Milk Thistle - One of the Top Twenty Herbs Sold in the US in 2011

Milk Thistle: 2011 Yılında Birleşik Devletler’de En Fazla Satılan Yirmi Bitkiden Birisi

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SUMMARY
Milk Thistle (MT) ranks 5th or 6th, according to the venue surveyed, in the top 20 herbs sold in the US in 2011. MT has also been assigned a grade of “B” from the Natural Standard Database staff scientists. These two ratings in combination give the impression that MT is one of those herbs that it would be important to understand from both an historical and a safety standpoint. This short monograph discusses MT from an historical perspective as well as laying out the myriad of safety concerns that accompany all botanicals used as alternative medicines.

Key words: Milk Thistle; United States; Herbs.

ÖZET

Anahtar kelimeler: Devedikeni, Birleşik Devletler, Bitkiler.

Received April 25, 2013; accepted May 16, 2013
DOI 10.5455/spatula.20130516033306
Published online in ScopeMed (www.scopemed.org).
Spatula DD. 2013; 3(2):75-79.
INTRODUCTION

Milk Thistle (MT) was imported to the Americas and Australia from its native habitats of Southern Europe and Russia. Northern Africa and Asia Minor can also claim MT as a native plant [1] has been used medicinally as far back as the Roman Emperors. MT was used for liver disease as well as snake bites and other conditions [2]. The use of MT seeds for liver ailments has continued throughout the centuries, being eminent during the middle ages and again rising to prominence in the twenty-first century placing 6th or 7th in the top twenty herbs since 2008 [3-6]. It is a good sign when a popular herb is graded “B” or better by the Natural Standard Database scientists (NS) [7]. Not only does MT have the NS “B” grade, it has also been approved for liver problems by the German Commission E (this is an advisory board made up of scientists and doctors) [8]. This combination of approval suggests an agreement between empirical evidence and scientific studies.

Uses

The two uses that have received a grade of “B” are cirrhosis and chronic liver disease [7]. The seeds of the plant contain Silymarin a compound consisting of several flavanolignans which are phenolic compounds [9, 10]. Phenols are a two-edged sword; being good and bad based on which one you are talking about. Silymarin appears to be composed of “good” phenols. Table 1 gives the list of all diseases for which MT has been used for self medication and the grade assigned that particular use.

Constituents and mechanisms of action

The flavanolignans, silibinin (AKA silybin) A and B, appear to be the major constituent of the silymarin complex [9, 10]. Silibinin is one of the many flavonolignans all of which are phenolic compounds [11]. In its pure form, MT demonstrates a low bioavailability due to its low absorption in the GI tract [9, 10]. Because there is often a low bioavailability for herbs and their constituents, addition of some other compound may be used to increase absorption. This combination of a “pure” botanical component and a phospholipid is known as a phytosome [12, 13]. The phytosome used in one study with silybin contained phosphatidylcholine [14]. MT impacts the body in several ways, see Table 2. Animal studies have demonstrated several actions such as free radical scavenging and prevention of apoptosis [12,15,16]. Studies have shown that silymarin has anti-inflammatory as well as immune-modulation activities that can impact several cellular organelles and pathways [17]. Table 2 lists several other mechanisms of action demonstrated through research.

<table>
<thead>
<tr>
<th>Diseases – graded by the Natural Standard Database Scientists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis “B”</td>
</tr>
<tr>
<td>Chronic liver disease “B”</td>
</tr>
<tr>
<td>Acute viral hepatitis “C”</td>
</tr>
<tr>
<td>Amanita phalloides mushroom toxicity “C”</td>
</tr>
<tr>
<td>Cancer “C”</td>
</tr>
<tr>
<td>Diabetes mellitus (associated with cirrhosis) “C”</td>
</tr>
<tr>
<td>Drug/toxin induced hepatotoxicity “C”</td>
</tr>
<tr>
<td>Dyspepsia “C”</td>
</tr>
<tr>
<td>Hyperlipidemia “C”</td>
</tr>
<tr>
<td>Menopausal symptoms “C”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Some Mechanisms of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silymarin</td>
<td>Anti oxidant [12,15,16]</td>
</tr>
<tr>
<td>Flavonolignans</td>
<td>Membrane stabilization [7]</td>
</tr>
<tr>
<td>Silibinin (50-70% of herb)</td>
<td>Enhanced neuron cell growth in vitro [18]</td>
</tr>
<tr>
<td>70% of herb</td>
<td>Inhibits gram negative bacteria [19,20]</td>
</tr>
<tr>
<td>Flavonoid</td>
<td>Inhibits TNF alphas (tumor promoting) [21]</td>
</tr>
<tr>
<td>Taxifolin</td>
<td>Inhibits a nuclear transcription factor (cancer promoting) [22]</td>
</tr>
</tbody>
</table>

This is not an exhaustive list of constituents or effects on the body.

Metabolic pathways

MT appears to impact three different metabolic pathway’s enzymes. Besides decreasing the p-glycoprotein (Pgp) transporter system, MT inhibits the Cytochrome P450 (CYP) pathway – inhibiting CYP3A4 and 2C9. The third system inhibited is the UDP-glucuronosyltransferase (UGT) enzyme pathway. All of these enzyme systems can be inhibited or enhanced by several other xenobiotics (drugs, food, etc.) which can lead to herb-drug interaction [11, 23, 24].

Herb drug interactions

Even though MT has been shown to inhibit several pathways in animal studies it does not mean that it will act exactly the same in humans. Studies have shown that rats have the same CYPS as humans but the reaction to xenobiotics is not always the same. Many of the statements about herb-drug interactions are theoretical or inferred based on understanding how metabolism works. Although, these inferences are not always correct, they need to
Table 3.

<table>
<thead>
<tr>
<th>Some classes of drugs</th>
<th>CYP2C9 drugs</th>
<th>CYP3A4 drugs</th>
<th>p-Glycoprotein transporter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti diabetic agents</td>
<td>Naproxen</td>
<td>Acetaminophen</td>
<td>Vinblastine</td>
</tr>
<tr>
<td>Glucuronidated agents</td>
<td>NSAIDs</td>
<td>Digoxin</td>
<td>Colchicine</td>
</tr>
<tr>
<td>P-glycoprotein modulators</td>
<td>Viagra</td>
<td>Haloperidol</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Antiretroviral agents*</td>
<td>Phenytoin (Dilantin®)</td>
<td>Diazepam</td>
<td>Digoxin</td>
</tr>
</tbody>
</table>

Table 3: Gives examples of drugs that are metabolized by the same metabolic pathway inhibited by MT. This suggests a possible interaction if taken concomitantly.

be considered. More human clinical trials are needed to sort out what is actual versus inferred. The short list of drugs in the Table 3 will give you an idea of the broad spectrum of xenobiotics metabolized by the same pathways and transporter system as MT [25]. Note* one small study explored the possible interaction with MT and antiretroviral agent darunavir-ritonavir in HIV patients and reported no problem [26].

Dosing and method of use
MT is taken orally for the listed disorders. MT can be taken as a tea or liquid extract or in solid form such as a tablet or capsule. In liquid form one can take between “4.5 and 8.5 ml each day.” In solid form the usual concentration is “70-80% of silymarin”. In this form “200-600 mg” can be taken a day [27].

Safety issues
People allergic to the Asteraceae family may have an allergic reaction to MT. Anaphylaxis has been reported in rare instances. Having a compromised liver makes it more difficult to determine if liver problems that arise are due to the disease or the MT. In one study several women took MT while pregnant and no harmful effects were observed in their babies and in animals studies no fetal damage was reported [27]. One preliminary study tested MT in children undergoing chemotherapy for Leukemia. In this small, double blind, study MT appeared to provide hepatic protection from the chemotherapy agents being used [28]. However, any herbal use must be approved and monitored by a doctor.

Table 4.

<table>
<thead>
<tr>
<th>Species</th>
<th>LDsa 1IV Route/LDsa mg/kg</th>
<th>Oral Route/LDsa mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>400</td>
<td>1050/970</td>
</tr>
<tr>
<td>Rats</td>
<td>385*</td>
<td>825/920</td>
</tr>
<tr>
<td>Rabbis</td>
<td>140</td>
<td>300</td>
</tr>
<tr>
<td>Dogs</td>
<td>140</td>
<td>300</td>
</tr>
</tbody>
</table>

This information was from studies in the 1970s and are not available. Citation used was from Medscape [30].

*If perfusion is slowed to 2-3 hours, numbers may go as high as 2000mg/kg.

#This level fits in toxicity rating #6 —“Practically Non-toxic” range 5,000-15,000 [29].

Table 4 gives the LDsa for several species. In research if the dose of a compound reaches10g/kg before killing 50% of the rats it is considered relatively safe for human consumption. It must be noted that toxicity over time is not measured by LDsa. Only an acute toxic reaction is being measured [31].
**Toxicity/Side effects and LD<sub>50**
Gastrointestinal (GI) problems were seen in clinical trials. Headaches were also observed. However, it appears that the percentage of these adverse events were similar to the placebo/control patients so it is not clear that the herb was responsible for the events. There have been very few serious events with MT [8, 27, Table 4 was adapted from information on the Canadian Centre for Occupational Health and Safety (OSH) [29]]. This table gives information on route and milligrams/kilograms dose to reach LD<sub>50</sub> in various animals.

**Pregnancy and lactation**
Studies, using peripheral mononuclear cells from women who were suffering from preeclampsia, showed a reduction in anti-inflammatory activity, such as cytokine synthesis. There are not many studies on lactation and the one reported in the NIH Drugs and Lactation Database (LactMed) was poorly designed. However, the results showed and increase in milk production without side effects [32, 33].

**The bottom line**
Viral hepatitis and cancer appear to be the diseases that future studies will be exploring. Current studies using breast and ovarian cancer cell lines have shown MT to be an antiproliferative agent [34]. Currently you may find MT useful in treating liver diseases. If you and your doctor have researched the herb to understand the benefits and pitfalls and you both agree that the risk to benefit ratio is good then you can be relatively safe to use.

REFERENCES