

To Heal or Not to Heal? Medicinal Mushrooms Wound Healing Capacities

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Abstract: Several compounds are responsible for the therapeutic activities of many medicinal mushrooms genera; the main groups of these compounds are polysaccharides, terpenes, phenolic compounds, and essential amino acids, as well as minerals such as calcium, potassium, magnesium, iron, and zinc. In this review we focused on the wound healing promoting effect of some medicinal mushrooms of interest including: *Handkea utriformis*, *Hericium erinaceus*, *Morchella esculenta*, *Sparassis crispa* and *Agaricus blazei*

Keywords: Wound healing; Medicinal Mushrooms; *Handkea utriformis*; *Hericium erinaceus*; *Morchella esculenta*; *Sparassis crispa*; *Agaricus blazei*.

1. INTRODUCTION

The medicinal properties of mushrooms have been known about for millennia and were exploited for the benefit of humans by many ancient civilizations, including those in Ancient China, Eastern Europe, Mesoamerica and Africa. Mushrooms are known to be medically active in several therapies, such as antitumor, antibacterial, antiviral and other, the therapeutic effect is linked to the presence of bioactive compounds [1,2].

Searching for novel effective compounds that enhance wound healing is a new interest in the modern biomedical sciences. Nowadays, many researchers focus on the phyto medicine due to the ability of various plants to heal wounds via natural repair pathways. Exceeding 70% of pharma products for wound healing depend mainly on plants, however, only 20% of those products depend on mineral compounds [2,3]. In this respect, more attention was attracted towards higher fungi that show a vast range of vital therapeutic properties.

However, the ability of mushrooms to heal wounds have not been completely identified. Hence, the study of the effect of mushrooms on wound healing is crucial. In addition, the results depend mainly on the fungus type, its strain, the composition of culture medium for fungus cultivation, the fungus part used in the study (Spores, mycelia, fruit bodies), as well as the methods of its active ingredients production (the medium for suspending, the extractant) [1-3].

Several studies have presented promising wound healing activity of *Handkea utriformis*, *Hericium erinaceus*, *Morchella esculenta*, *Sparassis crispa* and *Agaricus blazei*, many of those studies use relatively crude extracts. Further research is required to isolate and identify more bioactive compounds responsible for wound healing activity.

2. HANDKEA UTRIFORMIS (PUFFBALL)

Numerous studies showed that many mushrooms are considered a valuable source of many biologically active compounds that may have a great beneficial influence on human health [2, 3].

Since many mushroom species have been used long time ago in traditional medicines, many scientists directed their efforts for the use of these mushrooms in modern medicine.

Handkea utriformis which is known as mosaic puffball is one of the mushroom species that belongs to puffballs mushrooms. This group of mushrooms is characterized by producing globose and enclosed fruiting bodies [4]. When young, *H. utriformis* are edible and characterized by being firm with white color, but when get mature the mushroom fruiting bodies undergoes an autolysis process resulting in changing the mushroom insides (gleba) into a dark mass bearing powdery spores [5,6].

Puffballs have gained an importance for being used as wound dressings as well as a remedy for different skin conditions [6]. This could be attributed to the presence of some biologically active compounds that play vital roles in skin health. These compounds include ergosterol, α -tocopherol and GlcNAc thus *H. utriformis* gained an importance as a promising member for both wound healing and several cosmetic products [8,9].

It was reported that *H. utriformis* extract of the fruiting bodies during maturation produces 26 mg/g of N-acetylglucosamine (GlcNAc) which is an amino sugar and a vital building unit of the fungal chitin polysaccharide due to the chitinolysis process [10]. The ^{13}C NMR spectra of *H. utriformis* extract revealed the presence of signals for carbonyl (δ 174.54), methyl carbons (δ 22.23 and 21.96) and anomeric carbons (δ 94.99 and 90.90) which are specific for GlcNAc [11]. As GlcNAc plays an important role in the fungi structure, it also showed an important role in the human beings. It is a major building unit of human glycosaminogly can of human connective tissue which is the hyaluronic acid. GlcNAc is a sparked an ingredient in many cosmetics, pharmaceuticals and nutritional supplements as it improves the skin hydration, reparation, and to contribute as anti-wrinkle agent which is attributed to the important role of hyaluronic acid in the skin's integrity and health [7].



Fig1. *Handkea utriformis* (Photographs taken by eddi bisulli, Locality: Italy, Trentino-Alto Adige, 38046, Lavarone, Trentino-Alto Adige, IT, hosted by <http://mycoportal.org>).

3. *HERICIUM ERINACEUS* (LION'S MANE MUSHROOM)

Hericium erinaceus is an edible, medicinal mushroom of family Herinaceae [12]. *H. erinaceus* has been known with several names including lion's mane, bearded tooth carpophores and yamabushitake. Various therapeutic importances have been reported for both its fruiting bodies and mycelium. *H. erinaceus* has been used in the Chinese and Japanese medical systems, where it has been used to nourish the gut, spleen as well as it has been used as an anticancer drug [13]. It finds also a great application for the treatment of stomach and duodenal ulcers [14]. Beside its existence in Asia, this species is also found in North America and the northern hemisphere in Europe.

When getting mature, *H. erinaceus* can be easily identified by the presence of conspicuous basidiomes that is formed of numerous single fleshy long spines with white color that turns yellow and finally brown by aging. However, the microscopical examination revealed the presence of amyloid basidiospores [15]. *Hericium basidiomes* differentiate from primordia as a single clump; the branches are formed as it grows older [16].

Many bioactive compounds have been isolated from *H. erinaceus*, including high molecular weight compounds such as polysaccharides that shows antitumor in vitro, including activity against mammary carcinoma (MCF-7) [17] and malignant hepatocytes (HepG2) [17], or low molecular weight compounds such as terpenoids [19] and polyketides [20].

An interesting study showed that the topical use of *H. erinaceus* fruiting bodies aqueous extract exhibited a promising wound healing activity. In that study, five groups of male Sprague-Dawley rats were employed to evaluate the wound healing ability of *H. erinaceus* extract. Uniform wound areas of about 2 cm in diameter each were made in the posterior neck area. This was followed by applying the *H. erinaceus* aqueous extract to the wounds. Sterilized distilled water was used as a negative control while Intrasite gel was used as a positive control. The macroscopical examination results showed that, the rats whose wounds were treated by applying *H. erinaceus* extract dressings and those groups treated with the Intrasite gel- healed much faster than those treated with the negative control (sterilized distilled water). While the histological examination revealed that the wounds that were healed after applying *H. erinaceus* extract contained fewer macrophages and more collagen, also it showed less scar width at wound enclosure comparing to wounds treated with distilled water dressings [21]. These results gave evidence that *H. erinaceus* may be a promising treatment for wound healing.

Another study showed that the aqueous extract of *H. erinaceus* exerted a protective effect toward the gastric mucosa as well as inhibited leucocytes infiltration of gastric wall when the aqueous extract of *H. erinaceus* was used as a pretreatment in rats with ethanol induced gastric ulcer [22]. It was reported that pretreatment with *H. erinaceus* extract before ethanol administration resulted in a significant reduction in the leucocytes particularly the gastric mucosa neutrophils infiltration which indicates the healing of the gastric ulcer [23, 24]. Ethanol administration can damage the gastric mucosa and lead to the increase in the neutrophil infiltration. The neutrophils are considered a major source of inflammatory mediators which can release reactive oxygen species (ROS) that are cytotoxic and can induce tissue damage [23]. However, the neutrophil infiltration suppression during inflammation process plays a vital role in the healing of the gastric ulcer [25]. Taken together, the aqueous extract of *H. erinaceus* showed an important role in the healing of the gastric ulcer through the suppression of neutrophils infiltration as well as antioxidant activities.



Fig2. *Hericium erinaceus* (Photographs taken by Patricia R. Miller, USA, Mississippi, Lafayette, North Cypress Trail, Holly Springs National Forest, hosted by <http://mycoportal.org>).

4. MORCHELLA ESCULENTA

Morchella esculenta (L.) Pers. (morel) is one of the most widely appreciated wild edible mushrooms. *Morchella esculenta* is a highly expensive, edible beneficial wild species of mushroom hence it is called growing gold of mountains, also it is known as guchi, common morel, yellow morel, morel mushroom as well as sponge morel. It is one of the most important and economically beneficial wild species of mushroom. It is commonly found as a mycorrhizal or saprobic relationship with hardwood and coniferous trees. Its growing season is from March to July [26]. It grows in cold environments and usually found in coniferous thick forest and humus rich loamy soil with a saprobic or mycorrhizal relationship [27, 28].

Morchella esculenta consist of cylindrical structure. The upper part is called as pileus possesses 70-80% of total plant weight. Its pileus is oval and often globular, yellowish white to yellowish brown in color [29]. Pileus is about 3-9 cm long, 2-5 cm wide, round or irregular pits are present, it shows yellow, brown, pale or black color.

It contains carbohydrates, proteins, fibres, all important vitamins, minerals and aromatic compounds. Due to its unique flavour, taste and texture it is used in different recipes all over the world. It contains a wide range of pharmacological properties which includes antioxidant, antitumor, antimicrobial and anti-inflammatory properties [30]. *M. esculenta* gains a great importance for its medicinal and nutritional value due to its enrichment with several biologically active compounds such as proteins, dietary fibers, polysaccharides as well as some vital vitamins [30]. These compounds help *M. esculenta* extract to exhibit several important biological activities including antimicrobial properties [31, 32], as well as platelet aggregation inhibition. Moreover, the presence of polysaccharides and tocopherols allow its extract to show strong antioxidant and antitumor activity [33, 34]. Interestingly *M. esculenta* powder exhibited an antiseptic activity which affect positively in wound healing for digestive system symptoms [35]. It also acts as an immune stimulant due to the presence of various active constituents. It may be used as purgative, laxative, body tonic, emollient [32] and also used for stomach problems, heal the wound and for general weakness. Due to its high price it plays a very important role in the economy of country.



Fig3. *Morchella esculenta* (Photographs taken by Walt Sturgeon, Locality: USA, Ohio, Columbiana Co., East Livepool, hosted by <http://mycoportal.org>).

5. SPARASSIS CRISPA (CAULIFLOWER MUSHROOM)

Another important edible medicinal mushroom with several medicinal properties is *Sparassis crispa*. This mushroom belongs to family Sparassidaceae and also known as cauliflower mushroom. Recently it has been very popular in Japan for its medicinal importance [36]. Its occurrence is distributed throughout the North Temperate Zone where it grows on the stumps of coniferous trees a brown rot fungus [36].

Various compounds with human health promoting abilities have been isolated from *S. crispa*. Its fruiting bodies contain about 90% water, carbohydrate, protein, lipid, dietary fiber and ash [35]. *S. crispa* has a characterized scent due to the presence of 3-octanone, DL-3-octanol, and 1-octen-3-ol that is contributed to this specific aroma [37]. The presence of vitamin D₂ that plays vital role in the intestinal calcium absorption was also reported with a concentration that is much higher compared to that found in other mushrooms [38]. A large amount of glucosyl ceramide (nearly 0.2%) was also detected in *S. crispa* extract [36]. And it is important to mention that more than 40% of the dry weight of *S. crispa* fruiting bodies the beta-glucan [36].

As mentioned before, *S. crispa* exhibits high medicinal value due to its unique active components. Hot water extracts from *S. crispa* fruiting bodies showed HIV-1 RT inhibitory effect, as it interferes with reverse transcriptase enzyme that is very important for human immunodeficiency virus (HIV) replication [39]. Moreover, Antihypertensive effects for *S. crispa* was also reported as it delayed the

occurrence of stroke and death in stroke-prone spontaneously hypertensive rats since it decreased blood pressure and increased blood flow[40].

Regarding the wound healing activity, *S. crispa* also showed promising activity in diabetic mice where impaired wound healing is a major problem. When rats with streptozotocin- (STZ-) induced diabetes (type 1 diabetes mellitus model) ingested *S. crispa* for 4 weeks at a dose of 1,000 mg/kg body weight/day, the wound healing was accelerated [41]. In addition, it was observed a significant increase in the migration of the fibroblast and the macrophage, also an increase in the collagen regeneration was also observed compared to the control groups.

It was noticed that the rate of wound healing in diabetic mice that consume a diet containing about 2.5% *S. crispa* was nearly the same as that in diabetic mice after being treated with topical trafermin (fibroblast growth factor formulation). It is noteworthy that the topical application of *S. crispa* glucan significantly enhanced wound healing in diabetic mice, where the wound contraction ratio was found to be 37% after 9 days administration, this result that was higher than that of trafermin [42]. Hence, the application of *S. crispa* could be extended to the clinical levels, where it may promote wound healing in diabetic patients.



Fig4. *Sparassis crispa* (Photographs taken by Robert Chapman, Locality: USA, Arizona, Chiricahua Mountains, hosted by <http://mycoportal.org>).

6. AGARICUS BLAZEI

Agaricus blazei is an edible, basidiomycete fungus that belongs to the Agaricaceae family. It is found in China, Japan and Brazil [43]. *A. blazei* extracts are able to inhibit the growth of different types of tumor cells in vivo such as including Lewis lung carcinoma, sarcoma-180, Shionogi carcinoma and Ehrlich ascites carcinoma [44-47]. This antitumor activities can be attributed to the induction of apoptosis, restoration of the suppressed host immune system as well as tumor induced neovascularization inhibition[48-50].

As it was known that the burn injury leads to many immune and hence inflammatory dysfunctions. The acute response to burn wounds causes an influx of leukocytes including polymorph nuclear, macrophages and leukocytes to the site of the burn wound [51]. The studies proved that the administration of *A. blazei* polysaccharides was able to increase the wound contraction percentage, indicating the effect of *A. blazei* polysaccharides on rapid collagenization and epithelization. In conclusion, the application of *A. blazei* polysaccharides enhanced the process of burn wound healing after 20 days where polysaccharides (100 mg/kg body weight) resulted in 63.2% recovery rate [52].

It is relevant to mention the important relation between the skin sensitization potential and the ability of chemicals to alter the expression of the epidermal cytokines. These cytokines include IL-1 which is a molecule found in mouse skin and is expressed by Langerhans cells [53, 55]. In that study, real-time fluorescent semi quantitative PCR is employed to detect the expressions of IL-1 β mRNA exists in the skin sample over 20 days. It was observed that the ratio of IL-1 β / β -act in in model control group increased significantly with $P < 0.01$, on the other hand, the treatment with *A. blazei* polysaccharides resulted in the decrease of IL-1 β / β -act in ratio in a dose dependent manner [52].

These results indicate that the rats skin burn wound induced the expression of IL-1 β mRNA. However, the application of *A. blazei* polysaccharides in the burn wound site increased the macrophages accumulation which in turn decreased production of IL-1 β , and this could be the major

reason for the acceleration of wound healing of *A. blazei* polysaccharides. Taken together, the results suggest that administration of *A. blazei* polysaccharides may be employed as an effective treatment that enhance the burn wound healing via influencing the immune activity.



Fig5. *Agaricus blazei* products: (a) *Agaricus blazei* powder capsule (www.amazon.com). (b) *Agaricus blazei* powder capsule (www.vitalabo.com).

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