**Cassia siamea** Induced Hepatitis, a Case Report of Phytomedicine Side Effect

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**Abstract**  
*Cassia siamea* is widely used in Thailand as an anxiolytic drug. A case of a middle-aged non-alcoholic female patient who presented to the physician with the abnormal elevation transaminase enzyme is reported in this paper. She was investigated for hepatitis profile and negative serological result. She revealed the use of the traditional herb capsule of *Cassia siamea*. Her liver function returned to normal within 1 month after stopping use of this herb.

**INTRODUCTION**  
*Cassia* (Pheasant Wood or Kassod Tree) is a tropical tree, native to Southeast Asia, India, and Sri Lanka. Although many *Cassia* sp. are unpalatable and toxic, some species, especially *C. siamea*, are grown for several purposes in some tropical countries. Thai copperpod (*C. siamea* Lamk.) is commonly used as hedges in Nigeria and Zaire, and has also been recommended as shade tree and for soil improvement in Rwanda (Behmel and Neumann, 1982).

Presently, Thai copperpod is widely used as an anxiolytic drug in Southeast Asia, especially Thailand. Barakol (3a,4-dihydro-3a,8-dihydroxy-2,5-dimethyl-1,4-dioxaphenalene), is an active chemical in the alcoholic extract of Thai copperpod (Bulyalert, 1993; Gritsanapan et al., 1998; Hassanali-Walji et al., 1969; Wagner et al., 1971). It was shown to be dopamine agonist and possibly serotonergic antagonist in a behavior study. In a recent study, barakol (10 mg/kg, i.p.) had an anxiolytic profile in rats using elevated plus maze model of anxiety. The compound showed anxiolytic effect in a manner similar to diazepam (1 mg/kg, i.p.) but differs from diazepam in that it also increased the exploratory and locomotor behavior which is not found with diazepam. Barakol (100 M$^6$) inhibited K$^+$ stimulated dopamine release from rat striatum in vitro in a manner similar to the non-selective D1/D2 dopamine receptor agonist, pergolide (100 M$^6$) and the selective D2 dopamine agonist, quinelorane (10 M$^8$) (Thonsaard et al., 1996).

The effect of barakol was antagonized by selective D2 antagonist, etclopride (10 M$^6$) and inhibition of dopamine release was not due to increased dopamine uptake suggesting the capacity of barakol to suppress dopaminergic neurone activity in a way similar to dopamine agonist. The results that are from another additional study of serotonergic antagonist properties are in a behavior study. A recent study (Thongsaaard et al., 1997) indicated that barakol might act as a dopamine agonist to inhibit endogenous dopamine release without a change in dopamine uptake.

Subhadhirasakul and Khumfang (2000) reported that barakol is specifically found in the Thai copperpod, but not in other species such as Pink shower (*C. grandis*), Pod bush (*C. floribunda*), Guajava (*C. alata*), Canafistula (*C. fistula*), Scrambled eggs (*C. surattensis*) and Senna (*C. tora*). In addition, the antioxidative activity was approximately 1.3 times greater than that of the well-known antioxidant, BHT.

Traditionally, Thai copperpod is believed to have an effect in reduction of anxiety, promoting better sleep, promoting appetite and relieving constipation (Plengvidhya and Suvagontha, 1957). Pooviboonsuk et al. (2000) reported on the human hypnotic effect of the Thai copperpod, a 2-phase study of modified herbal extract from the Thai copperpod.
leaves performed on human subjects. Results showed that the drug produced sleepiness in healthy subjects and also improved quality of sleep upon insomniac volunteers. It can be concluded that this modified herbal extract from the Thai copperpod leaves could be used as a herbal hypnotic remedy for sleeplessness.

Here, we report the case of a middle-aged non-alcoholic female patient who presented to the physician an abnormal elevation of transaminase enzyme. This case report of the Thai copperpod phytomedicine side effect as herb-induced hepatitis can be useful information to the physician in taking care of patients with hepatitis.

**CASE REPORT**

A 50 y old non-alcoholic female patient presented to the physician with abnormal elevation transaminase enzyme from health screening test, which was not in agreement with recent screening results in the previous 3 months. Her other biochemical profiles (including glucose, lipid profile, uric acid and creatine kinase), hematology profiles (including complete blood count), and urinalysis test were within normal limits. She was investigated for the hepatitis profile with negative serological result (HBsAg -, AntiHIV, AntiHBC). She was also sent to the gastrohepatologist for full physical examination and revealed no abnormality. The abdominal ultrasonography revealed normal imaging. The additional molecular study (PCR) to identify the possible hepatitis particle was also done and revealed no infectious hepatitis particle. However, she revealed the use of traditional herb capsule (Table 1) of Thai copperpod for 2 months. She was advised to stop using this herb. On follow up, her liver function test returned to normal within 1 month after stopping ingestion of the herb (Table 2). Finally this case was diagnosed to have Thai copperpod related hepatitis.

**DISCUSSION**

Many conventional drugs (for example, isoniazid and valproic acid) are well recognized as possible hepatotoxins (Goldfrank et al., 1998). Several herbal medicines have also been reported to have hepatotoxic effects. However, herbal medicines may be neglected and not be considered as the etiologic agent in cases of unexplained liver injury. Current mechanisms to track adverse effects of herbal medicines are inadequate (Sheikh et al., 1997). A recent study showed that only 40% of people who use herbal medicines informed their primary care physicians (Eisenberg et al., 1998). Therefore, cases of herbal medicine toxicity may go unrecognized. Establishing a diagnosis of herbal hepatotoxicity can be difficult. Even when herbal-related toxicity is suspected, a definitive diagnosis is difficult to establish without proper analysis of the product or plant material.

Some herbs are thought to be intrinsic hepatotoxins and show dose-related liver toxicity, either through direct hepatocellular damage, such as with Chameleon flower (*Atractylis gummifera*), or through the generation of a reactive metabolite, as is the case of pennyroyal oil (*Mentha pulegium*) (Anderson et al., 1996). In many instances, herbal hepatotoxins are thought to cause a hypersensitivity or idiosyncratic reaction. This appears to be true of L-tetrahydropalmatine. For example, recent cases of hepatitis have been reported in adults with history of administration of the Chinese herbal formulation *jin bu huan* (Woolf et al., 1994). Often the mechanism of herbal-induced liver injury is unknown, and the pathologic findings are nonspecific, with cholestasis, hepatocyte necrosis, and acute and chronic inflammatory cell infiltrate.

In general, the documentation of herbal toxicity is inadequate and does not provide definitive proof of causality. However, due to medical ethics, it is not possible to perform such experimental research aiming to study the side effect of any medicine. The case report is, therefore, useful in such cases. Physicians may not ask patients about their use of herbal medicines, or patients may be reluctant to discuss their use of alternative remedies. As a result, many cases of herbal-related toxic hepatitis may go unrecognized and unreported. Inadequate product labeling, multiple-ingredient herbal products, batch-to-batch variation, and adulterants or contaminants may complicate attempts to accurately identify the toxic component.
Here, a case of Thai copperpod induced hepatitis is documented. This is a first report of this phytomedicine hepatotoxic effect. Due to the good anxiolytic effect of Thai copperpod (Scientific Research Division, 1981), the Thai copperpod is mentioned as phytomedicine capsule in Thailand (Table 1). In this case, the patient presented with unsevere hepatitis, and if this were not detected, she would have had more serious liver damage. After the first usage of this drug, she felt better; therefore, she continued using it. Luckily, her routine blood-screening test revealed the hepatitis pattern (elevation of serum transaminase more than three times). She is non-alcoholic and presented no previous history of toxin exposure. According to the conclusion of the Annual Scientific Meeting of Thai Society of Hepatology (2002), the awareness of several Thai phytomedicines including the Thai copperpod has been promoted and the surveillance as registration of their side effects has been agreed. Based on this report, further study to investigate the pathophysiology mechanism in induction of hepatitis from Thai copperpod is suggested.

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Literature Cited


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(NAFLD). Annual Scientific Meeting of Thai Society of Hepatology, Nakornratchasrima Thailand. 5-6 Jul.


Tables

Table 1. Details of drug list of the commercially available Thai copperpod (Cassia siamea) tablet in Thailand1.

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug number</td>
<td>G455/41</td>
</tr>
<tr>
<td>Brand name</td>
<td>Cassia SIAMEA2</td>
</tr>
<tr>
<td>Ingredient</td>
<td>Dried young leaves of Cassia siamea L. 400 mg equivalent to Anhydrobarakol</td>
</tr>
<tr>
<td></td>
<td>not less than 10 mg</td>
</tr>
<tr>
<td>Pack size</td>
<td>6 x 10 tablet/box</td>
</tr>
<tr>
<td>Indication</td>
<td>For insomnia</td>
</tr>
<tr>
<td>Price</td>
<td>50 USDollar</td>
</tr>
</tbody>
</table>

1 Data available from http://thailabonline.com/herb1.htm
2 This drug was first launched in Thailand in 1998.

Table 2. Liver function test results for the patient reporting previous screening test, present illness, follow up after stopping intake of Thai copperpod (Cassia siamea) and reference range.

<table>
<thead>
<tr>
<th></th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>Alkaline phosphatase (U/L)</th>
<th>Total bilirubin (mg/dL)</th>
<th>Direct bilirubin (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous screening test (3 months before)</td>
<td>20</td>
<td>10</td>
<td>165</td>
<td>0.51</td>
<td>0.11</td>
</tr>
<tr>
<td>Present illness</td>
<td>145</td>
<td>125</td>
<td>157</td>
<td>0.53</td>
<td>0.12</td>
</tr>
<tr>
<td>Follow up (1 months after)</td>
<td>23</td>
<td>19</td>
<td>170</td>
<td>0.48</td>
<td>0.10</td>
</tr>
<tr>
<td>Reference range</td>
<td>&lt; 38</td>
<td>&lt; 38</td>
<td>58-279</td>
<td>0-1</td>
<td>0-0.25</td>
</tr>
</tbody>
</table>

AST = aspartate aminotransferase; ALT = alanine aminotransferase
* Values are given with conventional units referencing to the automated biochemical method (Hitachi machine) using the commercial reagent of Roche Boehringer Company.