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Case Report: The Association Between Ginseng and Mania: A Case Report and Literature Review

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ABSTRACT

Background: Ginseng has long been used as a tonic and panacea, a dietary supplement, or a therapeutic agent in different countries. Among many common side effects for this herbal, the affective disorder is one of the rare ones.

Case presentation and Intervention: We present a case of mania with psychotic features. The patient was an 18-year-old male who consumed Asian red ginseng for five months to treat his overweight. His physical examination was normal except for mild mental retardation. Mental status examination revealed increased psychomotor activity, anxious mood, unstable affect, irritability, aggression, pressured speech, grandiosity, auditory hallucinations, and persecutory delusions. After the admission, he was ordered to stop ginseng taking and supportive care and treatment with risperidone, lorazepam, and valproate sodium started. After 15 days, all symptoms were treated.

Conclusion: Despite the widespread use of herbal and dietary supplements, physicians and health care providers should be concerned about the side effects of these products, such as mania and psychosis.

Keywords: Herbal medicine, Bipolar disorder, Psychotic disorders, Mood disorders

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Highlights

- Ginseng abuse syndrome, including manic symptoms, can occur in people who consume even less than 15 g/d ginseng.

- Physicians and health care providers should consider inquiring about herbal consumption in suspicious patients.

Introduction

Ginseng has long been used as a tonic and panacea in Asian countries and also as a dietary supplement or therapeutic agent in Western countries [1]. This small perennial plant has been used for thousands of years in eastern cultures as a panacea for many different and even extravagant reasons, ranging from physical or mental weakness to sexual dysfunction [2]. Its main components are ginsenosides, of which at least 15 different types have been identified. Ginsenosides facilitate steroidogenesis across the hypothalamic-pituitary-adrenal axis [2]. Furthermore, they strengthen cholinergic nerves by promoting the generation and release of acetylcholine, which has important effects on memory, thereby exhibiting its impact on learning and memory [3].

The toxicity evaluation of ginseng preparations in human studies has shown a relatively low incidence of toxic events. Although it has been accused of various side effects such as nervousness, frank anxiety, insomnia, hypertension, headache, diarrhea, vomiting, and epistaxis [2], an affective disorder such as manic episodes has not been a common one.

Case presentation

An 18-year-old single, Iranian man, presented for the emergency assessment of his irritability and aggressive behaviors over the last two weeks. He was worried about the fear of the goblins who tried to make him guilty and control him with the camera and GPS. He was afraid of losing his abilities. He also claimed to be related to Imam-e-zaman (the twelfth imam for Muslims) and God. His father reported that the patient had insomnia and stronger sexual desire. There was no history of alcohol or substance use. Also, he or his first-degree relatives had no prior history of mental illness. In his medical history, there were childhood seizures controlled by sodium valproate, carbamazepine, and clonazepam. Although he discontinued his treatment from 8 months ago, he experienced no seizures.

He consumed Asian red ginseng during the last five months to treat overweight. His parents mentioned that he ingested ginseng approximately 10 g/d. His physical examination was normal except for mild mental retardation. His heart rate, blood pressure, and temperature were normal, too. Urine toxicology and blood alcohol levels were negative. He was alert and fully oriented. Mental status examination revealed increased psychomotor activity, anxious mood, unstable affect, irritability, aggression, pressured speech, grandiosity, auditory hallucinations, and persecutory delusions. Neurologic counseling revealed no abnormal neurological findings or symptoms in favor of seizure. After admission, we ceased his ginseng use and started supportive care and treatment with risperidone 2 mg BID, lorazepam 1 mg daily, and valproate sodium 500 mg BID for 15 days that resulted in the remission of all symptoms.

Discussion

Ginseng is purported to have "adaptogenic" effects that maintain homeostasis by normalizing the overall function of the body [4]. Ginseng has several effects on the body that increases nonspecific resistance to biochemical and physical stressors, improves overall well-being, and enhances mental capacity [5]. Although some studies suggest that ginseng decreases learning time and fatigue, increases adaptability to stress, lessens aggressive behavior, and may stabilize sleep, its activity has not been definitively documented [2]. Ginseng root contains a mixture of several saponin glycosides called ginsenosides. Ginsenosides inhibit cyclic AMP phosphodiesterase, and the effects of various ginsenosides on cortical steroid secretion and cyclic AMP phosphodiesterase activity appear to be similar.

This effect of ginsenosides may account partly for its psychoactive central effects both alone or in combination with monoamine oxidase inhibitors. The physiological properties of ginseng include corticosteroid-like, hypoglycemic, and immuno-modulating actions by affecting the hypothalamic-pituitary-adrenal (HPA) axis and monoamine systems [6]. According to the World Health

Table 1. Demographic and clinical characteristics of published cases with mania after ginseng intake

Author(s), Date (Reference)	Gender (Age, y)	Name of Preparation	Daily Dose	Reason for Taking	Time to Onset of Manic Symptoms	Family Psychiatric History	Medical History	Treatment Outcomes	Resolution of Symptoms (Days)
Jones et al., 1987 [8]	F (42)	Ginseng, bee pollen	45 mg	Depression	-	None	Unknown	Triazolam, lorazepam	-
González-Seijo et al., 1995 [10]	F (35)	Panax ginseng	One tablet	Unknown	Ten days	Unknown	None	Haloperidol, lithium	2
Engelberg et al., 2001 [9]	M (26)	Chinese red ginseng root	500-750 mg	Boost energy	Two months	None	None	Valproic acid, lorazepam	10
Vazquez et al., 2002 [2]	F (56)	Ginseng root extract solution	300 mg	Fatigue, general weakness	Two weeks	Unknown	Unknown	Haloperidol, Lorazepam	2
Joshi et al., 2005 [11]	M (26)	Chinese ginseng root	250 mg	Boost energy	Two months	Unknown	Unknown	Valproic acid	10
Norelli et al., 2015 [12]	M (23)	Asian red ginseng	~15 g	Boost energy	One month	None	None	Risperidone	3
Norelli et al., 2015 [12]	M (79)	Korean ginseng, yohimbine	~20 g	Erectile dysfunction	Two months	Unknown	Mild hypertension	Unknown	-
This paper, 2019	M (18)	Asian red ginseng	~10 g	Overweight	Four months	Unknown	Seizure, mental retardation	Risperidone, lorazepam, valproic acid	15

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Organization (WHO) review (2010), ginseng saponins depress blood prolactin, thereby increasing libido in male impotence [7]. WHO reports no known contraindications for Panax ginseng [7].

The adverse effects of ginseng intake are some symptoms, including indigestion, diarrhea, headache, insomnia, palpitations, hot flashes, and dry mouth. Nevertheless, the evaluation of adverse events is difficult as the information on the types and content of ginseng is usually insufficient. Ginseng abuse syndrome develops in cases, who take abnormally excessive doses (15 g/d or above) of ginseng, and when the dose is decreased to 1.7 g/d, the symptoms are rare [7]. In contrast to WHO recommendation, we observed symptoms of mania and psychosis in our patient with a low dose of ginseng (10 g/d). The first reported association of mania with ginseng was mentioned by Jones and Runikis [8], who reported the interaction of ginseng with phenelzine in 1987. To the best of our knowledge, only seven cases [2, 8-12] of the acute manic episode after consuming ginseng have been reported so far (Table 1).

In this paper, we presented a case with mania and psychotic features after ginseng intake. We believe ginseng was responsible for the development of a complete manic episode in this patient who had a previous convulsive disorder. In this regard, this hypothesis is supported by the temporary sequence with ginseng as the only therapy modification in an otherwise stabilized patient and the swift resolution after the product withdrawal. Both the presentation and clinical course were coincident with previously reported substance/medication-induced bipolar and related disorders.

DSM-5 has stated the diagnostic category of "substance/medication-induced bipolar and related disorder." According to this, the diagnosis needs a temporal link between the occurrence of mania and the use or withdrawal of substances or medications. DSM-5 also sets less restrictive criteria for the diagnosis of substance/medication-induced bipolar and related disorder than for mania. Criterion A for mania (as required for a diagnosis of bipolar disorder) is "a distinct period of abnormally and persistently elevated, expansive, or ir-

ritable mood and abnormally and persistently increased activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary)" [13].

The precise mechanism of ginseng action is still unclear, partly reflects our inadequate knowledge about the pathophysiology of mania and depression. Researchers have conducted several in vitro studies on the effects of individual ginsenosides or red ginseng extract on cytochrome P450 (CYP 450) enzyme and drug delivery systems. The saponin fraction of red ginseng suppressed CYP2E1; however, the effects of individual ginsenosides on CYP activity are not similar [3]. In a crossover study, Kim et al. found no clinical drug interaction between red ginseng and Cytochrome P450 (CYP) enzymes, as well as between red ginseng and drug transporter P-glycoprotein (P-gp) in healthy Korean volunteers [14]. Concerning interactions, ginseng may increase the effects of some widely-used psychiatric drugs such as haloperidol and monoamine oxidase inhibitors.

The general picture of cases with mania is predominantly the history of a male person between the second and fifth decade of life and a personal (and occasionally familiar) record of affective disorder. With respect to ginseng, patients are usually under antidepressant treatment. Someone can chew the ginseng root, or take it as a powder, liquid extract, decoction, or infusion. The ginsenosides level varies depending on steeping time and type of preparation. The ginsenosides concentration varies from approximately 64% to 77% [5]. The recommended short-term (three months) dose of dry ginseng root is 0.5-2 g, which is equivalent to 200-600 mg of extract. For continuous administration, the recommended dose is less than 1 g of the dry root [15].

Conclusion

Although herbal and nutritional supplements are marketed as safe, in this case, we presented a man with mania and psychotic features after consuming Asian red ginseng (about 10 g/d). Most probably, the potential adverse side effects could occur at a low dose of ginseng. Mania and psychosis can impair judgment, which can result in harm to oneself and or others. Physicians and health care providers should inquire about herbal products' consumption.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (No. IR.GUMS.REC.1398.465). All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki, 2013.

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Authors contributions

Drafting the original paper: Robabeh Soleimani and Zahra Gol; Writing, reviewing, and editing the paper: Robabeh Soleimani and Seyede Melika Jalali; Collecting resources: Zahra Gol and Seyede Melika Jalali; Supervising the research: Robabeh Soleimani.

Conflict of interest

The authors declared no conflict of interest.

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