



## Case Report

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## Bleeding Milky Way!



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## ABSTRACT

Many people regard herbal plants as a safe natural product and routinely consume them for maintenance of healthy life or as home remedies without considering their potential health-threatening side effects. Here, we presented manifestations of milk thistle toxicity. The milk thistle's flavonolignans, especially the silybin ingredient disturb the hemostatic process by dual anticoagulant and anti-platelet properties. This plant can inhibit serine proteases, including factors II and X as in the coagulation cascade as well as platelet activation by blocking adenosine diphosphate receptor and cyclooxygenase; hence, it causes bleeding diathesis.

## Introduction

The application of herbal medicine is rooted in Iranian culture [1]. Over a decade ago, natural herbs were the main therapeutic tool for physicians. Nowadays, over 80% of people consume herbals for some aspects of their health care globally. These remedies are wrongly thought to have no adverse effects, but we should keep in mind that plants contain diverse ingredients and like any other drugs are associated with side effects and

toxicities [2-4]. Here, we present an unusual overdose of natural plants, manifested by bleeding.

## Case Presentation

A 63-year-old man without any underlying disease was admitted to the emergency department with hematuria, melena, widespread ecchymosis, and petechiae/purpura. Along with bleeding manifestation, outspread vitiligo in facial and truncal areas was a striking physical sign. He was an opium and crystal meth (methamphet-

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amine) addict. Recently, he had traveled to Ardabil city and following methamphetamine abuse, he had drunk an herbal decoction containing more than 50 plants of milk thistle (Maritighal). He arbitrarily consumed daily aspirin on a Pro Re Nata (PRN) basis, but did not have any bleeding disorders in personal or family histories, and dined consumption of anticoagulants, including warfarin and superwarfarin or any other agents with bleeding properties, such as red clover or alfalfa.

Initial laboratory data showed the Prothrombin Time (PT) of more than 90 seconds, International Normalized Ratio (INR) of greater than 8, and activated Partial Thromboplastin Time (aPTT) of more than 160 seconds. The addition of normal plasma did not correct the mixing study, but concomitantly the activity levels of coagulation Factor II (FII) and FX were also decreased. Also, the serum cobalamin level was lower than normal (137.8 pg/ml). Platelet count, fibrinogen level, renal function

test, and liver enzymes were all normal. Serologic tests for hepatitis B and C viruses as well as human immunodeficiency virus were negative. Qualitative glucose-6-phosphate dehydrogenase level, antiphospholipid panel, and rheumatologic tests, including antinuclear antibody, anti-double-stranded DNA, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, as well as complement levels were all normal. Other test results are shown in [Table 1](#).

The patient initially received two units of fresh frozen plasma and was observed for the preceding days. The abdominal ultrasonography was normal without any evidence of cirrhosis, and the upper gastrointestinal endoscopy was normal. Over one week of admission, his symptoms did not recur, the coagulopathy gradually resolved ([Table 1](#)), and he was discharged.

**Table 1.** Laboratory results

Variable	Normal Range	On Admission	On 7 <sup>th</sup> Day
White Blood cell count (/μl)	4-10 ×10 <sup>3</sup>	11.4	8.9
Lymphocyte percent (%)	20-40	17.8	26.2
Neutrophil percent (%)	40-70	74.6	63
Red blood cell count (/μl)	4.2-5.4 ×10 <sup>6</sup>	3.76	3.3
Hemoglobin (gr/dl)	13-17	11.7	10.8
Mean corpuscular volume (fl)	81-99	97	97.6
Platelet count (/μl)	150-400 ×10 <sup>3</sup>	383	432
Corrected reticulocyte count	0.5-1.5	0.46	
Vitamin B12 level (pg/ml)	201-804	137.8	
Ferritin (ng/ml)	10-120	159	
Transferrin saturation (%)	20-45	60	
Prothrombin time (sec)	11-15	>90	10.8
International normalized ratio	0.9-1.2	>8	1.08
partial thromboplastin time (sec)	25-40	>160	38
Fibrinogen (mg/dl)	200-400	582	
D-dimer (ng/ml)	<255	718.8	
Factor II activity (%)	50-150	27	55
Factor V activity (%)	50-150	86	85
Factor VII activity (%)	50-150	57	65
Factor VIII activity (%)	50-150	194	183
Factor IX activity (%)	50-150	66	107
Factor X activity (%)	50-150	25	62
vWF activity (%)	50-150		123
vWF antigen (%)	50-150		149

Outpatient visit over preceding weeks was desirable, he did not complain about bleeding episodes, and coagulation tests remained normal.

## Discussion

The normal hemostatic process requires three bases, including normal platelet function, coagulation cascade, and blood vessels. Assessment of the patient with bleeding disorder requires meticulous history taking with special emphasis on drug history, physical examination, and finally, application of specified laboratory tests [5]. Drug history should encompass all over-the-counter and herbal medications, as many people do not mention them as a drug!

Herbal medicines can affect hemostasis in various ways because of their anti-platelet and anticoagulant effects or due to their coumarin [3, 4].

*Silybum marianum* or milk thistle (Maritighal [Persian]) gives its name from the milky secretion of leaves when crushed. Iran is a native habitat of this plant. Its "Silymarin" extract contains many flavonolignans, like silybin, and has been used as herbal medicine since ancient times (for instance, as a milk-stimulating agent). It possesses cell-signal pathway-modulating activity and has hepatoprotective, anti-inflammatory, anti-oxidant, anti-neoplastic, and many other beneficial therapeutic properties. Like other plants, the milk thistle also has side effects, such as hypoglycemia and gastrointestinal and dermal reactions [6-8].

This plant has a considerable influence on the hemostatic process and possesses both anticoagulant and anti-platelet properties.

Its flavonolignans interact with serine proteases of the coagulation cascade in two critical steps; they can inhibit amidolytic and proteolytic activities of thrombin and decrease thrombin-induced platelet aggregation [9], leading to inhibiting FXa activity [10].

On the other hand, these products affect platelet function by inhibiting platelet activation and aggregation; at first, similar to thienopyridines (e.g. clopidogrel), the flavonolignans interact with platelet P2Y<sub>12</sub> receptors and have a potential inhibitory effect on Adenosine Diphosphate (ADP)-induced platelets aggregation [11]; Then, they prevent arachidonic acid pathway metabolism via the inhibition of Cyclooxygenase (COX) activity, leading to blocking thromboxane A<sub>2</sub> formation (like acetylsalicylic acid) [12] and finally, inhibit collagen-in-

duced platelet activation and aggregation and platelet factor-4 secretion [13].

Studies on FXa and FIIa inhibitor drugs have mixing results, as the addition of normal plasma does not completely normalize coagulation studies. It is also proved that in spite of increasing serum anti-FXa concentration, there is a decrease in FII, FV, FVII, and FX activities [14, 15]. Consistent with the presented case and mechanism of action, it seems that the milk thistle is able to act as an inhibitor that explains the result of the mixing study and also justifies FII and FX reduced activity.

To differentiate coagulation factor deficiency from inhibitors, we first performed a mixing study on coagulation tests. Based on vitiligo and cobalamin deficiency (probably due to pernicious anemia, which was not confirmed with biopsy because of underlying coagulopathy) and the result of mixing study, first, the autoimmune inhibitor was considered, but the relatively rapid and spontaneous resolution of coagulation tests made this diagnosis less probable. Normal platelet count, serum fibrinogen, and coagulation factors (other than FII and FX) essentially exclude disseminated intravascular coagulation. Lack of any clinical, laboratory, or imaging evidence of the liver disease makes cirrhosis unlikely. Hence, after excluding other causes of coagulopathy and a history of recent herbal consumption with compatible pathophysiology that resolved after suspected herbal cessation, milk thistle toxicity was the most probable diagnosis. It should be noted that concomitant milk thistle with aspirin (COX-inhibitor) consumption explains the severe platelet dysfunction.

To the best of our knowledge, this is the first report of *Silybum marianum* toxicity presenting with bleeding symptoms in Iran.

## Conclusion

*Silybum marianum* or milk thistle has dual anticoagulant and anti-platelet properties and its toxicity can cause life-threatening bleeding. Awareness of herbal interactions is essential for meticulous physicians. It should also be noted that this interesting effect of milk thistle's flavonolignans on hemostasis might be a potential natural source for future synthesis of a drug with concomitant anticoagulant and anti-platelet activity.

## Ethical Considerations

### Compliance with ethical guidelines

All ethical principles were considered in this article. The participant was informed about the purpose of the study and laboratory data were taken with the patient's consent.

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### Conflict of interest

The authors declared no conflict of interest.

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