

## Safety and toxicity of silymarin, the major constituent of milk thistle extract: An updated review. 2019

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The review focusses on milk thistle fruit extract - the silymarin complex. The authors focused on its vast application profile, reported therapeutic doses and information on safety and toxicity in healthy volunteers or patient groups. The authors reviewed more than 40 papers investigating adverse responses. They conclude that silymarin is safe for human use at therapeutic doses with few adverse reactions having been reported [1].

### Silymarin

The silymarin complex is extracted from the milk thistle fruit (*Silibum marianum*), a medicinal plant of the Asteraceae family, indigenous to southern Europe, northern Africa, the American continent, Australia and some parts of Asia. The most active component of the silymarin complex is silybin and three other flavonolignans with numerous proposed therapeutic effects.

### Applications

Silymarin has been used traditionally in liver diseases for its hepatoprotective effects; some findings indicate favourable effects on Parkinson and Alzheimer diseases. Silymarin also seems to possess anti-carcinogenic properties and to exert anti-inflammatory effects in arthritis.

Because of the various applications of silymarin, a standard therapeutical dose has not been agreed upon. It is most commonly used orally with a dose ranging between 70-420 mg/d. Silymarin has also been used intravenously for hepatitis at 20 mg/kg/day or topically in gel formulations in case of melasma (*chloasma faciei*) or as pre-medication before radiotherapy in cancers.

For their safety assessment, authors searched peer reviewed publications (2007-2018) of clinical studies with healthy volunteers or patients. Their search terms included *S. marianum*, milk thistle, silymarin, safety, adverse reaction, toxicity, cytotoxicity, genotoxicity, mutagenicity, reproductive toxicity, human clinical trial, and drug interaction.

A total of 43 studies were analysed.

### Safety & toxicity conclusions

The authors found that silymarin seems safe for humans at therapeutic doses in the described applications.

Patients with pathologies like HIV, arthritis, allergic rhinitis or blood diseases seemed to show few treatment-related adverse reactions and overall very good tolerance. Minor reactions were found when silymarin was administered in patients with either cancer, ulcerative colitis, tuberculosis, liver disease or diabetes. The common reactions were of gastrointestinal nature (diarrhoea, abdominal pain, vomiting, nausea). Some subjects presented other reactions such as headaches, weight loss, muscle pain, irritability, hyperglycaemia, joint pain, heat sensation, hypercholesterolemia, asthenia or an increase in creatinine and calcium levels.

In the investigated trials, low drug interactions of silymarin were reported. It does not seem to present significant inhibitory or stimulant effects on cytochrome 450 1A2 and cytochrome 450 2D6, both liver enzymes being involved in the drug/xenobiotics metabolism. It does not seem to affect the metabolism for any drug that was reported. In one of the studies, a small inhibitory effect on cytochrome 450 2C9 (Warfarin) and cytochrome 450 3A4 was reported; thus, the authors call for caution when silymarin is co-administered with drugs that possess a narrow therapeutic window.

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#### References

- [1] Soleimani V, Delghandi PS, Moallem SA, Karimi G. Safety and toxicity of silymarin, the major constituent of milk extract: an updated review. 2019 *Phytother Res* 33(6):1627-1638. doi: 10.1002/ptr.6361