Turkey Tail Mushrooms and the Antifragility of the Immune System

by Renee Davis

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Interest in mushrooms is experiencing a resurgence in the West. Increasingly, people are growing oyster mushrooms (*Pleurotus ostreatus*) in laundry baskets, foraging for morels (*Morchella spp.*), and inoculating logs for shiitake (*Lentinula edodes*) production. Still, fear and confusion over mushrooms pervades in the form of disgust and repulsion toward anything fungal, fear of foraging and mushroom poisoning, and confusion over health effects between phyla of fungi (i.e., pathogenic fungi like *Candida albicans* versus immunomodulators like *Ganoderma lucidum*).

Medicinal mushrooms are relevant to herbal practice for several reasons. Firstly, they have constituents that are not found in plants. Fungal polysaccharides (such as ß-glucans, the focus of this article), novel antimicrobials, and many other secondary metabolites with unique bioactivity (such as herinacines and nerve growth factor upregulation) have been characterized and investigated.

Secondly, medicinal mushrooms are also complex in a manner that plants are not. While both are chemically complex, mushrooms go a step further: They mimic microbes in the human body, eliciting an innate immune response which has a regulatory effect on the immune system as a whole. This trickster-like characteristic is missing from the more straightforward kingdom Plantae. One reason for this is fungal-mammal coevolution being more intimate than that of humans with plants. Taxonomically, animals are closer to fungi than plants. The kindgom Animalia share more genetic material with Fungi than with Plantae—an insight offered by the past two decades of fungal genome sequencing (Galagan et al 2005). As a result, mammalian and fungal cells have remarkable cellular similarity with regard to sexual reproduction, intercellular signaling, and metabolism. Fungi similarly intake oxygen-rich air, exude carbon dioxide and secrete enzymes to digest macromolecules. However, unlike animals (who took the evolutionary path of engulfing nutrients in gastrointestinal lumen), fungi live in their food and secrete enzymes, with the mycelial networks functioning as external stomachs. The microbes that peril plants do not often affect mammals, but diseases that affect fungi frequently threaten mammalian health (Stamets 2003). Fungi have similarly developed defenses against bacterial, viral and other competitive fungal pathogens. This coevolution allows mushrooms a unique place in the material medica for use in conditions of immune dysregulation.

Turkey Tail: A Good Gateway Mushroom

The key constituents and core immune modulation mechanisms of turkey tail mushroom (*Trametes versicolor*, also known by its older name *Coriolus versicolor*) are a vignette into the vast and elegant complexity of the immune system. They also offer a lesson in antifragility, which I argue will become an increasingly important concept in medicine.

Turkey tail (*Trametes versicolor*) on an alder log. *Photo by Renee Davis*

Turkey tail mushrooms can be found in nearly every forested region, and grow on most wood types (deciduous and coniferous). They are highly aggressive and very easy to cultivate on logs using plug spawn. (In fact, they are the most common contaminant of mushroom log inoculation attempts as they fruit year-round in some places, saturating the air with spores.) I call them the "dandelion of the fungal kingdom" for these reasons. They're relatively easy to identify, harvest, and prepare as decoctions or double extractions. In formulae, they're easily combined with other mushrooms and botanicals. They're also very safe, with an extensive history of use in the East and very favorable tolerability studies (Hobbs 2003, Powell 2010, Torkelson et al 2012). Finally, they confer unique effects on the innate immune system, and have resultant modulating activity on the acquired immune system (Goodridge 2009, Tipping 2006). In this way, they can help point the way to novel immunotherapeutics. With the challenges that patients and practitioners face regarding the immune system—be it chronic infections, immune dysregulation or autoimmunity—now is an appropriate time to rethink immune therapies.

ß-glucans and Immunity

One of the key ways that mushrooms like turkey tail augment immune function is through polysaccharide fractions—the water-soluble ß-glucans that kick-start the immune response.

Most readers are familiar with the innate versus acquired (also known as adaptive) immune response. The innate immune response is associated with front-line defense against assault to the organism. In contrast, the acquired system confers long-lasting immunity and host protection through the regulation of inflammatory processes and production of antibodies. When either aspect is deficient or overactivated, host defense can become compromised or inflammatory processes become dysregulated.

ß-glucans (glucose units linked by ß- glycosidic bonds) stimulate an innate immune response, and have a regulatory and strengthening effect on the immune system as a whole. ß-glucans come from the fungal cell walls themselves, which are made of chitin. Chitin is one of the most abundant long-chain biopolymers/polysaccharides on the planet (second only to cellulose). It is the makeup of exoskeletons, lobster shells and butterfly scales. And while secondary metabolites can differ between fungal species, chitin is universal in fungi. Chitinous cell walls must be processed by heat to render the ß-glucans bioavailable. In herbal practice, this is easily accomplished through a decoction or hot water extraction, or as a double extraction with hot water and ethanol. Humans lack the digestive enzyme (chitinase) necessary to break down ß-glucans and similar ß-linked molecules. Therefore, upon ingestion as food, decoction, double-extracted tincture or concentrate, ß-glucans pass to the small intestine intact. Once in contact with epithelial cells in

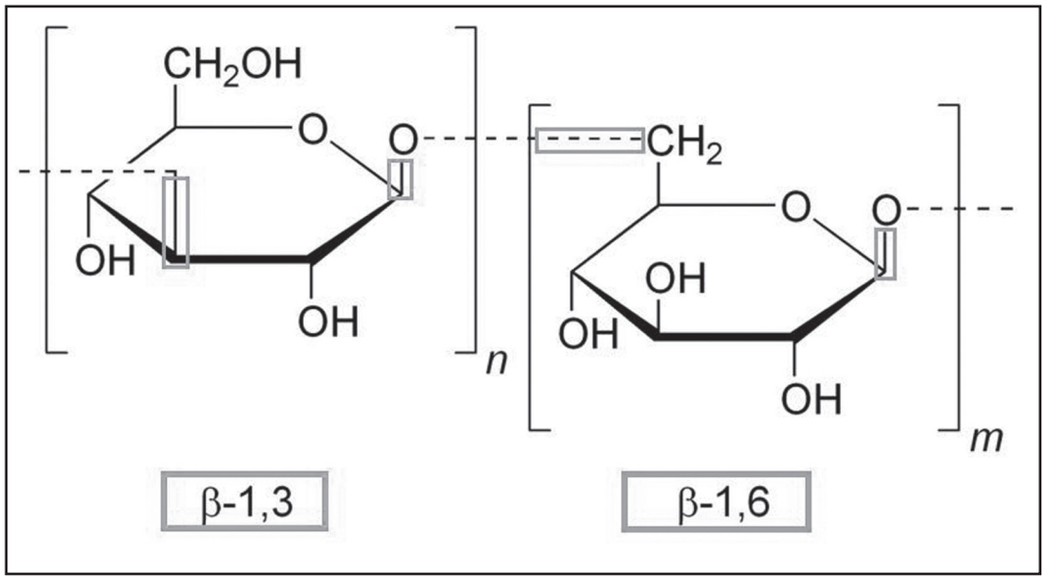


Figure 2: ß1,3-glucan molecule.

the gastric lumen, ß-glucans are active at several receptor sites. The key receptors are Dectin-1 and the toll-like receptors (TLRs), which signal an innate immune response. Their activation results in increased macrophage and NK cell production and activity (Torkelson et al 2012), dendritic cell maturity (Reid, Gow, and Brown 2009), and the normalization of the acquired immune response and inhibition of runaway inflammation (Chen and Seviour 2007).

Dectin-1

This receptor belongs to the pattern recognition receptor (PRR) family, which evolved to recognize microbes. PRRs are triggered by the recognition of pathogen-associated molecular patterns (PAMPs). PAMPs are fragments of microbes that receptors can identify (Reid, Gow and Brown 2009). They are usually pieces of microbial cell walls (bacterial lipopolysaccharides from Gram-negative bacteria, bacterial flagellin, viral fragments) (Turvey and Broide 2009, Plato, Willment and Brown 2013). Fungal polysaccharides, while not pathogenic, mimic these fragments (Dennehy et al 2009), triggering the same response but with a very different end result.

Dectin-1 is predominantly expressed on dendritic cells, but can also be found on innate immune cells such as macrophages (Seong and Kim 2010) and neutrophils (Chen and Seviour 2007, Shah et al 2008). This receptor is specialized to recognize fungal pathogens. When a molecule that looks like a fungal pathogen (in our case, a ß-glucan molecule from turkey tail) binds to the receptor, a cascade of immune activity is initiated. The exact effects vary between immune cells, and are well worth researching. Generally, once activated by a ligand like ß-glucan, the Syk/CARD9 signaling pathway is activated, resulting in phagocytosis, ROS respiratory burst, NF-kappaB activation and the secretion of several immune cytokines (Plato, Willment and Brown 2013; Reid, Gow and Brown 2009).

Dectin-1 activation stimulates dendritic cell maturation (Reid, Gow and Brown et al 2009). Dendritic cells can be thought of as messengers between the innate and acquired immune systems. They present antigens to T cells and B cells [hence they are known as antigen presenting cells (APCs)]. Dendritic cells signal naive T cells toward a Th1 phenotype via IL-12, helping restore balance in a Th2-mediated immune dysregulatory state (Baran et al 2007). They also play a direct role in the differentiation of Th1 and Th17 through this Dectin-1 mediated pathway (Reid, Gow and Brown 2009). When this receptor is presented with a ß-glucan molecule from turkey tail (or similar mushrooms), this immune cascade and enhanced messaging is triggered. Together with toll-like receptor activation (see below), T-regulatory cell development is favored, as is downregulation of IL-12 and cooperative

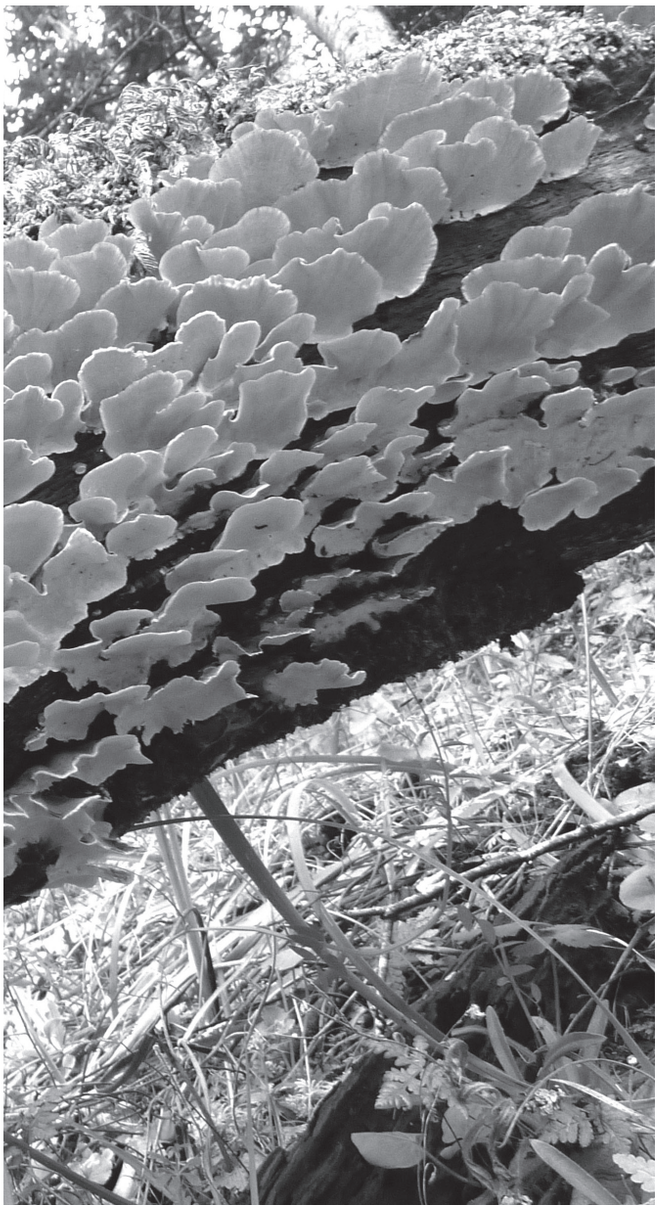
Trametes versicolor (turkey tail). *Photo by Brian Weissbuch.*

induction of tumor necrosis factor (TNF), IL-10, IL-6 and IL-23 (via MyD88 pathway) (Dennehy et al 2009, Plato, Willment and Brown 2013, Reid, Gow and Brown 2009). Ultimately, Dectin-1 signaling has a regulatory effect on immune signaling, adjusting and mediating inflammatory responses through increased communication between immune cells.

TLRs

Toll-like receptors (TLRs) work cooperatively with receptors such as Dectin-1 to coordinate a biological response. They also belong to the PRR family, and are expressed on epithelial tissues exposed to the external environment (like lung and intestinal epithelia) and select immune cells (Turvey and Broide 2009). Like Dectin-1, TLRs are trained to sense microbial assault through PAMPs. There are 13 different TLRs, and each has an affinity to a slightly different ligand and is associated with somewhat different cytokine profiles (Plato, Willment and Brown 2013; Takeda and Akira 2005). They often form groups (dimers) and cooperatively initiate immune signaling (Takeda and Akira 2005). Key TLRs induced by ß-glucans in turkey tail include TLR1, TLR2, TLR4, and TLR6.

Once activated, TLRs modulate mitogen-activated protein kinase (MAPK) and NF-kB expression via the MyD88 pathway (Takeda and Akira 2005), affecting gene transcription. TLRs also have MyD88-independent effects,



such as IFN-B activation and dendritic cell maturation (Plato, Willment and Brown 2013; Turvey and Broide 2009). As ambassadors of the innate and acquired immune response, dendritic cell regulation is a key mechanism by which TLRs orchestrate a harmonious immune symphony. Together, TLRs and Dectin-1 communicate and costimulate immune signals through the MyD88 and Syk pathways (Plato, Willment and Brown 2013).

To summarize, the innate immune system talks to the acquired immune system and lays the groundwork for its behavior. The innate immune system is evolutionarily older than the acquired immune response. The innate system is known for non-specificity and speed: when sensing attack, it puts up broad defenses, quickly. Specialized responses come later (Turvey and Broide 2009). Through cross-talk with the specialized cells of the acquired immune system (like dendritic cells), innate responses regulate production of inflammatory cytokines and long-term host protection.

Fungal polysaccharides like ß-glucans trick the system and stimulate an innate response. A common misconception is that innate immune stimulation will result in ramp-up of total immune function, exacerbating already-present immune dysregulation. On the contrary, such stimulation strengthens and modulates immune response as a whole. How does that work? Pathways and minutiae aside, there is a relatively simple and elegant manner of discussing this effect: the concept of antifragility.

Antifragility: A Key to Understanding Resilience

Over recent decades, a new field has emerged that articulates the emergence and behavior of complex phenomena such as cells, cities, bodies, ecosystems, and economies. Because such systems share some general characteristics, principles of emergence and complexity can inform wiser interventions. Herbalists typically have an orientation to and appreciation for the complexity and self-organization of the human body, and recognize its interdependence with other social and ecological systems. Herbal practice is therefore oriented to improving the vital force, resilience, and adaptive response of the organism. The language of complex systems and systems biology offers another way to discuss these phenomena and articulate the process of change.

Complex systems are composed of interdependent subsystems. Bodies are composed of organs, organs of tissues, tissues of cells, and so on. For these interdependent parts to stay connected, some kind of communication is necessary. Certain types of shocks, stressors, and volatility can serve as useful communication devices. These stimuli provide information about the external environment. Without adequate stressors and stimuli, the communication and connections between these subsystems atrophy,

and the whole organism weakens and suffers. The absence of low-level stressors is actually harmful.

There's a relationship between stimuli, order, and regulation of feedback mechanisms. Like a bored and unruly child in the crowded schoolroom who organizes and settles with a meaningful task, when a system is bored and unoccupied, that energy has to go somewhere, and patterns of dysregulation can develop. The Hygiene Hypothesis is a beautiful articulation of this effect. It states that early childhood exposure to pathogens and symbiotic microorganisms is necessary for the development of the immune system. Lack of exposure to these antigens may cause allergic responses, inflammatory disease, and defective immune tolerance (Okada et al 2010; Strachan 1989 and 2000). This is one example of the need for dynamic stimuli and stressors in a complex system.

The concept of "antifragility" describes the relationship between stress and growth. Former derivatives trader and statistician Nassim Taleb coined the term in his pointedly titled book *Antifragility* (Random House, 2012). Antifragile systems are those that actually thrive from shocks and volatility, seen in phenomena like post-traumatic growth, financial market volatility, and many biological processes. If something benefits more from stress than is harmed, there's an antifragile component. Not all volatility and stressors are the same; the quality, frequency and conditions surrounding the stress determine its effect on the whole organism. Acute stressors (like a lion charging at you in the savannah) enable long-term fitness better than grating, chronic ones (daily commuting traffic). Adequate recovery time from a stressor is important to receive its benefits. Additionally, the ability of an organism to overcompensate when recovering from a shock is the way in which fitness improves. This 'rebound effect' is what enables future adaptability.

Overintervention robs a complex system of stressors, and can cause it to become fragile. Mainstream medicine—its therapeutics as well as its patients—has become fragilized. The total loss of the antibiotic arms race is a potent example. Groups of organisms (i.e. microbes) require volatility—even harm—to evolve. Over the last century, our collective inability to think systematically laid the foundation for antibiotic overuse policies and unnecessary standards of care in medicine. To use another example, medical iatrogenics are a direct consequence of too much data and overintervention. This is illustrated by a recent client of mine, who was prescribed 21 different pharmaceuticals by two doctors, each to treat a subsequent side effect of the drugs and their combinations. That type of rigidity and pharmacological fragility denies the body much-needed randomness and overrides its self-organizing and regenerative capacities.

Because most herbalists are usually interested in strengthening body systems instead of bludgeoning them into a desired biological response, they are likely to appreciate the antifragile concept of prodding these systems into a heightened state of dynamic equilibrium through the use of appropriate "stressors" such as the fungal polysaccharides like ß-glucans in turkey tail mushrooms. These spark a reaction in the innate quick-defense immune system in a manner that organizes the rest of the acquired response. But while they initially look like pathogens, they're not real threats; in fact, they benefit the host by providing stimulus that is quick, acute, and allows the system adequate recovery time. The overall effect on the immune system is one of invigoration. Through improving our innate responses and regulatory systems, we can advance a set of therapeutics that actually encourages antifragility and resilience.

Fungi, Coevolution, and a Better Way Forward

As organisms, fungi differ significantly from plants, and therefore elicit diverse responses in the human body. There are two reasons for this. First, these receptor systems—Dectin-1, TLRs—have developed in association with a variety of fungal pathogens. The human body has distinct mechanisms by which it recognizes this onslaught, and this results in an overall improvement in immune fitness. Second, fungi and mammals have shared enemies, and fungi have therefore developed adaptive responses that may well come to our aid in the form of secondary metabolites.

Taken together, these insights support a resurgence of long-forgotten medicinal

mushrooms in Western materia medicas and apothecaries. Historically, Western cultures have been extremely mycophobic (an exception being Eastern European medicine traditions). As a result, most advances in clinical application and therapeutic uses of medicinal mushrooms have originated in China and Japan, where medicinal mushrooms (as well as their isolates and derivatives) are used in mainstream treatment for a variety of conditions.

The reemergence of mushrooms in Western clinical use is exciting for several reasons. Turkey tail is an example of a mushroom that is not only accessible and safe, but that also has an energetic neutrality that affords the practitioner flexibility in formulation as well as application to various client constitutions. They're useful in situations of complex or persistent immune disorders. Most importantly, the activity of fungal polysaccharides like ß-glucans invite reconsideration of traditional notions about complex physiological systems like the immune system and the possibility that small actions can have big effects on the overall resilience of the human body. The language of systems biology and concepts like antifragility can be employed to meaningfully discuss, explore, and improve the use of herbs and mushrooms in the clinic.

As the health needs of present-day populations change and become more complex, medicinal mushrooms like *Trametes versicolor* present an opportunity to meet these challenges with a unique set of tools. Going forward, I believe that medicinal mushrooms will inhabit a key place in Western materia medicas and formulary. Used together in the clinic, medicinal plants and mushrooms reflect ecological harmony and open the doors to better medicine.

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