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# Rhabdomyolysis Caused by *Commiphora mukul*, a Natural Lipid-Lowering Agent

Antonio Bianchi, Paola Cantù, Fabio Firenzuoli, Gabriela Mazzanti, Francesca Menniti-Ippolito, and Roberto Raschetti

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**OBJECTIVE:** To report a case of rhabdomyolysis caused by *Commiphora mukul*, a natural lipid-lowering agent.

**CASE SUMMARY:** A 55-year-old man was taking an extract of *C. mukul* 300 mg 3 times daily to lower his cholesterol level. He developed rhabdomyolysis with hemoglobinuria after 2 weeks of treatment. Laboratory tests showed creatine kinase 144 600 IU/L (reference range 24–195), myoglobin >3000 ng/mL (28–72), lactate dehydrogenase 7157 IU/L (230–460), aspartate aminotransferase 1115 IU/L (10–35), and alanine aminotransferase 205 IU/L (10–35). Analysis of a urine sample was 2+ positive for hemoglobin. All parameters returned to normal after the herbal preparation was discontinued.

**DISCUSSION:** The Naranjo probability scale indicates *C. mukul* as the possible cause of rhabdomyolysis in our patient. Drug-induced rhabdomyolysis is an established but rare adverse effect of high doses of cholesterol-lowering agents (statins) or interactions between drugs (eg, statins and fibrates). As of May 28, 2004, to our knowledge, this is the first reported case of rhabdomyolysis following *C. mukul* ingestion.

**CONCLUSIONS:** Our report describes a case of rhabdomyolysis possibly caused by *C. mukul* and underlines the need for active surveillance of natural products.

**KEY WORDS:** *Commiphora mukul*, guggul, herbal supplements, rhabdomyolysis.

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Rhabdomyolysis is a syndrome, caused by a large variety of diseases, that damages the integrity of the sarcolemma, leading to leakage of potentially toxic muscle cell components into the plasma. The causes of rhabdomyolysis can be hereditary or acquired. The hereditary causes consist primarily of enzyme defects causing disorders of carbohydrate metabolism, mitochondrial lipid metabolism, and other inherited disorders such as malignant hyperthermia and neuroleptic malignant syndrome. Acquired causes may be divided into traumatic (eg, burns, crushing), ischemic (eg, compression, vascular occlusion), metabolic (eg, diabetic ketoacidosis, hypothyroidism, hypokalemia), infectious (bacterial, viral), toxic (alcohol, drugs, toxins)

and exercise-related causes (eg, sports and military training, seizures). Finally, rhabdomyolysis can be induced by drugs such as opiates or some cholesterol-lowering agents.

Common final pathophysiologic mechanisms among these causes of rhabdomyolysis include an uncontrolled rise in unbound intracellular calcium and activation of calcium-dependent proteases, which lead to destruction of myofibrils and lysosomal digestion of muscle fiber contents.<sup>1</sup> The diagnosis of rhabdomyolysis is established in the presence of muscle symptoms with creatine kinase values >10 times the upper limit of normal and with creatinine elevation, usually with brown urine and urinary myoglobin.<sup>2</sup> The most severe complication of rhabdomyolysis is acute renal failure, which occurs in approximately 15% of patients with the syndrome.<sup>3</sup> Acute renal failure is believed to be chiefly caused by release of myoglobin into the blood that circulates to the kidneys, causing toxicity.<sup>4</sup>

Cholesterol-lowering therapy is the central approach in the primary and secondary prevention of cardiovascular

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Author information provided at the end of the text.

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diseases, the leading cause of death in industrialized countries. In systematic reviews, hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) have been shown to reduce total mortality, risk of myocardial infarction or reinfarction, and stroke.<sup>5</sup> In general, statins are well tolerated, although in a minority of patients, severe adverse effects like rhabdomyolysis may develop.<sup>6</sup> The risk of rhabdomyolysis increases with serum concentrations of the statin. Factors affecting the volume of distribution, as well as factors reducing drug metabolism, alter the risk of rhabdomyolysis. Concomitant medications, particularly fibrates, also increase the risk of rhabdomyolysis, primarily by altering statin catabolism. Such drug interactions are generally attributed to the effects on the CYP3A4 system.<sup>7</sup> Because of genetic polymorphism of these enzymes, CYP3A4 activity can vary tenfold among patients, resulting in individual variations in susceptibility to drug interactions.

In the last few decades, much interest has been focused on herbal supplements as possible alternatives to synthetic drugs. One of the reasons for this popularity has to be found in the naïve belief that herbal drugs are of natural origin and consequently free of adverse effects.<sup>8</sup> *Commiphora mukul* (Burseraceae family) is a bushy shrub common in the desert areas of India. The oleo gum resin secreted by this plant (guggul) has always been one of the main remedies of Ayurveda (the ancient Indian system of health care and medicine), mostly used in rheumatic and gastrointestinal disorders.<sup>9</sup> Since the early 1970s, accumulating experimental and clinical evidence has shown the antiatherosclerotic and cholesterol-lowering actions of *C. mukul*.<sup>10,11</sup> In 2 randomized trials, guggul reduced levels of total cholesterol by 11%, of low-density lipoprotein cholesterol (LDL-C) by 12%, and of triglycerides by 15%.<sup>12,13</sup> However, in a recent randomized controlled trial, guggul did not appear to improve levels of serum cholesterol over the short term.<sup>14</sup> The active ingredients, guggulsterone Z and E, are contained mainly in the sterol fraction.

Considerable interest has also recently focused on the innovative mechanism underlying the action of *C. mukul*. Previous results indicated that guggulsterone Z prevents endogenous hypercholesterolemia by stimulating the thyroid gland, thus increasing triiodothyronine production.<sup>15,16</sup> More recent studies suggest that guggulsterone is an effective inhibitor or modulator of the farnesoid X receptor (FXR), a hormonal nuclear receptor normally activated by the bile acids.<sup>17,18</sup> FXR mediates a number of biochemical processes that depend on bile acids and have a central role in the synthesis of cholesterol. Although several mild adverse events were reported during some clinical trials, including rash, nausea, vomiting, and headache, the extract of *C. mukul* is considered a well-tolerated product.<sup>14,19</sup>

In addition to its adverse effects, guggul has been found to significantly reduce the peak plasma concentrations of propranolol and diltiazem.<sup>20</sup> This report summarizes the development of rhabdomyolysis in a patient taking an herbal product containing an extract of *C. mukul* to lower his blood cholesterol level.

## Case Report

A 55-year-old man was admitted to the Department of Nephrology, Gallarate Hospital, Gallarate, Italy, in October 2002 after 2 episodes of macrohematuria, the second accompanied by fainting without trauma. The patient was taken to the hospital by his relatives. On admission, analysis of a urine sample showed 2+ positive hemoglobin without erythrocytes in the sediment. Further laboratory tests showed increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, creatine kinase, and myoglobinemia (Table 1). Even though the patient had no muscular symptoms, the laboratory findings, supported by a history of dyslipidemia, led to a diagnosis of rhabdomyolysis with hemoglobinuria.

The patient's past medical history contained no relevant information except that, 3 years before admission, laboratory tests showed impaired glucose tolerance and hypercholesterolemia (total cholesterol 286 mg/dL, high-density lipoprotein cholesterol 67 mg/dL, LDL-C 184 mg/dL, triglycerides 126 mg/dL). The patient was treated with simvastatin 10 mg/day for 6 months; the statin treatment was then suspended because the serum creatine kinase concentration transiently increased to 500 IU/L (reference range 24–195). After discontinuation of the drug, the serum creatine kinase concentration returned to within normal values.

On questioning, the patient reported that, 2 weeks earlier, he began taking daily three 300-mg capsules containing *C. mukul* to reduce his cholesterol levels (total cholesterol 250 mg/dL at that time). The herbal product was prepared by the local chemist using a standardized dry extract of the oleo gum resin without excipients and was used as self-medication. The patient had not taken any lipid-lowering drug for one year before starting treatment with the *C. mukul* preparation, and there was no other concomitant drugs in use on admission.

The herbal supplement was immediately stopped, and therapy was started with hydration and alkalinization with intravenous sodium bicarbonate (200 mM) for 48 hours. The patient's clinical condition progressively improved, no renal damage developed, and the urinary values normalized 24 hours later. Lactate dehydrogenase and myoglobin levels returned to normal within 6 days (290 IU/L and 63 ng/mL, respectively); AST returned to normal value at discharge (36 IU/L); creatine kinase and ALT remained above normal values at discharge (271 IU/L and 74 IU/L, respectively; Table 1), but returned to normal during the outpatient clinic follow-up.

## Discussion

This report describes the possibility of rhabdomyolysis after consumption of *C. mukul*. To our knowledge, this is the first case of rhabdomyolysis in a patient taking an herbal product containing an extract of *C. mukul* to lower blood cholesterol.

According to the Naranjo probability scale, *C. mukul* was the possible causative agent of rhabdomyolysis in our patient.<sup>21</sup> There was a temporal relationship between the herbal product administration and the adverse effect; moreover, the recovery correlates with discontinuation of the treatment and the adverse event was confirmed by blood tests. However, even though the patient was not taking any drug other than the *C. mukul* preparation, an alternative unknown cause of rhabdomyolysis cannot be excluded. The medical history of the patient reported that previous treatment with a statin had been suspended because of a transient increase in the creatine kinase concentration; however, rhabdomyolysis was not diagnosed.

Episodes of rhabdomyolysis due to medicinal plants or an interaction between herbal preparations and synthetic drugs have been described. For example, a recent report describes a renal transplant recipient in whom asymptomatic rhabdomyolysis (limited to abnormal laboratory findings) developed resulting from an interaction between

cyclosporine and a product based on red rice yeast (*Monascus purpureus*), a naturally occurring statin-containing product;  $\beta$ -sitosterol; dan shen root (*Salvia miltiorrhiza*); and garlic (*Allium sativum*).<sup>22</sup> A recent Italian review highlighted 77 cases of rhabdomyolysis caused by licorice (*Glycyrrhiza glabra*)—some were complicated by severe arrhythmia.<sup>23</sup> It could be possible that some subjects, currently difficult to identify, may have a genetic deficiency of cholesterol in smooth and muscular cells, making them more susceptible to rhabdomyolysis.<sup>24</sup> The mechanism of action of *C. mukul* involves direct action on the expression of some components of the cytochrome P450 system (eg, CYP7A1, CYP8B1) that could interfere with the metabolism of guggulsterone.<sup>17,25</sup> Our patient, as mentioned above, presented with an increase in creatine kinase concentration during previous treatment with a statin; thus, we can suppose that the rhabdomyolysis reported here could be related to a particular susceptibility of the patient to lipid-lowering agents and/or to the specific mechanism of action of guggul.

The increasingly widespread use of herbal preparations raises several problems of safety. The case reported here, along with current literature on the adverse effects of herbal medicines, show that the natural origin is not a guarantee of safety.<sup>26</sup> The recovery of adulterants and contaminants in herbal drugs represents an additional problem. Moreover, pharmacologic interactions between the chemical components of herbal products and simultaneously administered synthetic drugs often cause serious consequences.<sup>27</sup>

## Summary

Adverse effects related to the use of herbal products are a growing problem. *C. mukul* was the possible causative agent of rhabdomyolysis in our patient. This episode underlines the need for active surveillance of natural products.

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**Table 1.** Changes in the Patient's Laboratory Findings During Hospitalization

Findings (reference range)	Hospital Day					
	1	2	3	4	6	10
Creatine kinase (24–195 IU/L)	144 600	86 976	52 855	37 087	6810	271
Lactate dehydrogenase (230–460 IU/L)	7157	3860	2406	1453	290	260
AST (10–35 IU/L)	1115	864	691	644	NA	36
ALT (10–35 IU/L)	205	186	183	201	NA	74
Myoglobin (28–72 ng/mL)	>3000	>3000	779	NA	63	NA
Urea (10–50 mg/dL)	41	28	21	19	NA	32
Creatinine (0.60–1.20 mg/dL)	1.07	0.97	0.97	0.97	NA	1.09
Hemoglobin (12.5–17.2 g/dL)	15.5	15	14	NA	NA	14.3
Hematocrit (39–49%)	48	44	43	NA	NA	43
Sodium (137–148 mEq/L)	141	139	146	NA	NA	NA
Potassium (3.6–5 mEq/L)	4.40	3.8	4.1	NA	NA	NA
Bicarbonate (24–29 mEq/L)	20	22	25	NA	NA	NA
Urine tests (600–1800 mL)	2000 mL: Hb 2+; absence of granulo- cytes and proteins	2000 mL	within normal levels	3000 mL	3600 mL: within normal levels	NA

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Hb = hemoglobin; NA = not available.

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## EXTRACTO

**OBJETIVO:** Informar el caso de una rabdomiólisis causada por *Commiphora mukul*.

**RESUMEN DEL CASO:** Un hombre que estaba tomando un extracto de la planta *C. mukul* para reducir su nivel de colesterol en sangre desarrolló una rabdomiólisis con hemoglobinuria luego de 2 semanas de tratamiento. Los resultados del análisis de laboratorio de su sangre fueron los siguientes: fosfoquinasa de creatinina 144 600 UI/L (230–460 UI/L), mioglobina >3000 ng/mL (28–72 mL), deshidrogenasa de lactato 7157 UI/L (230–460 UI/L), AST 1115 UI/L (10–35 UI/L), y ALT 205 UI/L (10–35 UI/L). El análisis de su orina reveló 2+ positivo para hemoglobina sin eritrocitos en el sedimento. Todos los parámetros volvieron a la normalidad luego de discontinuar el uso de la preparación botánica. El paciente tenía historial de elevación en las enzimas hepáticas debido al uso de una estatina, pero hacia ya un año que no recibía tratamiento al momento de comenzar a usar la *C. mukul*, un agente con propiedades antilipídicas.

**DISCUSIÓN:** Utilizando la escala de probabilidades Naranjo, el *C. mukul* está posiblemente asociado a este evento de rabdomiólisis. La rabdomiólisis inducida por fármacos es un efecto adverso bien establecido, pero raro que ocurre con el uso de dosis altas de agentes antilipídicos, como las estatinas, o que ocurre como parte de una interacción entre estatinas y fibratos. El caso aquí informado es, a nuestro entendimiento, el primer caso de rabdomiólisis relacionado al uso de *C. mukul*.

**CONCLUSIONES:** Este informe describe un caso de rabdomiólisis posiblemente causado por *C. mukul* y enfatiza la necesidad de farmacovigilancia activa de los productos naturales.

Jorge R Miranda-Massari

## RÉSUMÉ

**OBJECTIF:** Rapporter un cas de rhabdomyolyse causé par le *Commiphora mukul*.

**RÉSUMÉ:** Un homme de 55 ans a pris un extrait de *C. mukul* pour réduire son cholestérol. Il a développé par la suite une rhabdomyolyse avec hémoglobinurie après un traitement de 2 semaines. Les tests de laboratoire indiquaient les valeurs suivantes: créatinine phosphokinase 144 600 IU/L (normale 24–195), myoglobine >3000 ng/mL (28–72), lactate déshydrogénase 7157 UI/L (230–460), AST 1115 IU/L (10–35), et ALT 205 UI/L (10–35). L'analyse d'un échantillon urinaire a démontré la présence de hémoglobine 2+. Tous les paramètres sont redevenus normaux après l'arrêt du produit naturel.

**DISCUSSION:** La probabilité de Naranjo indique le *C. mukul* comme étant la cause possible de rhabdomyolyse chez ce patient. Cet effet secondaire est bien connu lorsque de hautes doses de statines ou lorsqu'une statine est combinée à un fibraté. Ce cas est le premier rapporté de rhabdomyolyse secondaire à *C. mukul*, un agent hypolipémiant naturel.

**CONCLUSIONS:** Notre rapport décrit un cas de rhabdomyolyse posiblement causé par le *C. mukul* et fait réaliser le besoin de surveillance des produits naturels.

Marc M Perreault