Mycology for Cancer Treatment and Prevention

The world of fungi extensively covers the globe, above and below ground, playing a central role in almost every ecosystem. Humans have utilized fungi for food, food production, medicine, and more. Their uses in medicine, including antitumor, antioxidant, antibacterial, antiviral, and antihypercholesterolemic benefits, date back over 2000 years (Kladar, Gavarić, & Božin, 2016). More recent studies reveal the medicinal uses of fungi and their abilities as physiologically active agents. In this report, we will examine the untapped potential of the fungi kingdom and the anticancer and immune system-enhancing abilities of the *Ganoderma* genus.

Whether you know it or not, life on Earth largely depends on the kingdom of Fungi. According to the publication by Deshmukh and Rai (2005), roughly 14,000 species of mushrooms have been recorded. Scientists believe this number to be merely 10% of all mushroom species in existence, forming “what is arguably the largest kingdom of higher organisms on the planet” (Moore, Robson, & Trinci, 2011, p. 4). Since then, estimates of total fungal species (of which some produce mushroom fruit bodies) in existence have risen to roughly 5.1 million, outnumbering plants 5-10:1, accounting for roughly half of all species of life on earth (Blackwell, 2011). Until recently, the oldest record of fungal fossils dated back 385 million years. In 2017, the discovery of a 2.4 billion-year-old fungi-like fossil in South Africa preceded the aforementioned by 2 million years, becoming the oldest known fossil of a multicellular organism (Hood,

2017). In 1998 in Oregon, the US Forest Service discovered the single largest living organism on the planet (see Fig. 1), a honey mushroom spanning roughly 3.7 square miles (Flemming, 2014). Though we may not realize it, fungi play essential roles in ecosystems at all ends of the planet. Below ground, fungi form vastly extensive networks. Roughly 30% of healthy soil mass is fungal, and over 95% of all plants rely on symbiotic mycorrhizal fungi (see Fig. 2), subterranean fungi which supports plants' root systems (Moore et al., 2011). The fabric of fungi is mycelium, which is composed of fibers of hyphae. In one square meter of soil, "there may be 20,000km of hyphae" (Moore et al., 2011, p. 7). Many hold the misconception that mushrooms are plants or bacteria. However, fungi have more in common with animals than plants (Broyles, 2008). As eukaryotic organisms, fungi intake oxygen and output carbon dioxide. Stamets (2012) tells of an 83-year-old woman diagnosed with advanced stage-4 breast cancer told she had less than three months to live. After taking Turkey Tail mushrooms, known to promote natural killer cell production, the woman made a full recovery (Monro, 2003; Stamets, 2012). Some mushrooms can heal, and others can kill. Vast

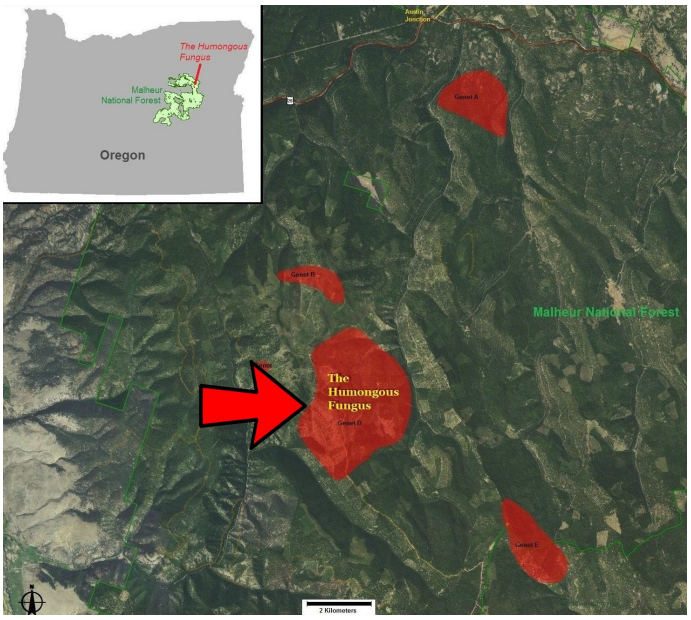

Figure 1. The largest single organism on earth, a honey mushroom.

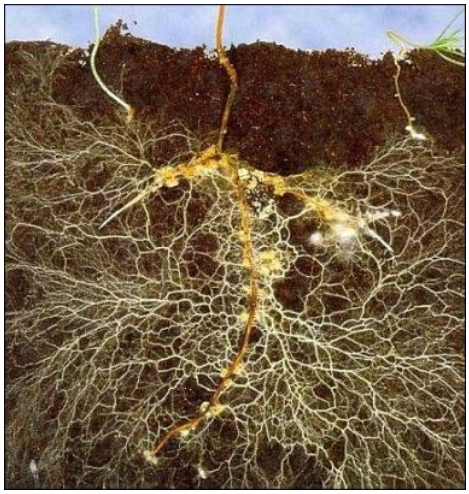
Figure 2. Mycorrhizae, to which most plants' roots are dependent.

in number, yet incredibly elusive, fungi hold untapped potential in medicine, manufacturing, and so much more.

Mushrooms have been used for medicinal purposes since at least the Neolithic age (Gargano, van Griensven, Isikhuemhen, Lindequist, Venturella, Wasser, & Zervakis, 2017). Around 450 BCE, Greek physician Hippocrates identified the amadou mushroom as an effective anti-inflammatory (Stamets & Zwickey, 2014). In the 5th century CE, Chinese scholar Tao Hongjing recorded the medicinal effects of *Ganoderma* lucidum and Dendropolyporus umbellatus (Stamets & Zwickey, 2014). Ötzi, the nearly 5300-year-old mummy known as the Iceman, was discovered with two species of mushroom (Stamets & Zwickey, 2014). Experts agree that one was used for medicinal purposes and the other for fire starting. Our ancestors attest to the vast benefits of medicinal mushrooms through millennia of written and archeological records. While many uses have been claimed of medicinal mushrooms, the fungi kingdom is vastly unexplored.

Fungi contain a variety of pharmacologically active constituents which show promising health benefits, including polysaccharides and triperpenes. Monosaccharides, also known as simple sugars, are bonded together in various ways to form polysaccharides, some of which exhibit anticancer properties. The polysaccharides found in fungi include cellulose, hemicellulose, pectins, chitin, starch, and glycogen (Moore et al., 2011). Triterpenes, groups of terpenes, are vast in number and also display various anticancer benefits. A few polysaccharides demonstrating antitumor potential have passed though Phase 1-3 clinical trials in Japan and China. However, the

US has not achieved the same results, for, “in many cases, the standards of these trials may not meet current western regulatory requirements” (Deshmukh & Rai, 2005, p. 290).

Used as a medical remedy in China, Korea, and Japan for centuries, the reishi mushroom, or *Ganoderma* lucidum (see Fig. 3), has shown great potential for its therapeutic effects and anticancer abilities (Silva, 2003). Reishi is a variety of polypore mushroom which grow at the base of trees. It is one of over 80 recorded *Ganoderma* species, of which over 400 bioactive compounds have been derived (Suárez-Arroyo, Loperena-Alvarez, Rosario-Acevedo, & Martínez-Montemayor, 2017). *Ganoderma* species have been used to treatment a long list of ailments, including migraines, hypertension, respiratory diseases, gastrointestinal disorders, diabetes, hypercholesterolemia, nephritis, autoimmune diseases, hepatitis, and cancer prevention and treatment (Kladar et al., 2016). *Ganoderma* mass consists of roughly 90% water, while proteins, carbohydrates, fats, fibers, vitamins, and minerals make up the rest (Kladar et al., 2016). Of the many constituents within *Ganoderma* species, polysaccharides, triterpenes, and peptidoglycans show the most physiological activity (Suárez-Arroyo et al., 2017). While *Ganoderma* species, mainly *G*. lucidum,

Figure 3. *Ganoderma* lucidum

have been utilized for ages for medicinal effects, modern western studies are in relatively early stages and in need of further insight.

Polysaccharides, a key agent in medicinal mushrooms, display potential anticancer effects and immune system benefits. These constituents fight cancers indirectly by enhancing immune system functions (Silva, 2003). Cells communicate by sending cascading signals to prompt other cells. Cancer destabilizes and reprograms these signals, causing a resistance to therapies (Suárez-Arroyo et al., 2017). Apoptosis is the natural process of cell death. In the growth of cancer, regular apoptosis is obstructed, allowing for the proliferation of cancer cells. *G*. lucidum polysaccharides are shown to stimulate production of signaling proteins interleukins IL-1β and IL-6, tumor necrosis factor-α, and interferon IFN-γ, which regulate immune function and apoptosis (Silva, 2003). Studies have identified that branched (1→3) beta-glucans (see Fig. 4), a subset of polysaccharides found in *Ganoderma*, are most "effective in signalling cascade modulation and cancer cell sensitization" (Silva, 2003; Suárez-Arroyo et al., 2017, p. 7). Silva's study (2003) reveals that *Ganoderma* derived polysaccharides "were demonstrated to prevent oncogenesis and tumor metastasis indirectly" by activating natural killer cells, T cells, and B cells (p. 358). Santesso and Wieland (2016), in a review of five different *G*. lucidum studies, further describe the fungi's ability to boost lymphocyte activity. In vitro studies on breast cancer cells have revealed

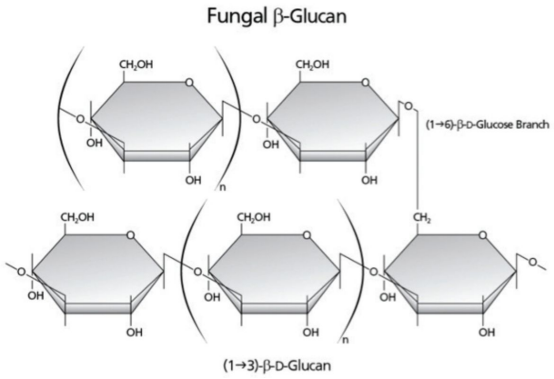

Figure 4. (1→3) beta-glucans.

Ganoderma's bioactive compounds to be "capable of inducing...antiproliferative effects, proapoptotic processes, and cell cycle arrest," indicative of *Ganoderma*'s ability to "inhibit the migration and invasive behavior of human breast cancer cells" (Suárez-Arroyo et al., 2017, p. 6, 7). A component isolated from *Ganoderma* polysaccharides, known as G009, was found to inhibit reactive oxygen species (associated with cancer growth) and reduce oxidative DNA damage, showing promising chemopreventive potential (Silva, 2003). Of the many polysaccharides derived from the *Ganoderma* genus, those effective in cancer treatment are glucuronoglucan, mannogalactoclucan, arabinoglucan, and glucogalactan (Silva, 2003). While polysaccharides hold potential for their immune system support, triterpenes display "direct activity against cancer cells" (Kladar et al., 2016, p. 469).

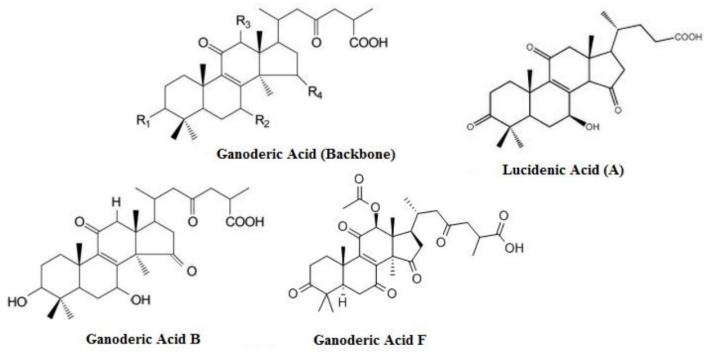

Figure 5. Some of the main triterpenes found in *Ganoderma* lucidum.

Researchers have categorized over 100 pharmacologically active triterpenes from *G*. lucidum (see Fig. 5) (Silva, 2003). In vitro tests described by Silva reveal *G*. lucidum triterpenes U-Y to have cytotoxic effects on liver cancer cells (2003). More recently, Weng and Yen (2010) reveal that ludenic acid, a group of triterpenes, causes anti-growth and anti-invasive effects on liver cancer cells. Triterpenes A and C have been shown to inhibit farnesyl protein transferase, an enzyme responsible for the transformation of cancer cells (Silva, 2003). The triterpenes lucidadiol and ganoderiol F demonstrate significant cytotoxicity

against HeLa cervical cancer cells (Kladar et al., 2016). In a more recent study using mice, triterpenes derived from *G*. lucidum exhibited cytotoxic effects on sarcoma and lung cancer cells, proving the ability of *G*. lucidum triterpenes to inhibit “primary solid-tumor growth in the spleen, liver metastasis, and secondary metastatic tumor growth in the liver” (Silva, 2003, p. 360). Triterpenes are vast in number and effects, yet further research is required.

Numerous studies have uncovered an array of anticancer benefits from *G*. lucidum. *G*. lucidum extracts boost a patient’s immune response, helping one’s body fight off cancers. Studies have been performed, yet stable results remain elusive. A study of 105 patients receiving chemo- or radio-therapy reveals improved immune system function when taking *G*. lucidum extract (Suárez-Arroyo et al., 2017). Researchers in China and Australia also discovered that chemo- or radio-therapy patients responded more positively to treatment when administered *G*. lucidum extract (Silva, 2003). While the benefits of *Ganoderma* for cancer treatment is debated, researchers largely agree that “G. lucidum has better effects when used in combination with other cancer treatments” (Santesso & Wieland, 2016, p. 620).

The *Ganoderma* genus exhibits a variety of immune system-boosting abilities and antitumor effects. *Ganoderma* polysaccharides have been demonstrated to boost lymphocyte activity in cancer patients, improving a patient’s ability to naturally fight tumors. Triterpenes show cytotoxicity against cancer cells and the capability to inhibit tumor growth. While these benefits have been proven to some degree, experts agree further research is needed, seeming to hold much potential. The discovered anticancer

abilities of *Ganoderma*, when combined with more conventional cancer therapies, constitute a powerful tool in the fight against cancer.

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