the therapeutic group during the 6 months of treatment, indicating inhibition of fibrogenesis in the hepatic tissue [7]. Our open studies similarly to the data of Ferenci et al. [4] showed that the long-term administration of silymarin significantly increased the life expectancy of patients with alcohol induced liver cirrhosis in a period by 5-10 years [17].

Silymarin and Non-Alcoholic Fatty Liver Diseases

Non-alcoholic fatty liver disease (NAFLD) is a multifactorial liver injury, one form a significant risk for HCC. It includes a wide spectrum of liver damage characterized by histological changes of alcoholic origin (ranging from uncomplicated fatty liver to steatohapatitis, fibrosis and cirrhosis) in non-alcoholics (< 20 g/day ethanol consumption). It is developed mainly by insulin resistance and oxidative stress, but the exact metabolic and cellular mechanisms are not fully understood [29-31].

Researches have identified the factors that can play a causative role: oxidative stress, abnormal cytokine production, fatty-acid metabolic disturbance and insulin resistance. The combination of these events causes hepatocyte injury via direct oxidative injury, tumor necrosis factor-alpha (TNF-\( \alpha \)) induced apoptosis, or inflammation [29-35]. This disease is a two hit alteration in the liver: first phase is the pure steatosis and the second phase is characterized by steatohepatitis (non-alcoholic steatohepatitis, NASH) or fatty liver cirrhosis. Currently, treatment of NAFLD is focused on modifying risk factors (obesity, diabetes mellitus, and hyperlipidemia). Many therapeutic approaches have been attempted with varying degrees of success [36, 37].

Mitochondrial dysfunction and oxidative stress are determinatent events in the pathogenesis of NASH. Silymarin has been shown to have antioxidant, anti-inflammatory, and antifibrotic effects in chronic liver disease. In several experimental models [38-40] and in clinical trial [31, 41-44] different authors have demonstrated the beneficial effect of silymarin silibinin, silybin-phospholipid complex, silybin-vitamin E-phospholipids complex. These therapy modalities were effective in preventing severe oxidative stress and preserving hepatic mitochondrial bioenergetics in NASH induced in different animal models or in human disease. The modifications of mitochondrial membrane fatty acid compo-
ston induced by methionine- and choline-deficient diet are partially prevented by silybin-phospholipid complex, conferring anti-inflammatory and antifibrotic effects. The increased vulnerability of lipid membranes to oxidative damage is limited by silybin-phospholipid complex through preserved mitochondrial function [40].

**Silymarin and Hepatitis C Virus Infection**

Silymarin inhibits hepatitis C virus (HCV) by displaying antioxidant, anti-inflammatory, and immunomodulatory actions that contribute to its hepatoprotective effects. Polyak et al. [45] evaluated the in vitro hepatoprotective actions of the seven major flavonolignans and one flavonoid that comprise silymarin. Activities tested included inhibition of HCV cell culture infection, NS5B polymerase activity, TNF-α-induced nuclear factot-kappaB (NF-kB) transcription, virus-induced oxidative stress, and T-cell proliferation. Silymarin suppressed TNF-α activation of NF-kB dependent transcription, which involved partial inhibition of inhibitory xB and RelA/p65 serine phosphorylation, and p50 and p65 nuclear translocation, without affecting the binding of p50 and p65 to DNA. Flavonolignans blocked JFH-1 virus-induced oxidative stress, including compounds that lacked antiviral activity.

There are several clinical studies on the use of herbal extracts, especially silymarin, for the treatment of patients with chronic hepatitis C, primarily in the belief that this drug improves response to antiviral agents and reduces adverse reactions [21, 46-54]. In a recent multicentre trial (HALT-C) the efficacy of a silymarin preparation added to pegylated interferon and ribavirin was also studied. The trial included a total of 1,145 individuals. In 10 centers there were also patients whose treatment was completed with silymarin as well. Although patients’ ALT levels and viral load showed no significant change as compared to those treated with pegylated interferon and ribavirin, the quality of life in patients receiving silymarin was better as they reported much less complaints relating to liver disease [55]. Recent studies revealed that silymarin reduces insulin resistance [56]. This effect has a major impact on chronic hepatitis caused by HCV because the rate of sustained virological response (SVR) to the combined treatment with pegylated interferon and ribavirin in patients with insulin resistance was only a half (25-33%) as compared to that in patients with no insulin resistance (60%). Based on the available references of literature a clearly higher rate of SVR can be attained by reducing insulin resistance prior to the initiation of treatment with pegylated interferon and ribavirin [57]. At the European Association for the Study of Liver (EASL, 2008) congress in Milan, Italy, Ferenci et al. [58] presented their most recent results which showed that silibinin infusion (10 mg/kg Legalon Sil; Madaus, Cologne, Germany), administered for 8 days in patients with chronic hepatitis caused by HCV, significantly (P<0.001) reduced HCV viral load, and thus it increased the efficacy of pegylated interferon plus ribavirin therapy and reduced ALT levels as well [58, 59]. The authors believe that silibinin, as it can be tolerated well also at high doses, can be helpful in the future when used in combination with up-to-date antiviral therapy in the treatment of patients with chronic HCV hepatitis not responding to pegylated interferon and ribavirin [59]. Pár et al. [60] confirmed the beneficial results of silymarin in HCV chronic hepatitis.

The nonresponse to combined peginterferon and ribavirin treatment in infection caused by genotype 1 is associated with the waist circumference, body mass index (BMI), diabetes, steatosis, and degree of fibrosis. We have published a history of a 59 years old obese (BMI = 46.47 kg/m²) male patient with chronic HCV infection. The weight reduction - after two ineffective antiviral treatments - helped the biochemical and virological response to combined peginterferon-alpha-2a and ribavirin treatment. Between the combined peginterferon and ribavirin therapy, the patient was treated with silymarin. Body-weight reduction and silymarin might have increased the effectiveness of combined peginterferon and ribavirin treatment and thus the sustained virological response in this patient [61]. A new silybin-vitamin E-phospholipid complex can improve the insulin resistance and liver damage in patients with non-alcoholic fatty liver disease and HCV virus infection [44].

**Silymarin and Hepatitis B Virus Infection**

Hepatitis B virus (HBV) infection is one of the most important etiologic factors of HCC. Previous studies have revealed that HBV infection is associated with an increased production of ROS within the liver and that this is responsible for the oxidation of intracellular molecules and activation of genes related to oxidative stress. In addition, induction of HBV replication in human hepatoma HepAD38 cells, in which HBV production is under the control of a tetracycline-regulated promoter, led to up-regulation of genes related to oxidative stress [62]. According to the study of Wu et al. [63] the real-time quantitative RT-PCR analysis revealed that the molecular mechanism of silymarin-mediated antioxidative effect may involve genes related directly or indirectly to glutathione (GSH) metabolism. Up-regulation of Idh2 facilitates the generation of NADPH and conversion of GSH from its oxidized to its reduced form. The increase in reduced GSH further facilitates the removal of H2O2 from cells. In addition, up-regulation of several glutathione S-transferases (Gst2, Gstt1, Gst1, and Mgst3), whose functions are involved in the conjugation reaction of GSH to diverse electrophilic substrates, reveals the presence of a higher concentration of GSH. Furthermore, genes upregulated by silibinin and involved in the glutamate metabolism, urea cycle, and citrate cycle may all indirectly contribute to the increase of GSH level and reversion of liver pathophysiology [63]. Valgimigli et al. [64] reported that ROS levels in HBV chronic hepatitis patients were higher than in healthy controls by radical probe electron paramagnetic resonance measurements of human liver biopsy specimens.

**Silymarin and Liver Transplantation**

The experimental work of Ligeret et al. [65] with silibinin deserves attention. They studied the effect of silibinin on cold preservation-warm reperfusion injury of the liver in rats. They found that silibinin reduced the signs of oxidative stress in the hepatocytes and it increased the mitochondrial ATP values in comparison to the control livers. Based on these, they suggest that it is worthwhile to take silibinin into consideration for modern interventions such as liver transplantation. In an ischemia/reperfusion experimental model, silymarin reduced ischemic renal damage in Wistar rats. The authors recommend that this propriety of sily-
Silymarin is worthwhile to be taken into account for the new therapeutic strategies to prevent ischemia/reperfusion injuries [66].

SILYMARIN AND LIVER CANCER

HCC is the third most common cause of cancer-related death worldwide. It can be found most frequently (80-90 %) in patients with liver cirrhosis. The most frequent causes of liver cirrhosis are chronic HBV [67] and HCV [68] infections and chronic alcohol consumption [69]. The occurrence of HCC is about 3-15 % in patients with alcoholic liver disease. Other predisposing causes can be: NASH [70], obesity [71], diabetes mellitus [72], autoimmune hepatitis, intrahepatic biliary inflammations (primary biliary cirrhosis and primary sclerosing cholangitis), copper and iron metabolic diseases (Wilson disease, haemochromatosis), and congenital alpha-1-antitripsin deficiency.

Silymarin was widely studied for preventing HCC [73]. Some of these experimental in vitro and in vivo studies are listed in Table 1. The biologically most active flavonoid, silibinin, inhibits cytochrome P4502E1 induction, ethanol metabolism and ROS generation in HCC cells in vitro. These silibinin-mediated effects also inhibit ethanol-dependent increases in HCC cell proliferation in culture [74]. Ramakrishnan et al. [75] have demonstrated that silymarin treatment inhibited the proliferation and induced apoptosis in the human HCC cell line HepG2.

Experiments were performed in order to investigate the effect of silymarin on the serum lipid components, free fatty acid levels and cyclooxygenase (COX-2) expression in rats with N-nitrosodiethylamine (NDEA)-induced HCC. Rats with NDEA-induced HCC developed severe hyperlipidemia that evolved in consequence of an expression overregulated by COX-2 as demonstrated by Western blotting and immunohistochemical analytic methods. Administration of silymarin in rats significantly attenuated hyperlipidemia and the expression overregulated by COX-2. Based on this, the authors recommend the increased use of silymarin as an adjuvant chemopreventive agent in the prevention of cancerous diseases of the liver [38]. Silymarin exerted beneficial effects on liver carcinogenesis by attenuating the recruitment of mast cells – which are involved in invasion and angiogenesis – and thereby decreased the expressions of matrix metalloproteinase (MMP)-2 and MMP-9 [76]. The same research group investigated the efficacy of silymarin on the antioxidant status of NDEA-induced hepatocarcinogenesis in Wistar albino male rats. Silymarin reduced the lipid peroxidation status, increased the levels of GSH and the activities of antioxidant enzymes. These findings suggested that silymarin suppressed NDEA-induced hepatocarcinogenesis by modulating the antioxidant defense status [77]. In addition silymarin treatment in the other study significantly attenuated the alterations of the level of alpha-fetoprotein (AFP), carcinoembrional antigen (CEA), activities of liver enzymes, and decreased the levels of malondialdehyde (MDA)-DNA adduct formation. Silymarin could be developed a promising chemotherapeutic adjuvant for the treatment of liver cancer [78].

SILYMARIN AND EXTRAHEPATIC CANCERS

The anticancer effects of silymarin in non-hepatic tumors has been established in several studies using in vitro and in vivo methods; it can exert a beneficial effect on the balance of cell survival and apoptosis with interfering cytokines regulating cell cycle and proteins influencing apoptosis [79,80]. In addition to this, anti-inflammatory activity and inhibitory effect of silymarin on the development of metastases have also been detected. Recently, silibinin have also been shown to exert significant anti-neoplastic effects in a variety of in vitro and in vivo cancer models, including skin, breast, lung, gastric, colon, bladder, prostate and kidney carcinomas. Some of the tumors in which silymarin had beneficial effect are demonstrated in Table 2. Silibinin inhibits colorectal cancer growth by inhibiting tumor cell proliferation and angiogenesis [81] and the invasion of human lung

Table 1. Liver Cancer Prevention and Treatment with Silymarin

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Experimental Model</th>
<th>Mechanisms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>HCC cell culture</td>
<td>↓ Cytochrome P4502E1; ↓ ethanol metabolism; ↓ ROS generation</td>
<td>[74]</td>
</tr>
<tr>
<td>In vitro</td>
<td>HepG2 cell line</td>
<td>↓ Proliferation; ↑ Apoptosis; ↑ cytosolic cytochrome c</td>
<td>[75]</td>
</tr>
<tr>
<td>In vivo</td>
<td>NDEA-induced rat hepatocarcinogenesis</td>
<td>↓ Levels of lipid peroxides; ↑ GSH; ↑ activities of antioxidant enzymes</td>
<td>[77]</td>
</tr>
<tr>
<td>In vivo</td>
<td>NDEA-induced rat hepatocarcinogenesis</td>
<td>↓ MDA-DNA adducts; ↓ AFP; ↓ CEA; ↓ ALT; ↓ AST</td>
<td>[78]</td>
</tr>
<tr>
<td>In vivo</td>
<td>NDEA-induced rat hepatocarcinogenesis</td>
<td>↓ COX-2; ↓ hyperlipidemia</td>
<td>[38]</td>
</tr>
<tr>
<td>In vivo</td>
<td>NDEA-induced rat hepatocarcinogenesis</td>
<td>↓ MMP-2; ↓ MMP-9</td>
<td>[76]</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoembrional antigen; COX-2, cyclooxygenase-2; GSH, glutathione; HCC, hepatocellular carcinoma; MDA, malondialdehyde; MMP, metalloproteinase; NDEA, N-nitosodiethylamine; ROS, reactive oxygen species.
Table 2. Sylimarin as Chemopreventive and Therapeutic Agent for Extra-Hepatic Tumors

<table>
<thead>
<tr>
<th>Organ/System</th>
<th>Target/Effects</th>
<th>Mechanisms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Reduces the risk of skin cancers initiated with UV-radiation</td>
<td>↓ Inflammation; ↓ oxidative stress; ↓ DNA-damage</td>
<td>[87]</td>
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<tr>
<td></td>
<td>Protective effect against chemotherapeutic agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mitomycin C-induced cell death in human melanoma A 375- S2 cells</td>
<td>↓ Mitochondria mediated apoptosis; ↓ p53; ↓ Bcl-2</td>
<td>[88]</td>
</tr>
<tr>
<td>Breast</td>
<td>Prevents TPA-induced MMP-9 expression in human breast cancer cells</td>
<td>↓ MMP-9; ↓ COX-2</td>
<td>[89]</td>
</tr>
<tr>
<td></td>
<td>Preventive effect of arsenite-induced cytotoxicity in two human breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>adeno- carcinoma cell lines</td>
<td>↓ Oxidative stress</td>
<td>[90]</td>
</tr>
<tr>
<td>Lung</td>
<td>Inhibits the invasion of human lung cancer cells</td>
<td>↓ Urokinase plasminogen activator; ↓ MMP-2</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td>Inhibits tumor growth in athymic nude mice</td>
<td>↓ NF-xB</td>
<td>[91]</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Suppresses TNF-α- induced MMP-9 expression in gastric cancer cell line</td>
<td>↓ MMP-9; ↓ MEK/ERK pathway</td>
<td>[92]</td>
</tr>
<tr>
<td></td>
<td>Suppresses spontaneous tumorigenesis in APC min (+) mice</td>
<td>▼ Beta- catenin; ▼ cyclin D1; ▼ proliferation;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>▼ apoptosis; ▼ c-Myc; ▼ phospho-glycogen synthase</td>
<td></td>
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<tr>
<td></td>
<td>kinase 3 beta; ▼ COX-2; ▼ NOS</td>
<td>[93, 94]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suppresses 1,2-dimethyl-hydrazine-induced carcinogenesis</td>
<td>Modulation of biotransforming activity of microbial enzymes</td>
<td>[95]</td>
</tr>
<tr>
<td></td>
<td>Inhibits the growth of LoVo cells</td>
<td>▼ Apoptosis; ▼ Caspases 3, 9; ▼ poly (ADP-ribose) polymerase</td>
<td>[96]</td>
</tr>
<tr>
<td></td>
<td>Causes strong cell cycle arrest at G(1), G(2)-M-phase</td>
<td>↓ Cyclins; ↓ cyclin-dependent kinases (1, 2, 4, 6);</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>▼ cyclin dependent kinase inhibitor (p21, p27);</td>
<td></td>
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<td></td>
<td></td>
<td>▼ phosphorilation of retinoblastoma protein</td>
<td>[96]</td>
</tr>
<tr>
<td></td>
<td>Inhibits proliferation and promotes cell-cycle arrest</td>
<td>↓ Angiogenesis; ↓ NOS; ↓ COX; ↓ HIF-1α; ↓ VEGF;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ proliferation; ↓ apoptosis</td>
<td>[97, 98]</td>
</tr>
<tr>
<td>Prostate</td>
<td>Inhibits cell proliferation in PC3 prostate carcinoma cell line</td>
<td>↓ Proliferation; ↓ HIF-1α</td>
<td>[99, 100]</td>
</tr>
<tr>
<td>Bladder</td>
<td>Inhibits the proliferation of RT4 human bladder papilloma cells and of</td>
<td>↓ Survivin protein; ↑ p53</td>
<td>[101]</td>
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<tr>
<td></td>
<td>bladder tumor xenograft in mice</td>
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<td></td>
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<tr>
<td>Other systems</td>
<td>Inhibits invasive properties of U87MG cells</td>
<td>↓ Cathepsin B; ↓ NF-xB; ↓ MMP-9; ↓ gelatinase B;</td>
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<td></td>
<td></td>
<td>↓ urokinase plasminogen activator;</td>
<td></td>
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<td></td>
<td></td>
<td>↓ intercellular adhesion molecule 1; ↑ stefin A</td>
<td>[102]</td>
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</tbody>
</table>

Abbreviations: COX-2, cyclooxygenase-2; HIF-1α, hypoxia-inducible factor-1α; MMP-2/9, metalloproteinase-2/9; NF-xB, nuclear factor-kappaB; NOS, nitric oxide synthase; TPA, 12-O-tetradecanoylphorbol-13-acetate; VEGF, vascular endothelial growth factor.

cancer cells via decreased production of urokinase-plasminogen activator and MMP-2 [82]. The alleviating effect of silymarin, particularly silibinin has also been demonstrated in relation to the reduction of cellular injury due to chemotherapeutic agents or radiotherapy [83]. This can obviously be explained by the free radical scavenger propriety of silymarin. Its possible inhibitory effects on neoplastic processes are summarized in Fig. (2) based on the publication of Ramasamy et al. [84].

Li et al. [85] examined the pharmacokinetics, mechanisms, effectiveness and adverse effects of silibinin’s anti-cancer actions reported to date in pre-clinical and clinical trials. The silibinin as an adjunct cancer treatment is able to influence such factors as histological subtype, hormonal status, stromal interactions and drug metabolizing gene polymorphisms. The results of these studies may help to more precisely target and dose silibinin therapy to optimize clinical outcomes for oncology patients [86].
CONCLUSIONS

Numerous studies as presented here suggest that silymarin may be useful in the treatment of patients with chronic liver diseases, which are risk factors for cirrhosis and HCC, especially alcoholic and non-alcoholic steatohepatitis in the current clinical practice and, as it can be expected, also in the future. In addition it can also be administered as adjuvant therapy in the chemoprevention of other cancerous diseases. The very marked viral load reducing effect of silibinin at high doses also deserves special attention. The molecular mechanisms of silibinin-mediated antiproliferative effects are mainly via receptor tyrosine kinase, androgen receptor, signal transducers and activators of transcription, NF-κB, cell cycle regulatory and apoptotic signaling pathways in various cancer cells. Targeting inhibition of proliferative pathways through silibinin treatment may provide a new approach for improving chemopreventive and chemotherapeutic effects.

Milk thistle is the dietary supplement taken most frequently by patients with chronic liver diseases. This supplement is one of the most widely used herbal medicines for a long time. Both milk thistle and its active ingredient silymarin are pharmacologically safe and well tolerated. This review demonstrates that silymarin is a safe and effective antioxidant drug in animal model systems, and further human studies are needed to establish its full potential for the treatment of chronic liver diseases as well as liver cancer prevention.

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