Uncommon cause for a common disease—Severe steatohepatitis secondary to Ayurvedic ‘Man-Lion Tonic’

Cyriac Abby Philips¹, Praveen Kumar², Philip Augustine³, Pushpa Mahadevan⁴

ABSTRACT
Narasimha Rasayana (Sanskrit for ‘Man-Lion Tonic’) is a frequently prescribed Ayurvedic herbal medicinal preparation in South India for treatment of fatigue, hair loss, rejuvenation and weight gain in young men and women. The preparation is also prescribed as a rejuvenative in Ayurvedic medicine known as Ashthanga Hridayam Uttara to improve fertility by acting as an aphrodisiac. We present the interesting case of a young male, who consumed 2 tablespoons (~15 grams) of the ‘Man-Lion Tonic’ daily for 2 years, presenting with loss of appetite and well-being and elevated transaminases with liver histology showing overlapping features unique to spectrum of acute alcohol liver injury not described with CAM before.

Key words: Steatohepatitis, Fatty liver disease, Complementary and alternative medicine, Ayurveda, Drug induced liver injury, Hepatotoxicity.

INTRODUCTION
Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of asymptomatic abnormal transaminases world-wide and of chronic liver disease in the developed world, found in 17-30% of the population in Western countries. The well-known primary causes of NAFLD are obesity, type II diabetes, dyslipidemia, and insulin resistance.¹ However, secondary conditions that cause similar clinical and histologic picture, should be considered in patients who present with NAFLD without traditional risk factors. These include disorders of lipid peroxidation such as, abetalipoproteinemia, hypobetalipoproteinemia, familial combined hyperlipidemia; glycogen storage diseases, lipodystrophy syndromes, hepatitis C infection, Wilson's disease, total parenteral nutrition, severe weight loss secondary to bariatric procedures, celiac disease, drugs such as amiodarone, tamoxifen and anti-retroviral therapy.² Here we present the case of severe drug induced steatohepatitis in a young man, who consumed a commonly used complementary and alternative medication, Narasimha Rasayana or ‘Man-Lion’ Tonic for weight gain for 2 years, presenting with loss of appetite and well-being and elevated transaminases for a period of 2 months’ duration and in whom unique histology of liver injury not previously described with CAM was noted.

CASE REPORT
A 23-year-old non-alcoholic male without known metabolic syndrome, was referred to our Liver Clinic with a 2-month history of fatigue, loss of appetite and well-being without nausea, diarrhoea, and abdominal pain. The patient reported no smoking, previous liver disease, family history of liver diseases, blood transfusion or exposure to toxins. His past medical history was significant for consumption of herbal alternative medicine, known as Narasimha Rasayana (Man-Lion Tonic, daily once, approximately 15 g for 2 years) taken for weight gain and ‘rejuvenation’. On physical examination, the patient was alert, and oriented to time, place and person without pallor, icterus, peripheral lymphadenopathy or stigmata of chronic liver disease. His weight was 56 kg and height 168 cm, with body mass index of 19.8 kg/m². Liver span was 18 cm in the right mid clavicular line. The laboratory evaluation revealed normal hemogram, total bilirubin 1.2 mg/dl with direct fraction 0.4 mg/dl, alanine transaminase (ALT) 514 IU/L, aspartate transaminase (AST) 338 IU/L, normal serum protein, albumin and globulin, international normalized ratio 1.1 with normal renal function tests. C-reactive protein level was mildly raised 12.3 mg/L (normal 0–5 mg/L). Results of serologic tests were negative for hepatitis B surface antigen; anti-hepatitis B core Immunoglobulin (IgM and core total); anti-hepatitis A and E virus IgM; anti-hepatitis C virus antibody; anti-Cytomegalovirus IgM; anti-Epstein–Barr virus IgM; anti-nuclear antibodies; anti-smooth-muscle antibodies; anti-mitochondrial antibodies; and anti-neutrophil cytoplasmic antibodies. Serum ferritin and ceruloplasmin levels were also normal. An ultrasound and a computed tomography (CT) scan of the abdomen revealed only steatotic hepato-megaly and Shearwave elastography showed liver stiffness of 9.2 kPa suggestive of F3 fibrosis. A percutaneous ultrasound guided plugged liver biopsy revealed features suggestive of severe mixed macro and micro-vascular-steatosis (Figure 1A) with lobular inflammation, ballooned hepatocytes (Figure 1B). The biopsy was consistent with non-alcoholic steatohepatitis (NASH) with advanced fibrosis (F3).

Cite this article: Philips CA, Kumar P, Augustine P. Uncommon disease-Steatohepatitis secondary to Ayurvedic ‘Man-Lion Tonic’. OGH Reports. 2017;6(2):51-5.
Philips et al.: Severe steatohepatitis secondary to Man-Lion Tonic

1B, thin black arrow), Mallory Denk bodies (Figure 1B, thick black arrow), micro-vesicular steatosis related foamy degeneration (Figure 1D, black arrow) and periportal and preisinusoidal (or chicken wire fibrosis, D; Masson Trichrome, 20x) fibrosis suggestive of severe steatohepatitis.

**DISCUSSION**

Narasimha Rasayanam or ‘Man-Lion Tonic’ is a commonly utilized Ayurvedic herbal medicine in South India for treatment of a variety of symptoms ranging from fatigue to loss of libido without scientific reasoning. The product is available over the counter and for purchase online. Advertisements and publicity about this product is rampant among lower class and lower middle class population who opt for cheaper and easy symptomatic treatment options without the need for investigational expenditure. The ‘Man-Lion Tonic’ has 10 herbal ingredients (Table 1), mixed in special proportions along with powdered iron alloy, water, honey and butter, heated till boiling and then cooled down to a semi-solid consistency. Dosage is usually 1-2 tablespoons once or twice daily without a specified duration limit. The herbal components of this concoction have a plethora of other non-medicinal uses such as being part of dyeing agents, drill oil viscosity regulators, construction grade wall plaster stabilizer and marking inks.

Excess alcohol consumption, glucocorticoids, total parenteral nutrition, amiodarone and methotrexate, chemotherapy associated steatosis related to 5-fluorouracil, tamoxifen, irinotecan, cisplatin, and asparaginase are also causes of macrovesicular steatosis.\(^{[3]}\) Valproate, tetracycline (intravenous administration), aspirin, nucleoside reverse transcriptase inhibitors, glucocorticoids, nonsteroidal anti-inflammatory drugs and cocaine are causative agents. Drugs rarely associated with steatohepatitis are amiodarone, methotrexate tamoxifen, and irinotecan.\(^{[4, 5]}\) It was interesting to note that in our patient, histopathology showed foamy degeneration of the hepatocytes. Foamy degeneration (AFD) of hepatocytes is classically seen in severe alcoholic fatty liver disease. It is closely related to alcoholic fatty liver with jaundice (AFLJ). Both are defined by steatosis involving > 75% of hepatocytes. In the latter, diffuse macrovesicular steatosis is noted in the presence of cholestasis. The histological diagnosis of AFLJ requires exclusion of alcoholic hepatitis (AH; the absence of chicken wire fibrosis, neutrophilic inflammation, or Mallory-Denk bodies) and is characterized by the presence of significant diffuse microvesicular, foamy-appearing steatosis involving the perivenular and often midzonal hepatocytes, similar to that seen in several non-alcoholic liver injuries with abnormal mitochondrial fatty acid oxidation.\(^{[6]}\)

The only report of CAM causing severe microvesicular steatohepatitis was secondary to Margosa oil use.\(^{[7]}\)

Schepfier and colleagues reported 12 cases of toxic hepatitis implicating Herbalife preparations (1998-2004) with 10 sufficiently documented to permit causality analysis. In their cohort, liver histology showed hepatic necrosis, marked lymphocytic/eosinophilic infiltration and cholestasis patterns. Fulminant liver failure with explant showing giant cell hepati-
Table 1: Components of *Narasimha Rasayanam* (Man-Lion Tonic), their contents and non-medicinal uses. *

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Common name/ Description</th>
<th>Content</th>
<th>Non Ayurvedic Properties</th>
</tr>
</thead>
</table>
| Leaves of *Acacia catechu* | Cutch tree or Black Cutch, Areca nut tree | Rich in flavonoids | Red colouring agent in Paan (betel leaf with areca nut and tobacco chewed for its stimulant and psychoactive effects)  
Agent in dyeing and leather tanning  
Preservative for fishing nets  
Viscosity regulator for oil drilling |
| Leaves of *Plumbago zeylanica* | Ceeylon leadwort or Doctorbush | Plumbagin Organic hexane compounds  
Methanols | Plumbagin is genotoxic and mutagenic  
Used for treating canine distemper  
Mosquito larvicide |
| Leaves of *Dalbergia sissoo* | Indian Rosewood | Rich in polyphenols | Molluscicide against eggs of freshwater snails  
Juiced leaves and bark used as bonding agent in construction grade wall plaster |
| Leaves of *Pterocarpus marsupium* | Indian Kino Tree or Malabar Kino | Stillbenoids, natural phenols, rich in resveratrol | Hypoglycemic agent  
Causes weight loss and diarrhea when used for longer periods  
GlaxoSmithKline in 2010 suspended a small clinical trial of SRT501, a resveratrol compound due to adverse effects |
| Fruit of *Terminalia chebula* | Black Myrobalan (plum-like fruit bearing tree) | Glycosides, triterpenes, gallic acid, coumarins, tannins, phenols | No potential uses  
Paste mixed with cattle urine used for treatment of skin and genital infections and ingested for respiratory infections in some parts of India |
<table>
<thead>
<tr>
<th>Fruit of <em>Embelia ribes</em></th>
<th>False Black Pepper</th>
<th>Benzoquinones, alkaloids, resins and tannins</th>
<th>Cyclodextrin-based polymers for therapeutic delivery As components of hydrogels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruit of <em>Semecarpus anacardium</em></td>
<td>Marking – Nut Tree</td>
<td>Biflavonoids, phenolic compounds, oxy-acids, non-volatile alcohols</td>
<td>Marking inks Fixator agent for color dyes</td>
</tr>
<tr>
<td>Flowers of <em>Clerodendrum serratum</em></td>
<td>Glory Bower or Bleeding Heart flower</td>
<td>Flavanoids, terpenoids and steroids</td>
<td>None</td>
</tr>
<tr>
<td>Flowers of <em>Eclipta prostate</em></td>
<td>False Daisy</td>
<td>Coumestans, polyacetylenes, thiophene derivatives, steroids, triterpenes, flavonoids</td>
<td>None</td>
</tr>
</tbody>
</table>

In our patient, we noted a mixed macro and microvesicular pattern of steatohapatitis with foamy degeneration and perisinusoidal fibrosis - a histopathology pattern encompassing AFD, AFLJ and AH - which is not described in literature, especially with CAM. We suspect that the presence of phytochemicals such as phenolic and carboxyl compounds along with alkaloids and tannins leading to mitochondriopathy, would have caused a mixed pattern of injury similar to histopathology of acute alcoholic liver disease spectrum. Drug induced steatohepatitis is a rare form of drug induced liver injury (DILI) and is regarded as an uncommon cause of a common disease. The common histological patterns observed in DILI are acute and chronic hepatitis, acute and chronic cholestasis, and mixed cholestatic hepatitis. A Spanish group study on DILI noted that only 2 out of the 110 cases on liver histopathology showed a predominant pattern of steatosis.[10] However, more recent data from the Drug Induced Liver Injury Network (DILIN) concluded that although this is rarely described as the dominant pattern, 26% of cases showed some degree of steatosis and macrovesicular type as the predominant pattern noted in over 70% of the cases.[11] In a study by Navarro et al on liver injury from herbal and dietary supplements in the DILIN, majority of patients used products that contained vitamins, minerals and botanical extracts. Majority of the patients took non-body building supplements and 81% of the total number enrolled had identifiable ingredients.[12] Use of pure Ayurvedic products and related liver injury has not been reported in any drug injury screening networks. In recent years, it has been shown that some monomers and certain functional mixtures of herbs have potential uses in NAFLD treatment. Xiao and colleagues carried out an extensive PubMed review on randomized trials on several herbal derivatives under intense basic and/or clinical investigations relevant to treatment of NAFLD, such as wolfberry polysaccharides, garlic-derived monomers, red grape-derived resveratrol, and milk thistle-derived substances. However, a more detailed mechanistic research methodology and long-term clinical evaluations are needed for their future applications.[13] Phytochemical such as Curcumin, Lycopene, Resveratrol and Silymarin have been shown in indexed complementary and alternative journal studies to have steatosis reversing effects. However, none of these studies are well designed and lacks scientific clinical assessment and proper study methodology.[14] Traditional medicinal systems such as Indian Ayurveda, Japanese Kampo and Traditional Chinese medicine have reported on the therapeutic role of polyherbal formulations in treating hepatic ailments including NAFLD. Not many Ayurvedic formulations have been put for a scrutiny in the treatment of NAFLD and widespread use of the same, targeting low costs and potential safety because of natural ingredients invites acceptance without scientific reasoning.[15] None of the phytochemical agents (except Resveratrol) noted in the CAM used by our patient are validated in clinical scientific reasoning.

Conflict of Interest
No conflict of interest are declared.

Acknowledgement
No Acknowledgement are declared.

REFERENCES