

Effects of canary seed on two patients with disseminated granuloma annulare

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Abstract

Treatment of disseminated granuloma annulare (GA) can be challenging and there is no gold standard for treatment. We observed two cases of generalized GA that were treated successfully with canary seed milk despite being resistant to other treatments. Canary seed milk has antioxidant (contains vitamin E), anti-diabetic (DPP-4 inhibition), and anti-hypertensive (ACE inhibition) properties.

Therefore, dermatologists can consider canary seed milk, also known as alpiste milk, as a sole or supplemental treatment for patients with GA with or without comorbidities such as diabetes and hypertension, who prefer alternative therapy or failed other treatments.

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Introduction

Granuloma annulare (GA) is a benign self-limited granulomatous disorder characterized by multiple smooth annular erythematous or violaceous papules coalescing into plaques that can involve any skin area but are most commonly seen on the dorsal hands and arms. GA can be characterized into different types, such as generalized, localized, subcutaneous, interstitial, and perforating.¹

GA has an unknown etiology but is likely a Th1- type delayed hypersensitivity reaction to a variety of triggers. Generalized GA is more often chronic when compared to the localized form and is more commonly associated with systemic diseases such as diabetes, hyperlipidemia, thyroid disease, and malignancy.² There is no gold standard treatment for GA,³ but current treatment options include topical and intralesional corticosteroids, topical calcineurin inhibitors, antibiotics, hydroxychloroquine, phototherapy, pentoxifylline, dapsone, isotretinoin, tumor necrosis factor a (TNF-a) inhibitors, topical and oral vitamin E, leukotriene inhibitors and others.⁴ Here, we present two cases of generalized GA treated with canary seed, commercially available as alpiste milk.

Case Report #1

An 80-year-old Hispanic female with a medical history of hypertension and diabetes presented with erythematous annular plaques on the neck, back, bilateral arms, and thighs for one year. She had failed treatment with topical steroids, topical calcineurin inhibitors, oral corticosteroids, and oral antihistamines treated by another dermatology provider. We performed a punch biopsy which confirmed the diagnosis of granuloma annulare. Subsequently, topical betamethasone and calcipotriene were prescribed along with pentoxifylline. Pentoxifylline was discontinued after one dose as the patient could not tolerate it due to diarrhea. At this time, ultraviolet B phototherapy treatment was started. The patient received phototherapy for 5 months, but the treatment was discontinued due to minimal improvement in her GA. At this time, we recommended that she take canary seed commercially available as *herbal solution alpiste milk powder* in the following proportion: 2 teaspoons of canary seed milk powder in 8 ounces of water, twice daily. The patient took canary seed milk exclusively for her GA for two months and her disseminated GA resolved with post-inflammatory changes (Figure 1). The patient stopped taking canary seed milk since the resolution of her GA.

Case Report #2

A 70-year-old Hispanic male with a past medical history of pre-diabetes, hypertension, hyperlipidemia, coronary artery disease, and obesity presented with worsening erythematous annular non-scaly plaques on his thighs and bilateral arms for approximately 6 months. The patient was on clopidogrel, metformin, tamsulosin, atorvastatin, and valsartan. The patient failed topical steroid treatment and one month of oral antibiotic therapy. Upon the biopsy diagnosis of GA, he started oral corticosteroids which were tapered off in one month as the patient had minimal improvement. At this time, he started exclusively taking two glasses of canary seed milk (the same product mentioned in Case Report 1) per day for three months until his granuloma annulare resolved with post-inflammatory changes (Figure 2). The patient stopped taking canary seed milk due to the resolution of his GA.

Discussion

Canary seed, *Phalaris canariensis*, is used as birdfeed but has gained interest for its nutritional benefit for humans, especially in Latin America.⁵ Canary seed contains starches and proteins like tryptophan. Canary seed has a higher percentage of unsaturated fats when compared to saturated fats and has suggested anti-diabetic, anti-hypertensive, anti-inflammatory, and anti-dyslipidemic effects.⁶ These properties may contribute to canary seed's efficacy as a treatment option for GA.

Canary seed has shown effective anti-diabetic properties through activity on dipeptidyl peptidase 4 (DPP-4). According to Estrada-Salas *et al.*, peptides from canary seed show a 43.5% inhibition of DPP-4.⁵ The DPP-4 enzyme acts on the hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), also called glucose-dependent insulintropic polypeptide.



Figure 1. Clinical photos of generalized granuloma annulare (GA) from Case Report 1. A) GA on arms before treatment with canary seed; B) Note resolution of GA two months after treatment with canary seed.

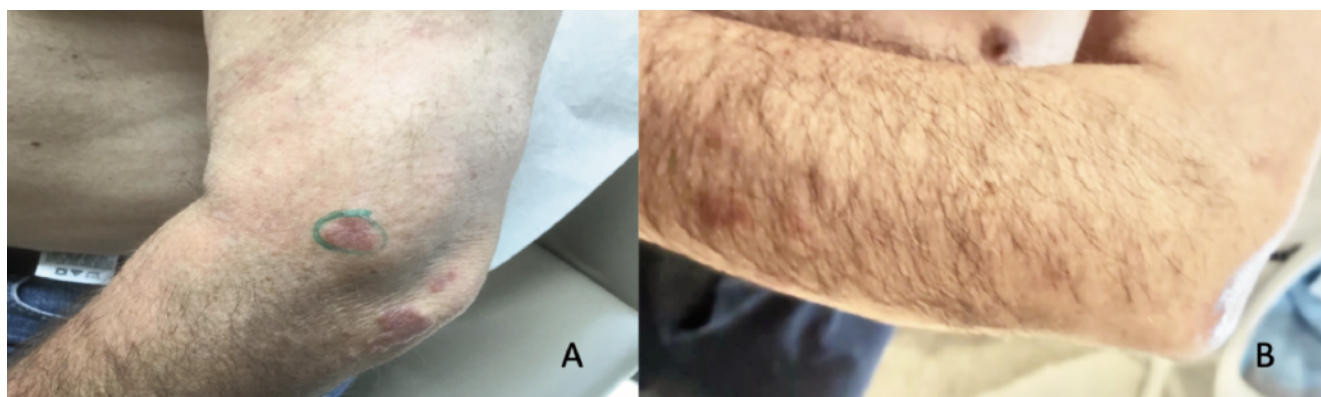


Figure 2. Granuloma annulare on the elbow from Case Report 2. A) Before taking alpiste milk; B) After taking alpiste milk. The slight color differences in the photos are due to the differences in lighting.

These hormones play a role in blood glucose maintenance.⁷ By inhibiting DPP-4 levels, canary seed increases the levels of GIP and GLP-1, which leads to a decrease in blood glucose levels.⁷ DPP-4 inhibitors, also known as gliptins, have effects outside of their role in blood glucose homeostasis. They have modulatory effects on the vascular system through an antihypertensive mechanism and have demonstrated anti-inflammatory and immunomodulatory effects.⁸ Gutierrez *et al.* showed that the diterpenes isolated from *Phalaris canariensis* lowered serum glucose levels in streptozotocin-induced type 2 diabetic mice through the effects of protein tyrosine phosphatase 1B (PTP1B) inhibition. PTP1B is present in insulin-sensitive tissues, and levels of PTP1B can be elevated in insulin resistance.⁹ Extracts of *Phalaris canariensis* have shown activity in inhibiting α -amylase and α -glucosidase. The inhibition of these enzymes decreases the levels of postprandial glucose by preventing the body's breakdown and thus absorption of sugars from the intestines.¹⁰ Granuloma annulare has shown associations with diseases like diabetes mellitus.¹¹ Our patients had a history of diabetes or prediabetes and may have benefited from canary seed with its inhibition of DPP-4, PTP1B, α -amylase, and α -glucosidase.

Canary seed has shown anti-hypertensive properties. Peptides from canary seed showed a 73.5% inhibition of angiotensin-converting enzyme (ACE) activity according to Estrada-Salas *et al.*⁵ ACE inhibitors decrease blood pressure by relaxing blood vessels and decreasing fluid volume by decreasing angiotensin II and aldosterone levels in the blood.¹² *Phalaris canariensis* is rich in tryptophan and has shown further antihypertensive properties in a study among normotensive and hypertensive rats. Tryptophan induces relaxation of smooth muscle *via* indoleamine 2,3-dioxygenase (IDO)-kynurenine pathway.¹³ The aqueous extract of *Phalaris canariensis* induced direct endothelial-mediated vascular relaxation and a decrease in sympathetic vasomotor tone and reduced systolic blood pressure in hypertensive rats through mechanisms mediated by the tryptophan metabolizing enzyme IDO. A significant increase in IDO enzymes was expressed in the kidneys of mice treated with aqueous extract of *Phalaris canariensis*.¹⁴ The patient in Case Report 2 reported improvement in his blood pressure, which could be in part due to the ACE inhibition and *via* IDO from canary seed.¹⁵

Patients with GA have shown statistically significant differences in levels of total cholesterol, triglycerides, and low-density lipoprotein-cholesterol when compared to controls.¹ In a study conducted by Wu *et al.*, the researchers found a statistically significant difference in dyslipidemia between patients with GA and controls. It was found that 79.3% of patients diagnosed with GA had dyslipidemia, compared to 51.9% of controls. This study further shows that the generalized form of GA has a statistically significant increase in dyslipidemia when compared to the disseminated and localized forms of GA. Therefore, the dyslipidemic properties of canary seed may alleviate generalized granuloma annulare.¹⁶

Canary seed also has an effect on reducing the inflammatory mediators, such as nitric oxide, myeloperoxidase activity, TNF- α , interleukin-6, interleukin-1 β (IL-1 β), prostaglandin E2, and leukotriene B4.^{14,17} It also contains vitamin E, selenium, and phenolic acid, all of which have anti-inflammatory and antioxidant properties.^{18,19} Patients with GA treated with oral vitamin E have shown improvement in previous studies. Vitamin E acts on free radicals and decreases levels of TNF and metalloproteinases.²⁰ An increase in mRNA expressions of proinflammatory IL-1 β with overexpression in the anti-inflammatory interleukin-10 was also seen in those who took canary seed in another study.¹⁴

Conclusions

Canary seed taken as alpiste milk could be a promising and safe management option for patients with GA who prefer alternative therapies or fail conventional medical treatments. While the literature has described the anti-diabetic, anti-hypertensive, and anti-inflammatory effects of canary seed milk, the precise mechanism responsible for its beneficial effects. The exact mechanism of action of canary seed milk on GA remains unclear. Furthermore, to distinguish its true effect on GA from a spontaneous resolution in the inflammatory dermatosis or a placebo effect, larger clinical trials of a standardized amount of alpiste milk product with blinding and controls are needed. These studies would validate the efficacy of canary seed on the treatment of GA.

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