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Research Article

Medicinal Mushroom, *Ganoderma Lucidum*, Improves Painful Symptoms in Patients with Restless Legs Syndrome

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Abstract

Introduction

Restless legs syndrome (RLS) is a prevalent sensorimotor sleep disorder that worsens quality of life. All the currently available drug treatments for RLS have limitations. Extracts of the mushroom Ganoderma lucidum (GL) have shown several beneficial biological effects in neurodegenerative diseases. The objective of the present study was to evaluate the effect of a 2-month course of GL extract on the intensity of painful RLS symptoms.

Methods

Twenty consecutive patients with primary RLS were included, and 18 were analysed for efficacy. The patients took 920 mg of GL extract a day for 2 months. The International Restless Legs Syndrome Study Group severity rating scale (IRLS) was assessed at baseline (IRLS0), after 1 month (IRLS1) and 2 months (IRLS2) of treatment, and two weeks after treatment discontinuation (IRLS3). At 2 months, patients were asked about the relief of painful symptoms and were divided into responders (patients with symptom relief) and non-responders (patients without symptom relief).

Results

IRLS1, IRLS2 and IRLS3 were significantly lower than IRLS0 ($p=0.015$, $p<0.001$, $p<0.001$ respectively). Thirteen (72%) patients reported relief after 2 months of treatment with GL. Relief was maintained in 11 patients (61%) two weeks after GL discontinuation. At baseline, there were no significance differences in demographic, clinical or laboratory variables between responders and non-responders.

Conclusion

Our results suggest that GL might be a useful dietary supplement for relieving symptoms in patients with RLS.

Keywords: Ganoderma lucidum; Mushroom; Restless legs syndrome; Sleep disorders

Introduction

Restless legs syndrome (RLS) is one of the most common sleep-related sensorimotor disorders, with a worldwide prevalence of 5-10% [1]. It is mainly manifests itself (especially before going to bed) as discomfort in the limbs, described variously as a "prickly", "stinging", "creeping" or "burning" sensation. RLS can occur on one or both sides of the body - specifically in the lower limbs, although the upper limbs may also be involved. The discomfort is usually unbearable and forces patients to move or massage their limbs to gain some relief [2]. RLS may be idiopathic or may result from other conditions, such as iron deficiency, kidney failure, diabetes, or treatment with certain medications [3]. The recommended drug treatments for RLS include dopamine agonists and calcium channel-alpha 2-delta receptor ligands [4]. However, the dopamine agonists' potential side effects (with sometimes even an augmentation of the symptoms of RLS) limits the drugs' use in some people [5].

In this context, medicinal mushrooms may be an interesting treatment option [6]. Indeed, preparations of certain mushrooms have demonstrated some degree of efficacy in a few neurologic, psychiatric and cognitive disorders, such as depression and Alzheimer's disease [7,8]. One of these (*Ganoderma lucidum*, GL), also known as "reishi" or "the mushroom of immortality" has shown interesting biological activities in preclinical studies, such as immunomodulatory, anticancer, antidiabetic, anti-inflammatory, anti-oxidant, anti-androgenic, antiviral, antihepatitis, cardio protective and (via the dopaminergic system) neuroprotective effects [9-12].

To the best of our knowledge, GL has not previously been clinically assessed in patients with RLS. Given the mushroom's potential neurological effects, the objective of the present study was to evaluate the effects of a GL extract on idiopathic forms of RLS.

Methods

Subjects

All participants were recruited at a private neurology practice between June 2022 and December 2022. The first 20 patients referred for idiopathic RLS were prospectively screened against the following inclusion criteria: a diagnosis of RLS, according to the criteria published by the International Restless Legs Syndrome Study Group (IRLSSG) [13]; age 18 or over; and the provision of written, informed consent. The non-inclusion criteria were as follows: diabetes, iron

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deficiency (defined as a serum ferritin level below 50 mg/L), kidney failure, treatment with medications capable of exacerbating RLS (e.g. neuroleptics, lithium, antihistamines, sodium oxybate, and all types of antidepressant); and previous treatment with GL.

A total of 67 consecutive RLS patients were screened during the study period (Figure 1). Forty-seven of these were excluded from the study: 21 had diabetes, 15 had taken drug treatments capable of exacerbating RLS, eight had iron deficiency, and two had kidney failure. The remaining 20 patients were included. Two of these withdrew prematurely from the study: one experienced moderate adverse events after consuming GL (headache and diarrhoea) and the other did not take the full dose of GL and was excluded. Ultimately, 18 patients were taken in consideration in the analysis.

The following demographic and clinical variables were recorded: age, sex, body mass index (kg/m^2), a family history of RLS (if known), and the time since onset of the condition. The following laboratory variables were also recorded: glomerular filtration rate ($ml/min/m^2$, as estimated with the four-component Modification of Diet in Renal Disease equation), and serum levels of ferritin (mg/L), vitamin D (ng/ml), and thyroid-stimulating hormone (mIU/L).

The patients were assessed using on the IRLSSG severity rating scale (IRLS) [14], which was developed to assess changes over time in RLS and the response to treatment in particular. The IRLS consists of a 40-point self-administered questionnaire. The RLS can then be classified as mild (a score below 10), moderate (from 11 to 20), severe (from 21 to 30), or very severe (31 or more). After baseline measurements, the participants took two capsules of GL per day before the evening meal (each capsule contained 460 mg of GL extract (Mico-Rei, Ganozumib®, Hifas da Terra/HdT488), over a period of 2 months. The IRLS score was determined before taking GL ($IRLS_0$), 1 month ($IRLS_1$) and two months ($IRLS_2$) after treatment initiation, and two weeks after treatment discontinuation ($IRLS_3$).

At the end of the 2-month course of treatment, patients were asked about the relief of painful symptoms and were divided into "responders" (i.e. patients who reported symptom relief) and "non-responders" (patients who reported a lack of relief). Patients were again asked about symptom relief two weeks after the end of the course of treatment.

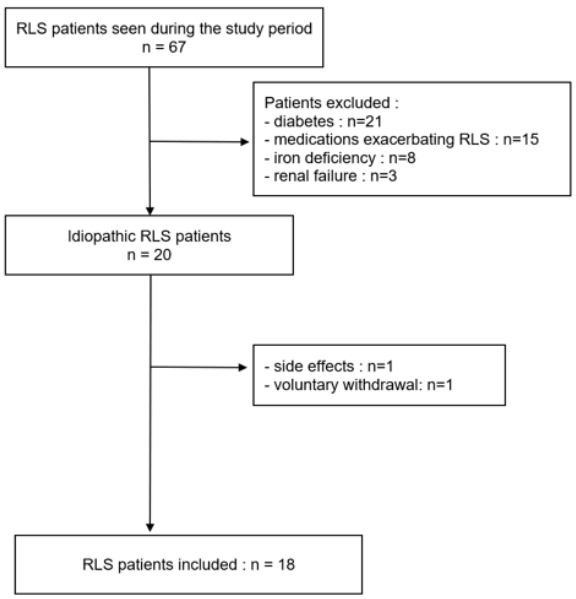

Figure 1: Flow-chart of the study-population.

Statistical analysis

The values of $IRLS_0$, $IRLS_1$, $IRLS_2$ and $IRLS_3$ were compared using a univariate analysis (Student *t*-tests). Responders and non-responders were compared using Student's *t* test for continuous variables and a chi-squared test for categorical variables. Statistical analyses were performed with pvalue.io online software [15].

Results

At baseline, there were no significance differences in demographic, clinical or laboratory variables between responders and non-responders (Table 1).

$IRLS_1$, $IRLS_2$ and $IRLS_3$ were all significantly lower than $IRLS_0$ ($p=0.015$, $p<0.001$, and $p<0.001$, respectively; Figure 2).

Thirteen (72%) of the 18 patients were responders, i.e. they reported relief after 2 months of treatment with GL. Relief was maintained in 11 patients (61%) two weeks after the end of the course of treatment with GL.

	Responders (n=13)	Non-responders (n=5)	p
Age (years)	52 ± 4.6	50 ± 3.8	0.5
Females (%)	9 (69)	5 (100)	0.3
BMI (kg/m2)	24.2 ± 2.8	22.2 ± 2.6	0.2
Family history of RLS (%)	7 (54)	3 (60)	1
Symptom duration (months)	14.2 ± 17.7	17.2 ± 12.6	0.3
IRLS0	23.1 ± 3.7	22.2 ± 2.6	0.2
Serum ferritin level	126 ±10.3	113 ± 8.5	0.5
Serum vitamin D level	35.0 ± 3.4	32.8 ± 2.9	0.9
TSH (mUI/L)	2.2 ± 1.5	2.0 ± 1.2	0.4
eGFR (ml/min/m2)	95.0 ± 8.5	75.0 ± 7.1	0.2
(BMI: body mass index; RLS: restless legs syndrome; TSH: thyroid-stimulating hormone; eGFR: estimated glomerular filtration rate)			

Table 1: Baseline demographic, clinical and laboratory parameters of the patients with restless legs syndrome (RLS), according to the presence or absence of symptom relief (i.e. responders vs. non responders).

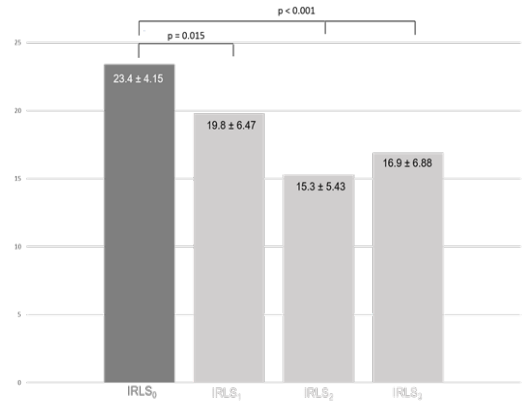

Figure 2: Change over time in the International Restless Legs Syndrome Study Group severity rating scale (IRLS): IRLS0: at baseline (mean ± SD); IRLS1: after 1 month of *Ganoderma lucidum* (GL) intake; IRLS2: after 2 months of GL intake; IRLS3: 15 days after discontinuation of GL.

Discussion

The main finding of the present study was that taking 920 mg of GL extract per day for 2 months relieved the symptoms of patients suffering from RLS. Although there is a growing body of research data on mycotherapeutics, the present study is the first to have assessed the effect of GL on patients with RLS.

Brain iron deficiency is thought to be the main disease mechanism underlying the symptoms of RLS, together with the autosomal dominant inheritance of genetic factors [16]. The main consequences of brain iron deficiency are likely to be (i) hypoxia, leading to a hyperdopaminergic state with an increase in the synthesis, liberation and turnover of dopamine and (probably) impairments in the descending dopaminergic pathway, and (ii) myelin loss and white matter alterations, leading to impaired somatosensory integration. Ingestion of GL might relieve painful symptoms in patients with RLS through its antioxidant capacity. Over the past few years, pharmacological analyses have shown that the natural bioactive compounds in mushrooms include polysaccharides with antioxidant and immunostimulant properties [9]. Thus, treatment with GL might alleviate the chronic oxidative stress that builds up progressively in the brain of patients with RLS.

The current study had several limitations. Firstly, and most importantly, the study population was small and lacked a placebo group. Secondly, the optimal dose level of GL extract and the optimal duration of treatment have not been defined. However, the present results demonstrated the safety of GL: only 1 patient experience a moderately intense headache a few days after starting to take the GL extract. This might have been due to a detoxication process, such as a Herxheimer reaction [17].

Conclusion

In conclusion, our results showed that GL extract is a safe, efficacious nutritional strategy for the treatment of moderate-to-severe RLS. More detailed studies will now be needed to confirm GL's potential ability to relief the symptoms of RLS.

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