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Silibinin in Human Breast Cancer: Scope Beyond Placebo!

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Abstract

Chemotherapies for breast cancer generally have strong cytotoxicity and severe side effects. Thus, significant emphasis has been placed on combinations of naturally occurring chemopreventive agents. Silibinin is a major bioactive flavonolignan extracted from milk thistle with known chemopreventive activity in various organs. However, the mechanism underlying the inhibitory action of Silibinin in breast cancer has not been completely elucidated. Several investigations have been and are being conducted, to study the effect of Silibinin in human breast cancer cells and protective effect in normal cells. The aim of the present article is to review and summarize the physical properties, mechanism of action, pharmacokinetics, role and potential of Silibinin in breast cancer.

Keywords: Breast cancer; Chemotherapy; Chemoprotection; Phytotherapeutics; Silibinin

Introduction

Breast cancer is the second leading cause of cancer death among women and also is the most common malignancy in women, worldwide, accounting for 1.2 million new cases annually. Breast cancer alone is expected to account for 29% all new cancer diagnoses in women [1]. Individualized, multimodality treatment including surgery, radiation, chemotherapy, with/without immunotherapeutic agent and hormone therapy is presently being used for the treatment of breast cancer. Although many anti-cancer therapies are clinically applicable, they generally have strong cytotoxicity and severe side effects [2]. In an effort to increase the therapeutic efficacy and minimize the systemic toxicity of chemotherapeutic agents, dietary supplements and other phytotherapeutic agents are being investigated for their synergistic effects with anticancer drugs. Silibinin is one of such agents that has shown chemopreventive and anticancer effects in various studies [3-6]. Silibinin is major and active constituent of Silymarin, which is a mixture of flavonolignans extracted from milk thistle (Silybummarianum). Milk thistle extracts are being used over years in traditional medicine, and are widely consumed herbal remedies with several putative beneficial effects on health. Consuming Silibinin has been found safe and no substantial adverse effects have been reported when Silibinin is given to humans and rodents at doses as high as 1% (w/w) or 2g/kg body weight [7,8]. Many studies have shown that Silibinin blocks experimentally induced malignancies of the prostate, skin, and colon [8-10]. Human trials of Silibinin are underway for treating prostate cancer, and a completed phase I study has shown no toxic effects [11]. Silibinin plays an important role in breast cancer cells [2-12]. However, the molecular mechanisms associated with the chemopreventive effects of Silibinin have not been clearly and systemically elucidated for breast cancer. In the present article we have tried to summarize the possible mechanisms of action of Silibinin on human breast cancer cells from the literature available so far.

Physical and Chemical Properties of Silibinin

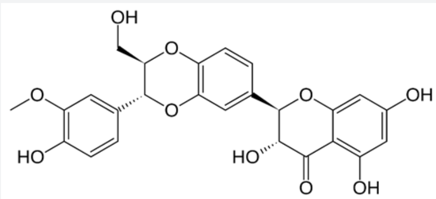

Figure1: Chemical structure of Silibinin.

Silibinin (Chemical formula: $C_{25}H_{22}O_{10}$), (Figure 1) has molecular mass of 482.44g/mol. It has stability of over 2 years at -20 °C. Silibinin has poor water solubility but is readily soluble in organic solvents like ethanol [13-20].

Pharmacokinetic Properties

Silymarin, the active substance in milk thistle, is a mixture of flavonolignans including isomerssilybins A and B, isosilybin A and B, silychristin (also known as silichristin), silydianin (also known as silidianin), and their flavonoid precursor, taxifolin. In the literature, the mixture of the silybins A and B is often referred to as Silibinin. Silibinin is prepared as glycosides of Silybin, which shows more water solubility [21]. Silymarin has very poor bioavailability due to the poor water solubility (<0.04mg/ml) of its flavonolignan structure [22]. The poor bioavailability considerably limits the clinical applications and therapeutic efficiency of oral Silibinin administration [23]. Newer formulations like Silipide and phosphatidylcholine (Lecithin) have ten times more bioavailability compared to Silymarin [24]. Silymarin inclusion complex with β-cyclodextrin is much more soluble than Silymarin [25].

Metabolism and Excretion

Silymarin undergoes Phase I and Phase II metabolism. Phase II metabolism is by conjugation reactions. Excretion is through bile and urine. Silymarin is known to inhibit P-gp-mediated cellular efflux. The modulation of P-gp activity may lead to altered absorption and bioavailability of drugs. Silymarin is known to inhibits cytochrome (CYPs) enzymes [26,27].

Toxicity

Milk thistle is being used for thousands of years and is generally well tolerated by humans. In rare instances, acceptable and mild side effects may be noted with Silibinin ingestion, which include headache and fleeting gastrointestinal distress [26]. Other possible side effects include- allergic skin reactions, itching, bloating, blood clots, loss of appetite, nausea, constipation or diarrhoea, thrombocytopenia, elevated liver enzymes and bilirubin, fever, giddiness, heartburn, hives, impotence, increased creatinine, insomnia, irritability, joint pain, non-specific muscle and joint pains, taste changes, tremor, and weakness.

The more serious concerns about safety stem from possible drug interactions. P450 substrate agents may interact negatively with *Silybummarianum* supplementation [27].

Since, milk thistle extracts are known to suppress PPAR, (peroxisome proliferator-activated reactor gamma) individuals suffering from diabetes must seek endocrinologist opinion before taking milk thistle or Silymarin. Milk thistle extract supplements are also known galactogogues. Galactogogues stimulates lactation (milk production). Silibinin or milk thistle supplementation may not be appropriate for pregnant or nursing women. It's also not advisable to take Silibinin or Silymarin with medications used to treat autoimmune diseases or conditions.

Mechanism of Action of Silibinin in Breast Cancer

Several publications have suggested the presence of Silibinin activity in breast cancer cell lines. The combination of Silibinin and cytostatic drugs was analyzed by Tyagi et al. [28] Combination of Silibinin and Carboplatin showed strong apoptotic effects in Michigan Cancer Foundation-7 (MCF-7) cells. However, this effect was not observed when Cisplatin was used. The combination of Silibinin and Doxorubicin resulted in higher rates of apoptotic death compared to each agent alone in the MCF-7 and MDA-MB468 cell lines [28].

Kim et al. [29] while studying the effect of Silibinin on triple negative breast cancer (TNBC) cell motility, found that it suppresses TGF-β_2 expression and compared the effects with those in non-TNBC cells. The study suggested that Silibinin suppresses metastatic potential of TNBC cells. *In-vitro* studies conducted by Wang et al. [30] concluded that Silibinin promotes the sustained superoxide production that was specifically scavenged by exogenous superoxide dismutase (SOD) in MCF-7 cells, while the activity of endogenous SOD was not changed by Silibinin. Study by Tiwari P et al. [31] suggested that Silibinin-induced apoptosis in breast cancer cells (MCF-7 and T47D) is p53-independent and caspase-dependent, mediated by both extrinsic and intrinsic pathways of apoptosis. The action involves both casapase-8 activation and mitochondrial changes and includes loss of mitochondrial membrane potential and Bax/Bcl-2 redistribution. In another experiment they found that Silibinin-mediated cytotoxic effects were dose and time-dependent in both cell lines and T47D cells were more sensitive than MCF-7 [32]. Kim et al. [29] observed that Silibinin suppressed the epidermal growth factor receptor (EGFR) signaling pathway in SKBR-3 and BT-474 breast cancer cells and may be used as an effective drug for the inhibition of metastasis of human breast cancer [33].

Noh et al. [34] also observed that Silibinin, in pretreated MCF-7 human breast cancer cells, enhances UV B-induced apoptosis. Nejati-Koshki et al. [35] found, the cytotoxic effects of Silibinin on T47D to be dependent on inhibition of estrogen receptor β-expression levels and expression of leptin hormone. The anti-proliferative effect of Silibinin on SKBR3, an ErbB2-overexpressed and ER-negative human breast carcinoma cell line is regulated by the high inhibitory effect on NF-κB [35]. Lu et al. [36] observed that Silibinin inhibited Wnt/β-catenin signaling by suppressing Wnt co-receptor LRP6 expression in human breast cancer cells (MDA-MB-231 and T-47D). Dastpeyman et al. [37] while studying the effect of Silibinin on migration and adhesion capacity of MDA-MB-231 cells (a highly metastatic human breast cancer cell line), showed significant dose-dependent inhibitory effect of Silibinin on proliferation, migration and adhesion of these MDA-MB-231 cells to distant organs. Ohj et al. [38] suggested that Silibinin suppresses 12-O-tetradecanoyl-phorbol-13-acetate (TPA) induced cell migration and matrix metallopeptidase-9 (MMP-9) expression through the MEK/ERK-dependent pathway in MCF-7 breast cancer cells. Xu et

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al. [39] used Silibinin-loaded lipid nano-particles (SLNs) and found that those were quiet effective in inhibiting the growth of MDA-MB-231 cells. SLNs exhibited stronger inhibitory effects compared to free Silibinin, on invasion and migration of MDA-MB-231 cells. In an experimental work by Kim et al, Silibinin induced apoptosis in MCF-7 and MDA-MB-231 was found to be dependent on generation of reactive oxygen species (ROS). Silibinin induces cell death through an AIF-dependent mechanism in MCF7 cells and caspase-3 dependent mechanism in MDA-MB231 cells. This results in ROS generation and Notch-1 signaling act upstream of the ERK and Akt pathway [40,41]. Silibinin and Curcumin combination inhibited the growth of T47D human breast cancer cells in a study. The combination was also found to inhibit telomerase expression in T47D cells [42,43]. It was confirmed by Pirouzpanah et al. [44] that Silibinin induced apoptosis mediated by increase in p53, p21, Bak, ATM in mRNA levels. This study announced that Silibinin inhibited proliferation, induced apoptosis and caused cell cycle arrest at G0/G1 phase in human breast cancer (MCF-7) cells. In fact this was the molecular event which was associated with the up-regulation of Bak, p53, p21 and down-regulation of Bcl-xl.

Zheng et al. [45] elaborated the mechanism of Silibinin induced apoptosis. They found that it involved both the extrinsic and intrinsic pathways (ERα-MEK/ ERK and ERα-Akt/mTOR pathways). In another study, by using an Erβ-selective agonist, they demonstrated that ERβ served as a growth suppressor in MCF-7 cells, and the incubation of Silibinin elevated ER_{β} expression, resulting in tumor growth inhibition. Unlike ER_{α}, ER_{β} did not involve autophagic process in this regulation [45,46]. Khannazer et al. [47] reported that Silibinin treatment in MDA-MB-231 cells increased the expression of chemokine receptors like CXCR3, CCR5 and CCR7. Silibinin has also been found to induce autophagic cell death through ROS-dependent mitochondrial dysfunction and ATP depletion in MCF7 cells [48]. Gao et al. [49] studied the effects of Silibinin on IFNγ-induced FAT10 expression and chromosome instability in HCT116 and HepG2 cells. These cells were treated with Silibinin before karyotyping was performed. It was observed that Silibinin with FAT10 can modulate IFN-γ-induced chromosome instability, apoptosis sensitivity and suppression of TNF-α-induced tumor growth.

Efficacy and Results

Though the clinical studies for usefulness of Silibinin are in infancy, the extrapolation of outcomes in studies in various malignant conditions so far, leave us quite optimistic. Silymarin whole extract has been also used in clinical trials for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). Silymarin (at target dose of 5.1mg/kg/day) was administered orally for 28 days and it significantly reduced liver toxicity in children with ALL [50]. Recently, a new Silibinin drug formulation, Legasil® administration improved hepatic failure due to extensive liver infiltration in a breast cancer patient [51]. A Phase II trial of the Silibinin containing cream, Difinsa-53 has also been proposed (*ClinicalTrials.gov* Identifier: *NCT02534129*) to determine efficacy in delaying, ameliorating, or preventing the radiation dermatitis in patients with breast cancer, undergoing whole breast irradiation. Many other trials are also going on and are likely to guide us further.

Conclusion

Silibinin, a flavonolignan, the major active component of the milk thistle plant (Silybummarianum) has been used as medicinal herbs in the treatment of hepatic disorders. Silibinin has shown promising anti-neoplastic effects against skin, breast, lung, pancreatic, colon, cervical, prostate, bladder, and kidney cancer cells. It is safe and the adverse effects observed in the reviewed studies appear to be minimal. However, targeted randomized clinical trials on Silibinin are necessary to establish its safety, efficancy and synergistic effect with various chemotherapeutic drugs in human breast cancer cells. From our review of the literature into the mechanisms of Silibinin-induced apoptosis in MCF-7 and T47 D cells, many findings have contributed significantly to understanding the molecular mechanism of Silibinin-induced apoptosis *in-vitro*. It is hoped that a large clinical study would address the usefulness of Silibinin in breast cancer therapy.

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