<Review>

The Pharmacological Properties of Silymarin and Its Constituents

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Abstract – Silymarin is a standardized extract obtained from the seeds and fruits of *Silybum marianum* L., or commonly called milk thistle, a member of *Carduus marianum* family that contains mix of flavonolignans. Some epidemiological and preclinical studies revealed that *S. marianum* L. has been used for herbal remedies for centuries for its pharmacological activity. In this review, pharmacological studies *in vitro* and *in vivo* of silymarin are discussed thoroughly stressing on antioxidant, antimicrobial, antiviral, and anti-carcinogenic aspects of silymarin. In addition, the protective influences of silymarin on some organs such as heart, liver, bone, and neuron tissue are reviewed as well. This review would be useful for further study regarding the potential of natural plant, notably silymarin, and its therapeutic potential in the prevention and treatment of diseases.
Keywords – Silymarin, *Silybum marianum* L., milk thistle, anti-cancer, antiviral, hepatoprotection, neuroprotection

Introduction

Natural products derived from plants play a critical role in drug discovery and have been served for the treatment of various chronic diseases. The research of bioactivity from advanced plant-derived natural products has raised due to the increased cases of chronic diseases worldwide. The use of plants as medicines has a long empirical history, especially in developing countries, and has been developed into various herbal pharmacopeia.[1] A large number of medicinal plants and their derivatives have been employed in the protection of organs, as well as for the prevention and treatment of chronic[2,3] and infectious diseases.[4] Considering its potential properties, the purpose of this current review is to provide the potential pharmacological actions of silymarin on human health and the advancements of disease prevention and therapies.

Silymarin

Silymarin is a standardized extract obtained from the seeds and fruits of *Silybum marianum* L., or commonly called milk thistle,[5] which contains mix of isomer flavonolignans (Figure 1). Silymarin is composed of its main constituent, silybin (or silibinin), along with other flavonolignans including silydianin, silycristin, isosilybin, and taxifolin.[6,7] Many studies have reported that silymarin and its components display a broad range of pharmacological properties including as an anti-cancer,[8-11] anti-inflammation,[12] hepatoprotection,[13-16] neuroprotection,[17,18] and various diseases associated with liver.[5,19-21]

Pharmacological Activities of Silymarin

Antioxidant activity – Many pieces of literature revealed that silymarin could exert antioxidant properties in several mechanisms, including by directly scavenging the free radical, preventing the free radical formation, and activating several antioxidant enzymes via transcription factor. Silymarin employs *in vitro* antioxidant activity by scavenging the free radicals 1,1-diphenyl-2-picryl-hydrazyl (DPPH) and 2,2'-azino-bis (3-ethylbenzo-thiazoline-6-sulfonic acid diammonium salt) (ABTS).[22]

Koksal et al. (2009)[22] reported that the EC_{50} values of silymarin in scavenging DPPH and ABTS were 20.8 and 8.62 µg/mL, respectively. A lower EC_{50} indicates a higher DPPH and ABTS free radical scavenging activity. The scavenging activity of silymarin on refined sunflower oil against the DPPH and hydrogen peroxide radical was greater than references for radical scavenger activity such

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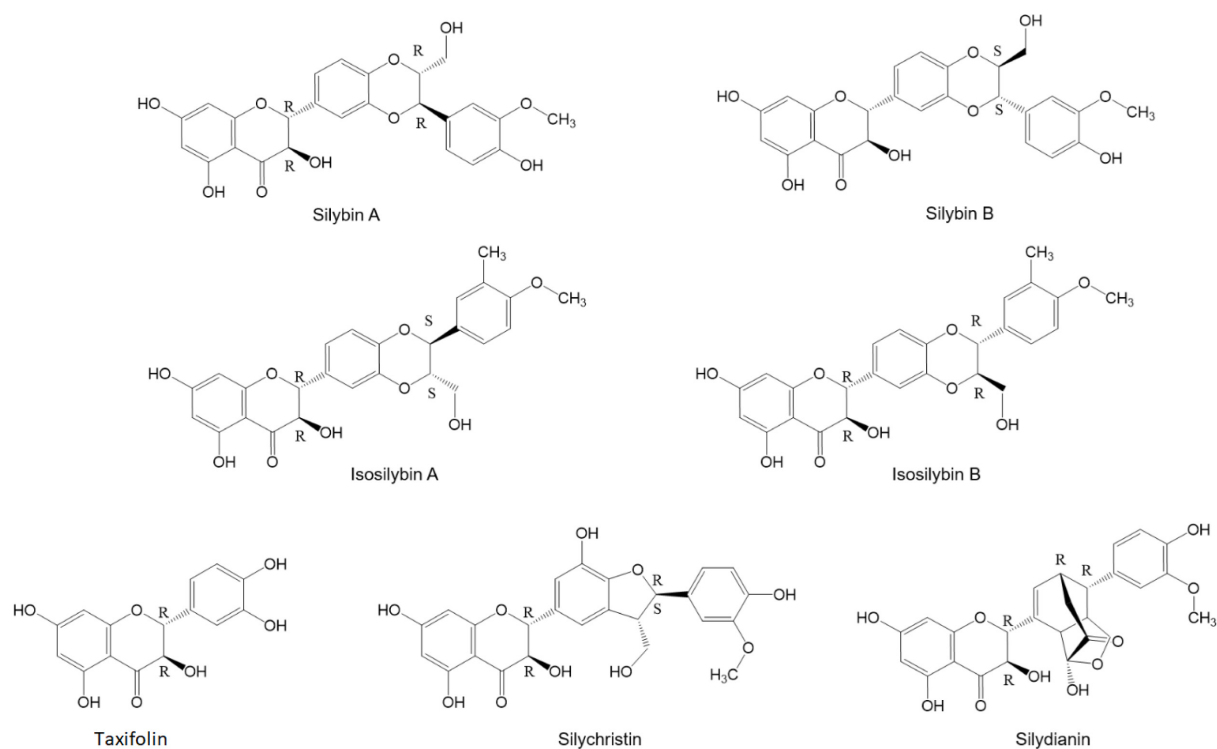Tel: +62-21-756-0929; E-mail: lucia.dwi.antika@lipi.go.id

Fig. 1. Chemical structure of the major constituents of silymarin.

as α-tocopherol and Trolox at the same concentration.[23] The scavenging activity of silymarin on ABTS was also found to be higher than α-tocopherol, but markedly lower than butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and Trolox.[22] Accordingly, silymarin was an effective antioxidant compared to other references of antioxidant compounds.[22,23]

In addition, silymarin shows protection action on mitochondria function. Mitochondria is the main source of free radical production in the cells. Reactive oxygen species (ROS) are potent inducers of oxidative damage and are generated by mitochondrial enzymes.[24] Silymarin and silibinin protect mitochondria by decreasing oxidative stress, thus stimulate pro-survival cell signalling and prevent mitochondrial dysfunction.[25] Further, silibinin was found to increase antioxidant enzyme superoxide dismutase (SOD) activity and mitochondrial membrane-potential against β-adrenergic agonist isoproterenol-induced injury in cultured rat neonatal cardiac myocytes.[26] These findings suggest that the protective mechanism of action of silymarin may be related to its ability to maintain mitochondrial structure.

Antimicrobial activity – A few studies have reported the potential activity of silymarin in displaying antibacterial and antifungal activities. Silymarin exhibited antibacterial activities against both Gram-positive bacteria

(e.g., *Bacillus substilis, Bacillus cereus, Staphylococcus aureus*) and Gram-negative bacteria (e.g., *Escherichia coli, Pseudomonas aeruginosa*). Moreover, disk diffusion test also displayed potent antifungal activity of silymarin against molds (e.g. *Aspergillus nigger, Aspergillus flavus,* and *Penicillium* sp.).[23,27] De Oliveira et al. (2015)[27] demonstrated the antibacterial and antifungal potential of silymarin and its derivative, silibinin, against multi-drug resistant bacterial strains from the clinical isolates. Silymarin and silibinin display moderate activity against multidrug-resistant bacteria,[27] however, other studies reported that silymarin and silibinin combined with antibacterial drugs such as ampicillin or oxacillin exerted remarkable synergistic effect against clinical isolates of *P. aeruginosa* and methicillin-resistant *S. aureus*.[28,29] Combination of silibinin with ampicillin and gentamicin also resulted in more rapid rate of killing on oral bacterial strains, including members of the genus Streptococcus, *Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum*, and *Porphyromonas gingivalis in vitro*, all displayed by MIC values.[30] These findings suggest that silymarin and its constituents may be potentially used as a natural product agent for the combination medication of bacterial infection, to prevent the spread of drug-resistant bacterial strains.

An *in vivo* study by Rodriguez-Flores et al. (2019)[31]

revealed that one or two months of treatment of silymarin produced a remarkable decrease in bacillary loads in the lungs of a progressive pulmonary tuberculosis (TB) BALB/c mice. Combination of silymarin with conventional anti-TB antibiotics showed potential synergistic effect and eliminated *Mycobacterium tuberculosis* in a more efficient way than drugs alone. In addition, silymarin contributes to the production of immune-suppressive cytokines such as Interleukin (IL)-12, Interferon-gamma (IFNγ), and Tumour Necrosis factor-alpha (TNF-α). The mechanism of the antibacterial action of silymarin has not been identified yet, however, it is possibly due to the presence of hydroxyl phenolic groups in flavonoid that can interfere with several enzymes including bacterial DNA topoisomerase.[27]

Antiviral activity – Viral infections represent an important public health concern, and due date, numerous viral infection diseases are without effective vaccines and/ or specific antiviral treatment. Numerous studies have demonstrated that silymarin and its derivatives have shown robust antiviral activity against a number of viruses, including hepatitis C virus,[32,33] hepatitis B virus,[34] dengue virus,[35] enterovirus family,[36] Mayaro virus,[37] and chikungunya virus.[38]

Hepatitis C virus – Antiviral activity of silymarin, particularly on hepatitis C virus, has been extensively studied ever since. Wagoner et al. (2010)[33] disclosed that silymarin possesses antiviral action by blocking viral entry and transmission to the host cell. Another study by Polyak et al. (2010)[4] also mentioned that silymarin treatment retarded the life cycle of hepatitis C virus by disturbing the processes of virus entry and replication, as well as virion production in the host cells. The authors further suggest that the mechanism of silymarin and its derivatives in inhibiting hepatitis C virus life cycle also was related to their antioxidant capability. Hepatitis C infection causes significant oxidative stress and increases reactive oxygen species (ROS) production, whereas silymarin treatment reduced viral-induced ROS production effectively.[4] Additionally, Skottova & Krecman (1998)[39] suggested the mechanism of silymarin's antiviral action may be related to its ability to alter lipid composition of cell membrane lead to lipid peroxidation inhibition and possibly to block virus transmission by targeting multiple components of fatty acid synthesis and metabolism.[40] Silymarin blunted TNF-α and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kβ) transcriptional pathway in hepatoma Huh-7 cells indicating that silymarin has both antiviral and anti-inflammatory action.[41]

Hepatitis B virus – An *in vivo* study displayed the preventive effect of silymarin on hepatitis B virus X protein (HBx) transgenic mice. Hepatitis B virus infection plays a significant role in the aetiology of hepatocellular carcinoma. Viral infection persistently generates oxidative stress and increases ROS production. *In vivo* radical production measurement using radical probe electron paramagnetic resonance displayed the excessive ROS level in human liver biopsy specimens of hepatitis B virus chronic hepatitis patients than in healthy controls.[42] However, HBx gene expression was not affected by silymarin treatment, indicating that the extract has no effects on viral replication. Silymarin showed no effect on HBx expression, nonetheless, it stimulates hepatocyte cell proliferation and recovers liver pathology in the early stage of fibrosis.[34]

Chikungunya virus – Silymarin has known for its broad spectrum of antiviral activity with low toxicity. Lani et al. (2015)[38] reported promise antiviral activity of silymarin against the mosquito-borne chikungunya virus. Silymarin exhibits virus inhibition by two mechanisms, by reducing chikungunya virus replication and down-regulating viral protein involved in the replication. Silymarin at low concentrations was able to reduce 70% of chikungunya virus measured by cytopathic effect (CPE) inhibition. Also, silymarin at the concentration of 100 μg/mL effectively blunted the *Rluc* marker expressed by chikungunya virus replicon up to 93.4%, indicating silymarin may interfere with chikungunya virus ribonucleic acid (RNA) replication during virus post-entry process. Western blot analysis displayed the production of chikungunya virus nsP1 and nsP3, which are responsible for the synthesis of DNA strand and viral replicase complex, as well as viral structural E2 protein levels were precipitously down-regulated following silymarin treatment.[38] These findings indicate that the beneficial effect of silymarin as an anti-chikungunya virus was associated with its activity in targeting both structural and non-structural proteins involved in viral replication *in vitro*. Further well-designed *in vivo* and pharmacokinetic studies are needed to evaluate the silymarin potential as an anti-chikungunya virus therapeutic.

Dengue virus – Qaddir et al. (2017)[35] demonstrated an *in-silico* study to examine the potential inhibitory effect of various medicinal plants to dengue virus, targeting non-structural protein 4B (NS4B). Silydianin and other phytochemicals from *S. marianum* were reported to be able to potentially inhibit dengue virus replication. However, future *in vitro* and *in vivo* studies are required to determine their efficacy in dengue virus.

Mayaro virus – Recent studies revealed that silymarin extract effectively inhibited Mayaro virus *in vitro*. Mayaro

virus, belonging to *Alphavirus* genus and *Togaviridae* family, is an arthropod-borne virus that has caused an outbreak in several countries of Central and South America, including Venezuela, Colombia, Brazil, Bolivia, Ecuador, and Peru.[43-46] Mayaro virus infection on HepG2 cells produced a high level of ROS production. However, silymarin treatment on the concentration of 25 µg/mL significantly reduced ROS production in response to Mayaro virus infection. The capability of silymarin in neutralizing free radicals is similar to standard antioxidant Trolox with a comparable concentration. In addition, silymarin also is able to protect more than 90% of the Mayaro virus-infected cell, confirmed by the result of CPE[37]. CPE refers to structural changes in a host cell due to viral infection. For validation, plaque reduction assay was performed, and the result showed that silymarin exhibits strong inhibition on Mayaro virus replication at 48-hour post-infection, a two-log reduction compared to untreated Mayaro virus-infected cells.[37]

SARS-CoV-2 virus – Coronavirus diseases 2019 (COVID-19) has been declared as a public health emergency of international concern due to its rapid spreading around the world.[47] This outbreak of COVID-19 is caused by the novel severe acute syndrome (SARS)-associated corona-virus-2 (SARS-CoV-2), which is belonging to envelope RNA β-coronavirus.[48] Coronaviruses have been identified in several animal hosts including bats, mice, camels, dogs, and cats,[49] and some reports have been revealed the transmission between species from animals to humans, as well as human to human.[50-52] Among the several coronaviruses that are infecting humans, SARS-CoV and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) have been reported to cause 774 and 866 death cases, respectively.[53] As June 2020, Covid-19 pandemic caused by SARS-CoV-2 has infected more than 8 million people and cause more than 400,000 death cases around the world.[47] Currently, there are no available vaccines yet nor effective antiviral drugs for the prevention and treatment of SARS-CoV-2. Several antivirals and immunomodulators have shown promoting results as treatment strategies for Covid-19 due to their ability in modulating antiviral response and immune cell activation.[54,55] To overcome this problem, scientists are racing to find the best drugs, including from natural products, to discover an advance therapy control for current Covid-19 pandemic.

There has been a growing understanding and evaluation of the inhibitory activity of silibinin as a potent antiviral agent. Molecular docking analysis of silibinin displayed that the free energy binding of silibinin to SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) showed a good correlation with the molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) value range 20 to 36 kcal/mol.[56] This value possessed a similar range obtained by remdesivir, an inhibitor of RdRp that identified as a promising antiviral candidate for Covid-19 due to its ability in inhibiting SARS-CoV-2 *in* vitro.[57] Molecular docking analysis predicted the strong binding behaviour of silibinin to SARS-CoV-2 RdRp.[56] The RdRp coronavirus protein is currently considered as a primary target for new antiviral therapeutic. Hence, computationally, silibinin is expected to possess antiviral activity targeting virus replication machinery and suppressing cytokine storm resulting from viral infection.[56]

In conclusion, these studies suggest that silymarin might be a potent antiviral with a broad spectrum of viral inhibitor activity, indicating that silymarin may act as an antiviral drug by blocking viral replication, down-regulating proteins involved in viral replication, and suppressing cytokine storm as a result of viral infection.

Osteoprotective activity – Bone loss diseases have become a global health issue of major concern. This condition is illustrated by the low mineral bone density, decreased bone strength, and micro-architectural deterioration of bone tissue leading to bone fragility and increased fracture risk.[58,59] Several phytoconstituents are proven to have beneficial effects on bone loss diseases.[60] Therefore, the study on the role of natural products in bone loss could be an alternative option to overcome bone loss diseases. Many pieces of studies investigated the bioactivity of silymarin and its constituents in preventing bone loss and enhancing bone regeneration.[61-64]

An *in vitro* study by Kim et al. (2015)[65] demonstrated that silymarin inhibits NF-kβ lead to a morphological change in lipopolysaccharide (LPS)-induced Raw 264.7 macrophage cells line. NF-kβ is a pivotal pathway for primary function in cellular interaction, macrophage-activated-association changes in cell morphology, and gene expression of inflammatory mediators.[66] Silymarin blocks the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and phospho-c-Jun N-terminal kinase (pJNK), resulting in the inactivation of mitogen-activated protein kinases (MAPKs) pathway in LPS-induced macrophages. Further, the inhibition of MAPKs phosphorylation reduced inflammatory cytokines production *in* vitro.[65] In addition, Kim et al. (2013)[62] also reported that milk thistle extracts notably increased alkaline phosphatase (ALP) in MC3T3-E1 cells, whereas diminished tartrate-resistant acid phosphatase (TRAP) activity in receptor activator of nuclear factor kappa-B-ligand (RANKL)-differentiated Raw 264.7 macrophages.

ALP is a biomarker for the matrix maturation of osteoblast,[67] meanwhile, TRAP is highly expressed in osteoclasts as a well-established biomarker for mature osteoclasts that resorb bone.[68] The same authors in two independent studies demonstrated that silibinin, a constituent of silymarin, blocked osteoclastogenesis by counteracting TNF receptor-associated factor 6 (TRAF6)-responsive signalling, responsible for the gene regulation and protein production of cathepsin-K lead to osteoclastic bone resorption.[61,69]

An *in vivo* study on the bone regeneration and fracture healing potential of silymarin was carried out using mouse fracture model. MicroCT radiographic images showed notably tibia fracture repair on silymarin-treated mice, indicating that silymarin serves better bone healing and remodelling than fractured mice.[61] Other studies using ovariectomized (OVX) mice models were carried out to mimic oestrogen deficiency-induced bone loss.[70] Ovariectomy is associated with increased bone turnover since it causes a significant reduction in oestrogen levels accompanied by bone mass loss.[70] Histological uterus transverse section analysis displayed decreased uterine diameter (atrophied endometrial) and the number of hyperplastic endometrial glands in OVX rats compared to control SHAM-operated rats. On the other hand, treatment of OVX rats with silymarin resulted in improved uterus condition with mild hyperplastic endometrial glands.[62,63] A significant loss of femoral BMD was observed in OVX group, in contrast, either milk thistle extract or silibinin treatment at the concentration 10 mg/kg/day resulted in an increase in BMD and bone mass content (BMC). Immunohistochemical analysis also displayed cathepsin-K induction enhanced in femoral bone tissue section of OVX group, which was then diminished after eight weeks oral administration of 10 mg/kg/day milk thistle extracts or silibinin.[62] El-Shitany et al. (2010)[63] also reported that silymarin prevents bone loss induced by oestrogen deficiency, observed by improved trabecula thickness in silymarin treated-OVX rats. In addition, silymarin treatment highly up-regulated the transcription and serum level of ALP and osteocalcin via Bone Morphogenic Protein (BMP)-2-responsive signalling, suggesting osteogenic differentiation.[61] Taken together, those studies indicate silymarin prevents bone resorption and accelerates bone condition in the fracture healing model, however, further studies are still necessary to identify the molecular mechanisms underlying the fracture healing and bone regeneration of silymarin.

Cardioprotective activity – Arterial hypertension is considered one of the significant risks for cardiovascular diseases responsible for high mortality rates across the world.[71,72] That condition promotes functional changes in the blood vessel and further can affect blood perfusion of other vital organs.[73] A growing interest particularly in determining the cardioprotective effects of herbal extracts took place in the last decade. A recent study summarized the potential action of silymarin for the prevention of metabolic-related diseases,[74] including cardiovascular effects. A study by Pourová et al. (2019)[3] discussed the cardioprotective activity of silymarin and its derivatives *ex vivo* in the animal model. Flavonolignans silymarin display vasorelaxant properties on rat aorta, showed by its ability to induce relaxation in endothelium-intact or denuded aortic rings on rat aorta, indicating the relaxant effect in vascular smooth muscle. The vasorelaxant activity of silymarin is possibly due to the stereomeric configuration of the compounds. Silybin A and silychristin appeared to show remarkable vasorelaxant effects out of silymarin's constituents.[3] The same author also reported that silybin B only exhibited weak antiplatelet activity.[3] However, this result showed inconsistency with other previous reports that suggesting the capability of flavonolignans in inhibiting platelet aggregation.[75,76] The discrepancy might be attributable to the absence of standard drugs in the previously mentioned study. These reports demonstrated that silymarin showed prominent vascular effects and could be potentially developed as a practicable vasorelaxation drug prevent and treat cardiovascular disorders.

Hepatoprotective activity – Liver plays an essential function in the human body such as providing protection against foreign substances by detoxifying and eliminating unnecessary substances, handling metabolism and expelling the drug overdose from the body.[77] Chronic liver disease is progressive destruction of liver function and regeneration of the liver parenchyma leading to fibrosis and cirrhosis, which cause the main liver-related mortality worldwide.[78] During chronic hepatic injury, the liver membrane permeability is altered, resulting in the leakage of enzymes to the bloodstream. Therefore, increased serum levels of transaminases, such as aspartate amino transaminase (AST) and alanine aminotransferase (ALT), commonly used as indicators of liver injury.[79]

For decades, plants and their secondary metabolites have been widely used to promote human health. Some of them have been proven to be useful for chronic hepatitis. The effect of silymarin as a hepatoprotective agent has been extensively studied and well documented. Some *in vivo* studies on the hepatoprotection action of silymarin and its flavonolignans have been published.[13,15,16] Silymarin

was reported to abrogate the serum level of AST and ALT hepatic enzymes, which previously were enhanced by the induction of carbon tetrachloride (CCl_4).[15,16,80] CCl_4 is commonly used to mimic oxidative stress and induce hepatotoxicity in experimental models.[81,82] Treatment with silymarin was found to repair hepatic histopathology in CCl_4-induces broilers chicken model, displayed by the reduction of cytolytic necrosis and granulomatosis compared to untreated group.[16] Another study reported that CCl_4 induction resulted in liver histopathological changes in rats, shown in large necrotic tissue area. In addition, CCl_4-treated rats appeared to increase Ki67 immunosignals, a marker for liver regeneration, and generate a significant number of ballooning hepatocytes in the rat's hepatic tissues.[15,80] Further, this condition was attenuated by silymarin treatment, indicating the potential of this natural compound in the prevention and treatment of hepatic fibrosis condition.

Combination therapy of silymarin and glycyrrhizin from *Glycyrrhiza glabra* also resulted in more effective effect, portraited by the lowest level of hepatic enzymes than when used individually.[80] Silymarin was also used as a complementary and alternative medicine among patients with chronic hepatitis B significantly reduced serum levels of AST and ALT, thus improve the liver function and quality of life in chronic hepatitis B patients.[83] In addition, a week treatment of silymarin was also found to rapidly stimulated hepatocyte cell proliferation, suggesting its potential capacity in improving liver regeneration to replace the function of the damaged liver cells.[34]

Anti-carcinogenic – Numerous studies suggest that milk thistle consumption may reduce the risk of developing some types of cancer, including breast cancer,[84] skin cancer,[85,86] prostate cancer,[85,87,88] and lung cancer.[89,90] The most accepted theory of carcinogenesis revealed that alterations in DNA lead to various types of cancer. A few studies have reported that silymarin may protect against DNA damage induced by different carcinogens,[91,92] thus exhibits a cancer-preventive property.

Silymarin and silibinin were reported to significantly reduced methyl methanesulfonate (MMS)-induced DNA damage in human blood cells, evidenced by alkaline comet assay.[91] MMS is considered harmful since it is classified as a genotoxic agent that damages cellular DNA resulting in cancer.[93] The percentage of DNA damage reduction ranged from 17% to 38% for silymarin and silibinin, compared to untreated group with 58% DNA damage.[91] The authors also examined the alteration of gene expression levels associated with DNA damage. Briefly, treatment with 7.5 mg/mL silymarin or silibinin

markedly down-regulated the expression of proapoptotic gene ABL1 and BCL2 associated X (BAX).[91] In contrast, those previously mentioned compounds extremely up-regulated tumour suppressor gene phosphatase and tensin homolog (PTEN), but not ets variant gene 6 (ETV6) in human whole blood cells. PTEN gene involves in cell migration and proliferation,[94] while ETV6 gene encodes transcriptional regulator binding protein and regulates cell growth.[95] Another study by Cui et al. (2018)[92] showed that silymarin blocked DNA topoisomerase 2-binding protein 1 (TOPBPI1) and cell division cycle associated 3 (CDCA3) genes expression, suggesting its action as an antitumor agent by suppressing human hepatocellular carcinoma growth.

It is also widely known that a malignant tumour likely possesses several capabilities that most healthy cells do not acquire including metastasize, support angiogenesis, tumour invasion, and resistance to apoptosis.[96-98] A number of reports have shown that silymarin and its constituents induce cancer cell death through apoptosis in different tissues.[86,99] Apoptosis involves in the disruption of mitochondrial function through the abnormal expression of apoptotic genes. During this process, mitochondria releases cytochrome C to cytosol and activates caspase-3 lead to apoptosis.[99,100] It has been studied that silymarin induced apoptosis on preneoplastic epidermal cell line JB6 C141 by up-regulating tumour suppressor protein p53 and phosphorylated p53 expression. By contrast, silymarin treatment correspondingly decreased the expression of anti-apoptotic proteins Bcl-xl and Bcl-2. Silymarin and silibinin induce cell apoptosis through mediating p53-induced apoptosis-dependent pathways, thus facilitating cytochrome c release and caspase-3 activation.[101] Apoptosis is regulated under the control of numerous signalling pathways.[102,103] Another study by Kim et al. (2019)[10] reported that silymarin at the concentration of 100 mg/kg markedly increases apoptosis and reduces the AGS human gastric cancer volume both *in vitro* and *in vivo* by regulating MAPK signalling pathway-related factors such as p-ERK1/2, p-JNK, and p-38. An *in vivo* study revealed that oral administration of silymarin significantly increased apoptotic cells up to 26% on xenograft tumour model mice compared to controls, examined by TUNEL assay.[10]

Existed study demonstrated that anti-carcinogenic properties of silymarin are better than its active compound, silibinin, possibly due to the synergistic effect of the constituents.[101] Further, it has been reported that silymarin could be used in combination with a few anti-cancer drugs to enhance their efficacy. Silymarin can selectively

Table 1. Preclinical studies of silymarin and its derivatives as anti-carcinogenic

Type of cancer	Substrate(s)	Suggested mechanism	Reference
Hepatic cancer	silymarin	Regulation of cell cycle	92
		Inhibition of cell proliferation by inhibiting β-catenin accumulation and inducing apoptosis	111
		Attenuation of hepatic proliferation, up-regulation of Bax and p53-mediated apoptosis	112
		Blockage of DNA liver damage	113
	silymarin nanoemulsion	Promotion of cell death by inducing ROS production	8
Skin cancer	silymarin	Induction of p53-mediated apoptosis	101
	silibinin	Prevention UVB-radiation induced skin damage, down-regulation of MAPK and Akt activation	85
Gastric cancer	silymarin	Inhibition of cancer cell growth and induction of apoptosis Modulation of MAPK signalling	10
Lung cancer	silymarin	Inhibition of myeloid-derived suppressor cells, and promotion the infiltration and functions of CD8$^+$ cytotoxic T cells	89
	silibinin	Inhibition of cancer cell invasion and motility, reduction of ERK ½ and AKt phosphorylation	114
	silibinin	Inhibition of NF-kβ signaling	87,88
		Inhibition of microvessel density and VEGF secretion	115
Prostate cancer	isosilybin A, isosilybin B	Induction of apoptosis and modulation of cell cycle arrest	116,117
	silymarin	Inhibition of transforming growth factor (TGF)-α mediated tyrosine phosphorylation	118
Breast cancer	silymarin	Suppression of cell proliferation, induction of G1 arrest through an increase in Cip1/p21 and a decrease of cyclin-dependent kinase (CDK)	119
	silibinin	Blockage of AP-1 activation via MAPK signalling	120
Bladder cancer	silibinin	Inhibition of NF-kβ dependent and -independent pathway	121
		Induction of p53-mediated apoptosis	122
Oral cancer	silymarin	Induction of apoptosis via activating death receptor 5/caspase-8	9

protect tissue from the toxicity of the most commonly used anti-cancer drugs including doxorubicin,[104,105] cisplatin,[106,107] and mitoxantrone.[108] These investigations indicate that silymarin may have clinical application for chemopreventive properties and as adjuvant therapy for cancer treatments.

Silymarin treatment was also reported to retard lamellipodia extension and spreading of cells induced by 6 to 12 hour-LPS stimulation.[65] The formation of lamellipodia and filopodia is related to cell adhesion activity and migration to inflammatory sites.[109,110] Further, silymarin also prevents p65 nuclear translocation, a key process for the activation of NF-kβ canonical pathway. It has been reported that NF-kβ also plays a critical role in regulating lamellipodia formation of actin cytoskeletal structure, lead to adhesion and migration of cell cancer. In summary, the studies that mentioned above identify silymarin and its constituents as a possible chemotherapeutic agent. The extract appears to work with multiple mechanisms by targeting various signalling pathways, thereby highlighting the robust anti-carcinogenic activities of silymarin and its derivatives. Table 1 summarized the suggestive mechanisms of silymarin as an anti-cancer.

Neuroprotective activity – Parkinson's disease is considered one of the most frequent neurodegenerative disorders worldwide. Parkinson's disease is occurred by the loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNc) due to the dysfunction of nigrostriatal pathway.[123] At the moment, there are no successful therapies available for the treatment of this disease, however, dopaminergic medications remain used for the mainstay treatment of Parkinson's disease to alleviate the symptomatic relief of motor symptoms.[123]

Many *in vitro* and *in vivo* studies have disclosed potential neuroprotective properties of silymarin using several models of Parkinson's Disease.[124] Silymarin exhibits neuroprotective actions through inhibiting oxidative stress and inflammatory mediators such as NO and TNF-α, leading to a decreased damage to dopaminergic neurons in LPS-induced neurotoxicity.[125,126] LPS induced a high level of cytokines and chemokines lead to inflammation. Neuroinflammation may not be the initial trigger,

however, this condition is considered the most important process involved in the pathogenesis of Parkinson's Disease.[127] *In vivo* studies remarked that silymarin treatment blunted up-regulated NF-kβ and caspase-9,[128,129] therefore, diminished apoptosis and maintain dopaminergic levels, indicating neuroprotective manifestation of silymarin.[130]

Conclusion

In this present review, the potential pharmacological properties of silymarin (milk thistle) have been briefly explained. Various scientific evidence has displayed that silymarin possesses a wide range of pharmacological activities including an antioxidant, hepatoprotector, neuroprotector, and a potent alternative medication for malignancies and infectious diseases. Even though a large number of studies have been done and reported that silymarin may serve as a potential agent for prevention and treatment for numerous diseases under *in vitro* and *in vivo* conditions, further clinical studies are necessary to evaluate its potential and toxicity in human.

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