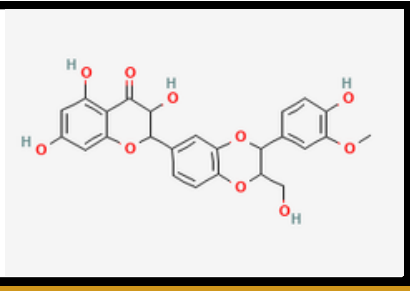
purobest
HIGH PURITY • BEST QUALITY

MILK THISTLE

SCIENTIFIC NAME: Silybum marianum
COMMON NAME: Milk Thistle
PART USED: Seed or Fruit
ACTIVE INGRIDIENTS: (Silymarin) Silybin, Silydianin, Isosilibin



CLINICAL APPLICATIONS IN ONCOLOGY

Oral Silymarin

- Liver toxicity: In children with ALL and liver toxicity, MT was associated with a trend toward significant reductions in liver toxicity. MT did not antagonize the effects of chemotherapy agents used for the treatment of ALL. (1) Reduction in severity of hepatotoxicity of Doxorubicin/cyclophosphamide-paclitaxel (AC-T) regimen. (2)
- Gastrointestinal toxicity: Simultaneous administration of silymarin is a potentially effective supplementation for reducing toxicities in mCRC patients undergoing first-line FOLFIRI plus bevacizumab, especially in diarrhea and nausea. (3)

Topical silymarin

- Radiotherapy-induced mucositis: Prophylactic administration of conventional form of silymarin tablets could significantly reduce the severity of radiotherapy-induced mucositis and delay its occurrence in patients with head and neck cancer. (4)
- Radiodermatitis: Prophylactic administration of silymarin gel could significantly reduce the severity of radiodermatitis and delay its occurrence after 5 weeks of application. (5)
- Hand and Foot Syndrome (HFS): Prophylactic administration of silymarin topical formulation could significantly reduce the severity of capecitabine-induced HFS and delay its occurrence in patients with gastrointestinal cancer after 9 weeks of application. (6)

MECHANISM OF ACTION

1. Proliferation

- ↓PI3K-PKB/Akt signaling pathway (15)
- ↓MAPK/ERK1/2 and MAPK/p38 signaling pathway (16)
- ↓PP2A/AKT/mTOR (17)
- ↓MEK/ERK (18)
- ↓ERK1/2 signaling pathway(19), (20)
- ↑JNK1/2 and p38 (20)
- ↑GSK-3β (21)

2.Metastasis

- ↓MMP-2 and MMP-9 levels (22)
- ↓AP-1(22), (21)
- ↓APAF-1 (23)

3.Inflammation

- ↓Inflammatory mediators (nitric oxide, TNF-α, IL-6, IL-1β, COX-2, iNOS, and NF-κB) (24)

4. Apoptosis

- ↓Bcl-2-mediated anti-apoptosis (16), (18), (25)
- ↓p53, ↑ Bax mediated apoptosis (23), (25)
- ↑Bim-mediated apoptosis (19)
- ↓Survivin (26)

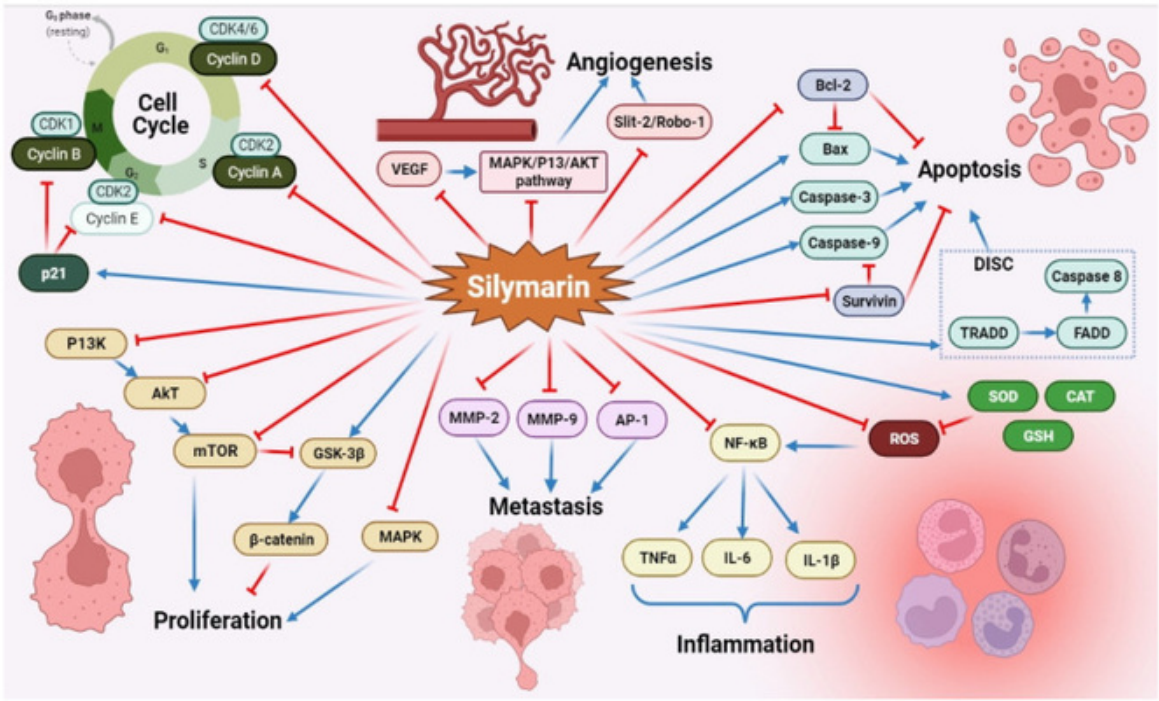


FIGURE A. The effect of Silymarin on multiple targets to exert antitumor effect

- ↑Caspase-9 (27) caspase-3, -8 (28), (29)
- ↑BCL2L11 (30)

5.Angiogenesis

- ↓MAPK/P13/AKT (31), (25)
- ↓Slit-2/Robo-1 pathway (21), (32)
- ↓VEGF protein expression (33)
- ↑MiR-20b (30)
- ↓ Notch pathway (34)
- ↓Wnt/β-catenin signaling pathway (31)

6.Cell cycle

- ↓Cyclin D1 (35)
- ↑p53, p21, and p27 protein expression, and ↓CDK2 protein expression (29), (33)
- ↓G1/S transition phase of the cell cycle (29)
- ↓CDK, (31)
- ↓DNA (TOPBP1), (NUSAP1) and (CDCA3), which are important for mitotic progression and regulation (36)

Clincal Properties: Antioxidant, (7) hepatoprotective, (8) anti-inflammatory, (9) immunomodulatory, (10) antiviral, (11) and antifibrotic (12)

Safety: ·No adverse reaction was reported by silymarin administration at 420 mg daily in three divided doses. (13) 13 g of oral silybin-phytosome daily, in 3 divided doses, appears to be well tolerated in patients with advanced prostate cancer and is the recommended phase II dose. Asymptomatic liver toxicity was the most commonly seen adverse event. (14)

ROLE OF SILYMARIN IN CHEMOTHERAPY-INDUCED HEPATOTOXICITY

1- Reduction of oxidative stress:
The reactive oxygen species produced in cancer induce oxidative stress in the body. This stress is:

- Directly reduced by silymarin.
- Reduced by activation of Heme-oxygenase 1(HO-1). (37)
- Reduced by stimulation of CAT,SOD, and GSH. (38), (39)

2- Decrease in inflammation:
Milk thistle reduces inflammation by:

- Directly inhibiting IL-1β, IL-6, and TNF-α produced by Nf-kB activation. (38)
- Upregulating Nrf2 which decreases the levels of IL-1β, IL-6 and TNF-α. (40)

3- Inhibits chemotherapy-induced apoptosis
Chemotherapy can cause unnecessary cell death of hepatocytes. Milk thistle regulates apoptosis-associated genes by:

- Negatively regulating pro-apoptotic proteins, caspase-3 and Bax. (41)
- Upregulating anti-apoptotic genes like Bcl-2. (41)

4- Inhibition of fibrogenesis:

- Inhibits MCP-1 (Monocyte Chemoattractant Protein-1), suppressing the recruitment of monocytes and macrophages. (42), (43)
- Inhibits kupffer cells either directly, or kupffer cells, toxins and macrophage mediated activation of inflammtory markers. (43)
- Blocks activation of Hepatic Stellate Cells (HSCs), a key trigger for fibrogenesis. (42), (44)
- Downregulates fibrogenic markers, including MMP-13, MMP-2, TIMP-1, TIMP-2, α-SMA, and COL-α1 to prevent altered Extracellular Matrix (ECM) degradation and remodeling. (42), (44)
- Upregulates PPAR-α, leading to the inactivation of HSCs and promoting hepatoprotective effects. (37), (38)

5- Decrease in hepatic enzymes induced by chemotherapy:

- Urea, creatinine, ALT, AST, and total bilirubin levels increased by chemotherapy were reduced by silymarin. (45)

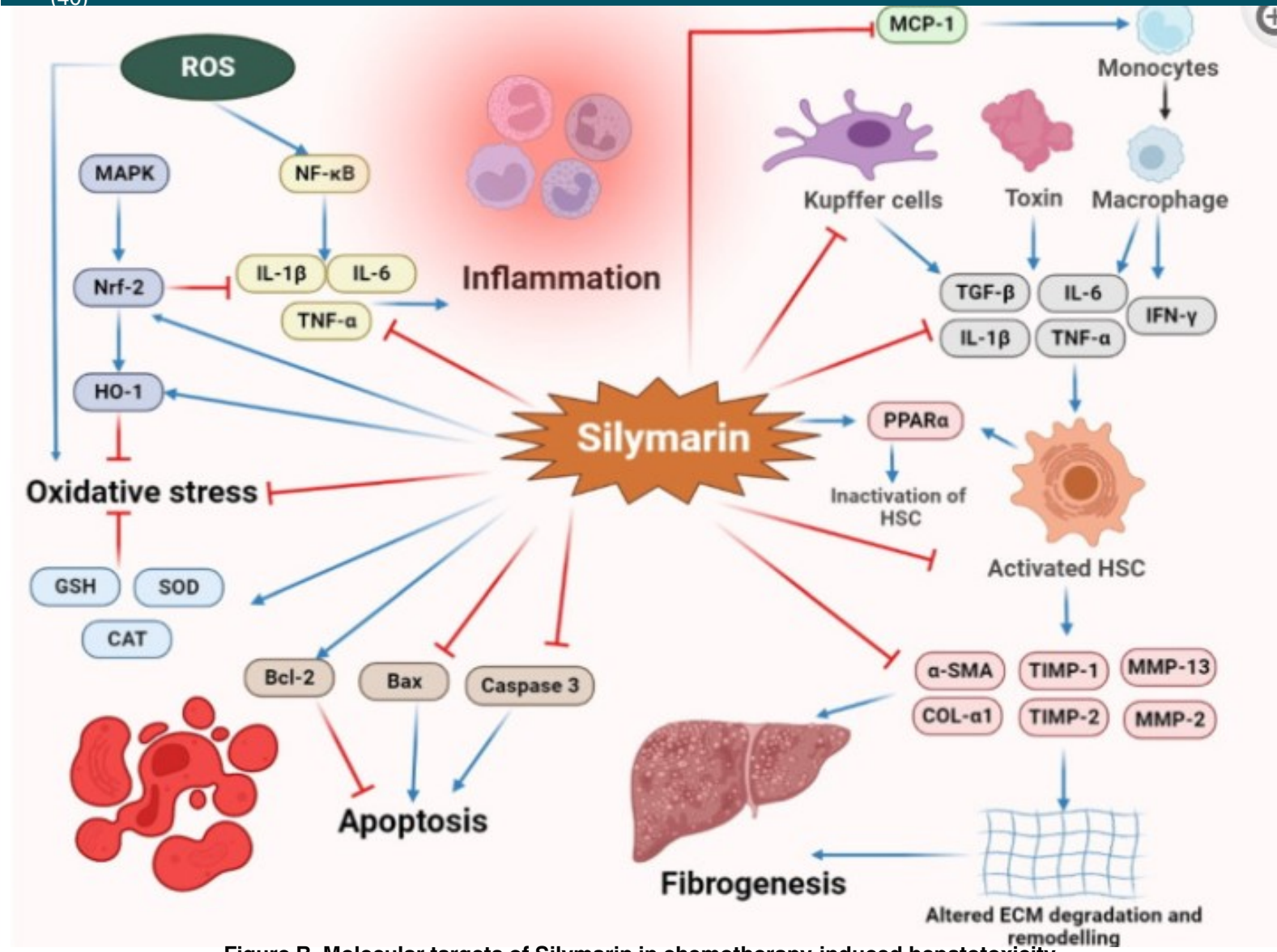


Figure B. Molecular targets of Silymarin in chemotherapy-induced hepatotoxicity.

DOSE RECOMMENDED IN PUBLISHED CLINICAL TRAILS OF CANCER	PUROBEST MILK THISTLE RECOMMENDED DOSAGE
Oral silymarin 140 mg three times a day (750mg silymarin). (2)	One to two capsules of Purobest Milk Thistle once a day or as recommended by the healthcare practitioner.

Formulation Characteristics: One capsule of Purobest Milk Thistle contains 500mg silymarin. Third quality testing ensures the quality and purity of silymarin in Purobest Milk Thistle.

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