

# The Use of *Ganoderma lucidum* (Reishi) in the Management of Histamine-Mediated Allergic Responses

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Allergies and asthma are two examples of histamine-mediated allergic responses. Both conditions are increasing in frequency and are difficult to target with modern medicine. The modern approach to drug research is target-specific and does not consider the natural defense mechanisms of the body or the causative factors (the shift to a predominantly TH2 cytokine profile) underlying histamine-mediated allergic responses. *Ganoderma lucidum* (Reishi) as immunonutrition, with its unique array of compounds working in concert, could play a major role in treatment of histamine-mediated allergic responses.

## What is Immunonutrition?

The potential to modulate the activity of the immune system by intervention with specific nutrients is termed immunonutrition. This concept may be applied to any situation in which an altered supply of nutrients is used to modify inflammatory or immune responses. However, immunonutrition has become associated most closely with attempts to improve the clinical course of clinically ill and surgical patients, who often require an exogenous supply of nutrients.<sup>1</sup>

Major surgery is followed by a period of immune suppression that increases the risk of morbidity and mortality due to infection. Improving immune function

during this period may reduce complications due to infection. Critically ill patients are at a greater risk of adverse outcomes than surgery patients. In these patients, complex variable immune and inflammatory changes occur that are only now being well defined. A biphasic response with an early hyper-inflammatory response, followed by an excessive compensatory response associated with immune suppression, is seen in many such patients.<sup>2</sup> Here, early treatment is aimed at decreasing the inflammatory response (reversing a TH1 to TH2 shift) rather than enhancing it, in order to stop the hyper-inflammation and prevent the resulting compensatory immune suppression.<sup>3</sup> In histamine-mediated allergic responses, treatment should be aimed at decreasing the inflammatory response (reversing a TH1 to TH2 shift).

## Historical Use of *Ganoderma lucidum* (Reishi)

The numerous legends surrounding the reishi mushroom provide an historical record that spans 2000 years. Traditionally, the reishi mushroom was used in China by Taoist monks to promote a centered calmness, improve meditative practices, and attain a long and healthy life.<sup>4</sup> Chinese royalty, seeking longevity, held the reishi mushroom in high esteem, and the mushroom became immortalized

throughout Chinese culture in paintings, statues, silk tapestries, and designs on the robes of emperors. The reishi mushroom has also been revered in Japanese culture where it is considered the most important of all Japanese medical polypores (Matsumoto 1979).<sup>5</sup>

Variouly known as the "mushroom of immortality," "ten-thousand-year mushroom," and "mushroom of spiritual potency," *Ganoderma lucidum* (Reishi) has been used for many centuries in the traditional herbal medicine of China and Japan for its immunomodulatory and adaptogenic properties.<sup>6</sup> In the most comprehensive Chinese materia medica, the "Ben Cao Gang Mu," published in 1578 AD, reishi was listed as the most respected herb out of 120 superior herbs (shang pin) (Masumoto 1979, Unschuld 1986). Superior herbs were classified as the highest category of medicines, since they were considered to prolong life, prevent aging, boost energy (qi), and make the body light and limber.<sup>7</sup>

Modern research has shown *Ganoderma lucidum* (reishi) has anti-allergic, antioxidant, anti-tumor, antiviral, cardiogenic, and liver-protective properties. Reishi mushroom has a long history of use in Traditional Chinese Medicine (TCM) for treatment of chronic bronchitis (Tasaka et al., 1988). In one small uncontrolled study of 20 patients with chronic bronchitis, reishi



mushroom was administered for four months. According to the review, in all but two patients there was a significant decline in blood cholinesterase activity, suggesting a reduction in the excitability of the parasympathetic nerves (Chang and But, 1986).<sup>8</sup>

## *Ganoderma lucidum* (Reishi)'s Anti-inflammatory Properties

### Animal Studies

Water extracts of reishi mushroom were found to possess significant activity against carrageenin\*-induced paw oedema when administered subcutaneously (sc) to rats. In one controlled study, groups of animals received either saline as a placebo control, indomethacin as a positive control (10 mg/kg sc), or a test article, one of which was a reishi mushroom water extract (2 g/kg). Both indomethacin and reishi mushroom showed significant anti-inflammatory effect ( $P < 0.01$ ) against carrageenin-induced oedema at all time intervals from one to six hours (Lin and others, 1993).<sup>9</sup>

### Chemical Identification and In Vitro Studies

More than 100 different highly oxygenated lanostanoid triterpenes have been identified in reishi mushrooms. The predominant triterpenes are ganoderic acids A-Z.<sup>10</sup> As well as its general health-enhancing action, *Ganoderma lucidum* has been shown to have specific anti-inflammatory properties, and this traditional usage has been linked to the presence of these ganoderic acids that exhibit anti-inflammatory properties.<sup>11</sup>

The compound Ganoderic Acid C (Figure 1), isolated by careful fractionation of a non-polar solvent extract of *Ganoderma lucidum*, was found to account for most of the anti-inflammatory activity from the herb as determined by *in vitro* tests, such as

histamine release from mast cells.<sup>12</sup> An ethyl acetate extract rich in ganoderic acids was later found, by another group of researchers, to exhibit both systemic and topical anti-inflammatory activity in standard animal models, such as the croton, oil-induced, mouse ear inflammation test.<sup>13</sup>

## *Ganoderma lucidum* (Reishi)'s Immunomodulating Properties

### Chemical and Biological Properties

In 2003, the Portuguese Instituto Superior de Engenharia de Lisboa (Biotechnology Section), led by Professor Amin Karmali, conducted an analysis of the enzyme properties of 500 mg of *Ganoderma lucidum* (reishi) biomass (mycelium and primordia [young fruitbody]). The results are shown in Table 1. Professor Karmali concluded that the immunotherapeutic properties in mushroom nutrition are due to the delivery of the following:

i) Protein-bound polysaccharide complexes responsible for immune enhancement.

ii) Enzymes that both prevent oxidative stress (laccase activity and superoxide dismutase [SOD] activity) and inhibit cell growth (protease activity).

iii) enzymes involved in detoxification process (cytochrome P-450).<sup>14,15</sup>

In summarizing the immunomodulating effects of reishi mushroom polysaccharides, researchers Lin and Lei (1994) state that reishi mushroom polysaccharides significantly promote

mixed lymphocyte response, antagonize the inhibitory effects of immunosuppressive and anti-tumor drugs, display a biphasic effect on interleukin (IL)-2 activity, increase both L3T4+ and Lyt 2+ cell subpopulations (L3T4 and Lyt 2+ cells are thymocytes responsible for producing significant quantities of interleukin 2 (IL-2) following mitogen stimulation), enhance cytotoxic activity of T lymphocytes, and promote the secretion of IL-1 in peritoneal exudate cells. Chang (1994) concluded that the polysaccharide fraction, with  $\beta$ -glucans, has stimulatory effects on these white blood cell lines: leukocytes, monocytes, macrophages, natural killer (NK) cells, lymphokine-activated killer (LAK) cells, tumor-infiltrating lymphocytes (TIL), and other lymphocytes. He considers these actions to be responsible for the antiviral, anti-tumor, anti-inflammatory, granulopoietic, and bactericidal effects that have been reported for reishi mushroom in laboratory animal studies.<sup>16</sup>

### Histamine-mediated Allergic Response is a Cytokine TH1 to Cytokine TH2 Shift

The body is considered to be in a "balanced" immune state when there is a constant movement between TH1 and TH2 immune states in a 24-hour period (Table 2). These two arms of the immune

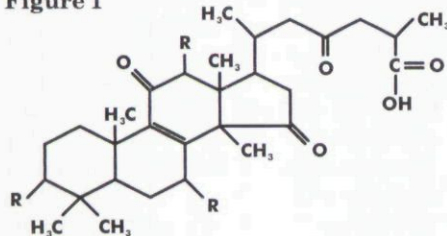
**Table 1: Results of *Ganoderma lucidum* (Reishi) analysis**

<i>Ganoderma lucidum</i> (Reishi) biomass Analysis of Enzymes, Proteins, and Sugar in Presence of Trypsin ( <i>in vitro</i> )	Content per 500 mg
1 Protein-bound polysaccharide	65.2 mg
2 Peroxidase activity	10.6 $\mu$ U
3 Laccase activity	461.3 $\mu$ m
4 Glucoamylase / Beta-glucanases activity	2.5 U
5 Protease activity	3.7 $\mu$ U
6 Glucose 2-oxidase activity	8,4 U
7 Superoxidase dismutase (SOD) activity	51.4U
8 Cytochrome P-450	0.63 nmoles
9 Cytochrome P-450 reductase	6.98mU

**Table 2: Cytokine TH1 vs. Cytokine TH2 Immune Responses**

TH1	TH2
8:00 to 20:00	20:00 to 8:00
Cytokine TH1 Immune State	Cytokine TH2 Immune State
Cellular Immune System	Humoral Immune System
Antiviral activity	Pro-inflammatory
Anti-bacterial activity	(Histamine-mediated allergic response)
Anti-parasitic activity	
Interleukin 2 (IL-2)	Interleukin 4 (IL-4)
Interleukin -12 (IL-12)	Interleukin -6 (IL-6)
Gamma Interferon ( IFN)	Interleukin -10 (IL-10)

**Figure 1**



\* carrageenan (= carrageenin): Sulphated cell-wall polysaccharide found in certain red algae. Contains repeating sulphated disaccharides of galactose and (sometimes) anhydrogalactose. It is used commercially as an emulsifier and thickener in foods and to induce an inflammatory lesion when injected into experimental animals (probably activates complement). Please see <http://www.mblab.gla.ac.uk/~julian/dict2.cgi?1090>.



# Reishi

► system are mutually inhibitory and in a balanced state: the body spends 12 hours in a TH1 state (antiviral, antibacterial, and anti-parasitic activities) and then 12 hours in a TH2 state (pro-inflammatory activity).

Factors such as stress and chemical exposure weaken our body's ability to defend itself, not through impairing the cellular immune response (TH1 – the ability of the body to recognize and destroy foreign bodies) per se, but because such factors lead to a chronic elevation of the humoral immune response (TH2), a pro-inflammatory state, which normally predominates in cases of local wound healing or histamine-mediated allergic response.

When a chronic elevation of the humoral immune response is prolonged, this is known as a "TH1 to TH2 shift." In a TH1 to TH2 shift, the pattern of cytokines has moved from an antiviral, antibacterial, and anti-parasitic pattern (TH1) to an inflammatory-repairing pattern (TH2) but **does not return** to a TH1 state within 12 hours as usual. This chronically elevated, pro-inflammatory immune response is termed a TH2 immune state. Histamine-mediated allergic responses are prolonged TH1 to TH2 shifts. For this reason, allergies and asthma are considered "TH2 conditions." As long as the shift continues, there is little relief from symptoms caused by such TH2 conditions.

Recent clinical studies have established that mushroom nutrition (using the mushroom *Coriolus versicolor*) is able to rebalance the TH1 and TH2 immune states, thereby reversing a TH1 to TH2 shift.<sup>17,18</sup> In addition, studies have supported the ability of reishi mushroom polysaccharides to restore the level of IL-2 production that has been inhibited by aging. In three studies, this result was demonstrated in aged mouse splenocytes (spleen cells) (Lei and Lin, 1991, 1993; Zhang, et al., 1993). An additional study in mice showed that reishi mushroom can

promote cell proliferation in murine splenocytes (Xiao, et al., 1994).<sup>19</sup>

## Existing Treatment Modalities for Histamine-mediated Allergic Responses

The currently used topical and systemic anti-inflammatory drugs have serious drawbacks; for example, corticosteroids can suppress pituitary-adrenal function, dangerously unbalance fluids/electrolytes, and cause undesirable changes in skin texture,<sup>20</sup> while the salicylic, acid-derived prostaglandin inhibitors can result in severe gastric irritation.<sup>21</sup> Consequently, the potential use of *Ganoderma lucidum* (reishi) supplementation could offer a safe and effective alternative for the reduction of histamine-mediated immune responses.

## Case Studies: Hay Fever Patients

Case studies were carried out to assess the efficacy of non-fractionalized *Ganoderma lucidum* supplementation in two hay fever patients. The principal parameters used were symptom elevation.

## Study Design

Open label study in United Kingdom in two patients. Patients were interviewed during the *Ganoderma* supplementation period, in order to assess changes in perceived quality of life, with reference to general hay fever symptoms.

## Supplementation Scheduling

For the first patient, supplementation commenced at three grams (six tablets x 500 mg) per day and was maintained at this level until the symptoms abated, at which point the dose was reduced to a maintenance dose of 1.5 grams (three tablets x 500 mg) per day until the end of the hay fever season (Table 3). For the second patient, supplementation commenced at two tablets per day and was maintained at this level through the season.

## Results

### Patient 1

Thirty-nine-year old male. Chronic hay fever sufferer since childhood with little relief from conventional herbal medication. After three to four days supplementation at three grams (six tablets x 500 mg) per day of *Ganoderma lucidum*, there was a marked decrease in drowsiness, itchiness, and sneezing. After ten days, the patient was able to mow the grass without significant discomfort. Continued alleviation throughout the season. Repeated benefit the following year.

### Patient 2

Five-year-old male. Developed hay fever at age four. Unable to go outside for much of early summer. Supplementation started at two tablets x 500 mg a day, 1 AM and 1 PM. After one week, there was a 90% reduction in symptoms. No red/sore eyes or sore throat. Only occasional sneezing. Able to play football outside again. Dosage maintained at two tablets a day until the end of the season.

## Discussion

In both cases, there was a rapid and significant alleviation of symptoms on commencement of supplementation with *Ganoderma lucidum*, indicating that *Ganoderma* supplementation may have a role to play in the management of histamine-mediated immune responses.

## Conclusion

Histamine-mediated allergic responses are provoked by chronically elevated, pro-inflammatory immune responses. For this reason, allergies and asthma are considered "TH2 conditions." As long as the cytokine TH1 to cytokine TH2 shift continues, there is no relief from symptoms caused by either asthma or allergies. To date, medical tools have focused on treating the symptoms of asthma and allergies, but not the prolonged TH2 condition. The modern approach to drug research is target-specific and does not consider the natural defense mechanisms of the body or the causative factors (cytokine TH1 to cytokine TH2 shift) underlying histamine-mediated allergic response.

*Ganoderma lucidum* (reishi) as immunonutrition, with its unique array of compounds working in concert, could play a major role in current treatment practices for histamine-mediated allergic response. *Ganoderma lucidum* (reishi) is an effective agent to restore the normal balance between the TH1 and TH2 immune states in patients with histamine-mediated immune response. Such an approach treats the underlying cause for the TH2 condition. Given that adult *Ganoderma lucidum* (reishi) supplementation costs between £14 and £28 (approximately \$24 and \$48) per month, the daily cost of the immunonutrition would be £0.50 to £1.00 (approximately \$.85 to \$1.72) per day. *Ganoderma lucidum* (reishi) supplementation as immunonutrition in patients with histamine-mediated allergic responses offers the clinician a cost-effective option for such clinical cases.

Table 3: Adult - Chronic Hay Fever

Week	Tablets/day	Total tablets
1	6	42
2	6	42
3	3	21
4	3	21
5	3	21
6	3	21
7	3	21
8	3	21



Martin Powell is a traditional Chinese medicine (TCM) practitioner and lecturer who has been involved in the clinical use of mushroom nutrition for over ten years. After graduating in Biochemistry from the University of Birmingham, he went on to study acupuncture, Chinese herbal medicine, and Chinese massage (Tui Na), initially at the London School of Acupuncture and Traditional Chinese Medicine, and then in Taipei and Shanghai. As well as running a practice in Luton, he co-edits Mycology News and lectures on TCM and on mushroom nutrition at the University of Westminster and abroad.

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### Additional Resources

For more information on *Ganoderma lucidum* (Reishi), please access the following web site: www.mycologyresearch.com.

For more information on extracted Ganoderic C compounds, please contact Essential Nutrition Ltd at +44 (0) 1482 667634 2

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