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## ***Hericium erinaceus*, a medicinal fungus with a centuries-old history: Evidence in gastrointestinal diseases**

Gravina AG *et al.* *Hericium erinaceus* in gastrointestinal diseases

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### **INTRODUCTION**

Gastrointestinal disorders are one of the most prevalent diseases in the general population. They are associated with a significant epidemiological and economic burden, with an estimated annual cost of over a hundred and thirty billion in the United States alone<sup>[1]</sup>. Many gastrointestinal disorders require a pharmacological approach; however, the possibility of adopting naturally derived complementary therapies whenever possible is emerging<sup>[2,3]</sup>.

Among the abundant natural compounds studied, there is a Chinese mushroom, *Hericium erinaceus* (*H. erinaceus*) that has shown <sup>4</sup> the potential to prevent and treat digestive diseases, such as gastric ulcers<sup>[4]</sup>. Furthermore, its therapeutic potential has been demonstrated in several conditions, including diabetes, hyperlipidaemia, neurodegenerative disorders, and cancer<sup>[5-8]</sup>. In addition, mild cognitive impairment is another disorder in which *H. erinaceus* has shown encouraging results in randomised clinical trials<sup>[9,10]</sup>.

Therefore, <sup>6</sup> *H. erinaceus* has traditionally and historically been used as a natural remedy for epigastric pain caused by chronic gastritis, gastric ulcers, or even atrophic gastritis<sup>[8]</sup>.

Despite the strong need for clinical studies, several experiments, mainly preclinical and mouse model-based, have been conducted on the beneficial effects of many *H.*

*erinaceus* extracts and components on gastrointestinal diseases. Therefore, this narrative review aimed to provide overall evidence of the therapeutic potential of *H. erinaceus* in gastrointestinal tract diseases.

### **H. ERINACEUS: GENERAL CONSIDERATIONS**

*H. erinaceus*, also known as Yamabushitake (in the Japanese language), Houtou (in the Chinese language), or also as “lion’s mane” is a fungus that belongs to the class *Basidiomycetes*, subclass *Holobasidiomycetidae*, order *Hericiales*, and family *Hericiaceae*<sup>[4]</sup>. This fungus is mainly distributed in European, Asian, and American regions<sup>[11]</sup>. It is a saprophytic fungus or weak parasite that typically grows on hardwoods, such as beech, chestnut, and cherry<sup>[12]</sup>.

Many active metabolites of *H. erinaceus* that are structurally different from each other and potentially bioactive have been discovered<sup>[13]</sup>.

The main constituents of *H. erinaceus* are erinacines (cyathane-type diterpenoid aromatic compounds as erinacines A-I), steroids (such as ergosterol, erinarols A-F, and ergostane-type steroids), alkaloids (such as hericirine, 12 $\beta$ -hydroxyverruculogenTR-2, fumitremorgin, methylthioglioto, pseurotin A, and FD-838), and lactones such as vitamin B<sub>12</sub>-c-lactone (Figure 1)<sup>[13]</sup>.

In addition, each 100 g of dried *H. erinaceus* contains approximately 61.3-77.5 g of total sugars, of which  $\beta$ -glucans,  $\alpha$ -glucans, and glucan-protein complexes are the most abundant<sup>[14,15]</sup>. Among these, the  $\beta$ -glucans in the fungal cell wall have known and marked anti-inflammatory and anti-cancer potency and can positively modify the gut microbiota<sup>[16]</sup>.

Much of the research devoted to the chemical characterisation of *H. erinaceus* has focused on its polysaccharide components, which are generally obtained from its fruiting body, and various extraction methods have been developed<sup>[17-19]</sup>.

### **H. ERINACEUS IN UPPER GASTROINTESTINAL TRACT DISEASES: THE EVIDENCE**

### *The role of *H. erinaceus* in non-infectious gastric diseases: Gastroprotective effects and therapeutic potential in repairing gastric mucosal damage*

Gastric ulcers are a significant epidemiological burden<sup>[20]</sup>. Among the most common forms of gastric ulcers, those caused by non-steroidal anti-inflammatory drugs are also included. This is due to the pharmacological inhibition of cyclooxygenases 1 and 2, which are responsible for producing proinflammatory cytokines and prostaglandins, which help maintain the integrity of the gastric mucosal barrier<sup>[21]</sup>. An adequate balance between proinflammatory and anti-inflammatory cytokines is necessary for maintaining gastric mucosal integrity, such that polymorphisms in genes encoding proinflammatory cytokines can increase the risk of peptic ulcer and gastric cancer<sup>[22]</sup>. As anticipated, *H. erinaceus* has shown various anti-inflammatory, antioxidative, and gastroprotective properties. Boddy *et al*<sup>[23]</sup> showed, for example, that the action of several polysaccharides of *H. erinaceus* inhibits the secretion of proinflammatory cytokines interleukin 6 (IL-6), IL-8, and IL-12 and promotes the secretion of the anti-inflammatory cytokine IL-10 in a co-culture system of Cancer coli 2 (Caco-2) cells and Caco-2/RAW264.7 cells under bacterial lipopolysaccharide stimulation. This emphasises how this fungus can intervene in cytokine imbalance in an inflamed environment by shifting the balance toward an anti-inflammatory cytokine pattern.

To evaluate the gastroprotective, antioxidant, and anti-inflammatory activities *in vivo*, Wang *et al*<sup>[24]</sup> conducted experiments in a mouse model in which ethanol or ligation of the pylorus induced gastric ulcers. The study involved two polysaccharides, namely the crude polysaccharide of *H. erinaceus* [i.e., crude polysaccharide (HECP)] and the refined polysaccharide of *H. erinaceus* [i.e., refined polysaccharide (HERP)], obtained from the fruiting body using water extraction and ethanol precipitation methods<sup>[25]</sup>. The mice were divided into several groups, including control groups and those receiving *H. erinaceus* polysaccharides at different dosages (100 mg/kg, 200 mg/kg, and 400 mg/kg). In the ethanol-induced gastric ulcer model, there was a reduction in the severity of the ulcers in a dose-dependent manner in the HERP/HECP-treated groups, with a significant reduction when pre-treatment with 400 mg/kg of HERP/HECP was

performed. In contrast, in the pylorus-ligation-induced ulcer model, significant ulcer-inhibiting power was achieved when mice were administered HERP or HECP in a 200 mg/kg dosage. Nevertheless, the ulcers appeared to be more mitigated by HECP polysaccharide than HERP.

These results generally indicate a marked gastroprotective effect of HERP/HECP polysaccharides in ethanol-induced and pylorus-ligated gastric ulcers. However, the authors also showed results related to the control of gastric secretions. HERP/HECP administration provided a regulatory advantage over the imbalance in acid secretion induced by pylorus ligation.

Once the gastric mucosa has been damaged, the inflammatory process is activated, thereby increasing the mediators of inflammation, including tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$ , and IL-6. TNF- $\alpha$  stimulates neutrophil infiltration and apoptosis of epithelial cells, reduces gastric microcirculation around the ulcer region, and delays its healing. Leucocyte infarction in the gastric mucosa is generally assessed using myeloperoxidase (MPO) activity. IL-1 $\beta$  significantly promotes ulcer formation. Another defensive element that protects against gastric ulceration is the mucus-bicarbonate barrier. The mucus is a gel that adheres to the mucosa, preventing gastric acid penetration and injury. Mucus typically works in conjunction with nitric oxide (NO), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and epidermal growth factor (EGF) to maintain mucosal integrity. NO protects the mucosal barrier and integrity of the gastric epithelium by inducing the inactivation of gastric parietal cells that secrete hydrochloric acid, thereby reducing acidity. PEG<sub>2</sub> increases mucus and bicarbonate production, leading to a decrease in gastric epithelial permeability. EGF induces the proliferation of epithelial cells, thereby promoting tissue healing.

Wang *et al* discovered that rats administered with HERP or HECP had lower serum TNF- $\alpha$  and IL-1 $\beta$  levels and lower gastric tissue MPO activity than in the control group, indicating that these polysaccharides reduced the inflammatory response. In addition, the mucus content in the stomach was higher in the *H. erinaceus* polysaccharides-treated group than in the control group, suggesting that



polysaccharides may protect the integrity of the gastric mucosa. The latter was also promoted by the increased release of NO, PGE<sub>2</sub>, and EGF in the *H. erinaceus* polysaccharides-treated group. HERP/HECP also showed scavenging effects for 2,2-diphenyl-1-picrylhydrazyl, chelating capacity for Fe<sup>2+</sup> and OH *in vitro*, antioxidant activity, and increased superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities. It is known that SOD can rapidly convert peroxy radicals into biologically safe and inactive substances<sup>[33]</sup>.

Furthermore, GPx protects the gastric mucosa from reactive oxygen species (ROS)-induced injury and reduces lipid peroxidation<sup>[34]</sup>. Phenolic compounds appear to be the main contributors to the antioxidant capacity of *H. erinaceus*<sup>[35]</sup>. The antioxidant and scavenger properties of *H. erinaceus* exerted through its polysaccharide component have also been confirmed by other studies, in which it was shown to prevent H<sub>2</sub>O<sub>2</sub>-induced apoptotic cell death in gastric epithelial cell lines (*i.e.*, GES-1 cells)<sup>[25]</sup>.

In general, there are several studies on the use of *H. erinaceus* in ethanol-induced ulcers<sup>[36-38]</sup>, with some focusing on acetic acid-induced ulcers<sup>[39]</sup>. Mao *et al*<sup>[36]</sup> also highlighted a possible therapeutic mechanism for ethanol-induced ulceration in mice *via* epidermal differentiation by studying the differences in the expression of several keratins, including 16, 6b, and transglutaminase E, in mucosa treated with *H. erinaceus* and untreated mucosa.

In addition to its multidimensional gastroprotective properties, *H. erinaceus* can regulate chaperonins, including HSP70. For example, in a model of ethanol-induced ulcers in Sprague Dawley mice, immunohistochemical studies have demonstrated an increased presence of HSP70 and downregulation of pro-apoptotic Bcl-2-associated X proteins<sup>[40]</sup>. Heat shock proteins (as, for example, HSP70) have a well-defined role in the pathogenesis of gastric ulcers. They are among the key players in the intracellular defence mechanisms of gastric cells. Some maintain protein integrity under homeostatic and non-stressful conditions, while others are activated after noxious stimuli<sup>[41]</sup>.

However, the literature on this fungus has focused on both the erosive and atrophic patterns of gastric mucosal damage. Wang *et al*<sup>[42]</sup> examined the EP-1 fraction obtained

from *H. erinaceus* mycelium in chronic atrophic gastritis. They found the potential to reduce the proliferation of MC cells (a model of atrophic gastritis) by arresting them in the G<sub>0</sub>/G<sub>1</sub> phase of the cell cycle. However, there is a clinical, double-blinded, preliminary Chinese report for atrophic gastritis, although it was conducted in 1985 on 25 patients with atrophic gastritis who were administered *H. erinaceus* orally for three months. Clinical and histological improvements were observed in 63% and 52% of treated patients<sup>[43]</sup>.

Although there is a considerable amount of preclinical experience, there is a substantial lack of clinical trials that have evaluated this mushroom as a pharmacological intervention in erosive gastritis, gastric ulcers, and atrophic gastritis.

#### *H. erinaceus* properties against *Helicobacter pylori* infection

*Helicobacter pylori* (*H. pylori*) is a gram-negative spiral-shaped bacillus that contributes to several gastrointestinal disorders, including chronic gastritis, peptic ulcer, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma<sup>[44]</sup>. In addition, it is associated (to varying degrees) with several extra-gastric disorders, including vitamin B<sub>12</sub> deficiency anemia, primary immune thrombocytopenia, as well as ophthalmic conditions (such as glaucoma and central serous chorioretinopathy), dermatological disorders (such as rosacea and psoriasis), inflammatory bowel diseases (IBD), metabolic and neurological disorders<sup>[45]</sup>. The International Agency for Research on Cancer has designated *H. pylori* as a Group I carcinogen for gastric cancer<sup>[46]</sup>. Therefore, eradication is imperative when an infection is diagnosed<sup>[47]</sup>. However, we frequently encounter this bacterium's substantial antibiotic resistance; therefore, the guidelines suggest an algorithm based on several successive lines of treatment until eradication is achieved<sup>[48,49]</sup>. In addition to standard drug therapy, probiotics have been proposed to reduce adverse events associated with drug therapy<sup>[48]</sup>. *H. erinaceus* components (obtained by various extraction techniques) have shown marked antimicrobial properties against *H. pylori*<sup>[50-54]</sup>; however, the significant available evidence is preclinical. The minimum inhibitory concentrations (MIC) of the various

components of *H. erinaceus* against *H. pylori* are shown in Table 1. MIC values fluctuate by varying the extractive, qualitative, and quantitative characteristics of the extracted components while reaching interesting values in some cases, as in the experience of Liu *et al*<sup>[52]</sup>.

Therefore, it would be desirable to determine through clinical trials whether supplementation with *H. erinaceus* can have an additive effect on the anti-*H. pylori* efficacy of available antibiotic therapies, and whether such supplementation can reduce the adverse events associated with these antibiotic therapies.

### ***H. erinaceus* antineoplastic properties concerning gastric cancer**

Gastric cancer is now the fourth leading cause of cancer-related deaths, based on its incidence and prevalence<sup>[55]</sup>. Surgical and medical therapy take the lead in managing this neoplasm<sup>[56]</sup>; however, while not changing this premise, several natural substances have been studied as complementary treatments<sup>[57-59]</sup>.

Potential applications of *H. erinaceus* also extend in this context with a specific component of this fungus named in connection with these properties (*i.e.*, erinacines). They are diterpenoids with known neuroprotective properties, of which erinacine A is obtained from the ethanol extract of *H. erinaceus* mycelium<sup>[13]</sup>. With its exact origin, it is possible to obtain another extract, a sesterterpene, erinacine S<sup>[60]</sup>.

Tung *et al*<sup>[61]</sup> demonstrated a unique mechanism by which erinacine S could intervene in gastric carcinogenesis through epigenetic regulation. This molecule can induce selective apoptosis in gastric cancer cell lines (*i.e.*, AGS) mediated by ROS toxicity while sparing normal cells. A mouse model of AGS-xenografts in which erinacine S suppressed tumour growth also confirmed this phenomenon<sup>[61]</sup>. In general, erinacine S may promote apoptosis in gastric carcinoma cells by inducing a specific pathway involving several molecules, such as TNF-related apoptosis-inducing ligand T (TRAIL), Fas ligand (Fas-L), and caspases 3,8,9 which are known to be involved in apoptotic death. At the same time, erinacine S suppressed the expression of anti-apoptotic molecules (*i.e.*, Bcl-2 and Bcl-XL). In addition, cell arrest is promoted in the G<sub>1</sub> phase of



the cell cycle by the inactivation of specific cyclins and cyclin-dependent kinases<sup>[61]</sup>. Furthermore, erinacine S promotes the expression of Fas-L and TRAIL in gastric cancer cells undergoing apoptosis by trimethylation of histone H3 in the promoter regions of the Fas-L and TRAIL genes<sup>[61]</sup>.

Erinacine A exhibits characteristics similar to erinacine S with respect to apoptosis induction. Several studies have shown that erinacine S can inhibit the growth of colorectal cancer both *in vitro* and *in vivo*, which could be attributed to the inhibition of proliferation and induction of the apoptosis signalling pathway, such as the generation of ROS via the phosphatidylinositol 3-kinase (PI3K)/mechanistic target of rapamycin (mTOR)/ribosomal protein S6 kinase beta-1 (p70S6K) pathway<sup>[62,63]</sup>.

Proteomic analyses have confirmed that erinacine A reduces the growth and invasiveness of TSGH9201 gastric cancer cells via ROS-mediated phosphorylation of focal adhesion kinase (FAK)/protein kinase B (also known as AKT)/p70S6K and p21-activated kinase 1 (PAK1)<sup>[64]</sup>. Previous studies have shown that erinacine A-mediated apoptosis involves the actin depolymerisation pathway<sup>[65]</sup>. Furthermore, several PAK partners can phosphorylate or activate mitogen-activated protein kinases. The kinases PI3-kinase/AKT and LIM are involved in the regulation of the cytoskeleton<sup>[66,67]</sup>. In addition, erinacine A is believed to induce upregulation of the onco-suppressive proteins microtubule-associated scaffold protein 2 (MTUS2) and 14-3-3 protein sigma (1433S), associated with antitumour activity in gastric cancer cells<sup>[63]</sup>. Recent studies have shown that the 1433S protein appears to intervene in gastric cancer by exerting G<sub>2</sub>/M checkpoint regulation in the cell cycle<sup>[68,69]</sup>.

Furthermore, the MTUS2 gene plays a central role in controlling microtubule plus-end-tracking proteins (also known as +TIPs) by regulating cell division and migration through its mitotic kinesin-associated centromere, a microtubule depolymerase<sup>[70,71]</sup>. Moreover, the cytoskeleton depolymerisation pathway has been recognised as a critical cellular response that controls apoptosis and inhibits Rho GTPase-activated cell migration through its effector kinases, Rho-associated coiled-coil containing protein kinases 1 and 2<sup>[72]</sup>. These findings are significant and imply that phosphorylation of the

FAK/AKT/p70S6K and PAK1 pathways determines the downstream expression of the MTUS2 and 1433S genes, the execution of cancer cell apoptosis, and the role of erinacine A as an anti-invasive agent. This effect most likely reflects cytoskeleton rearrangement, reducing erinacine A-dependent cell motility<sup>[63,73,74]</sup>. Figure 2 summarises the primary antineoplastic mechanisms of erinacines.

An additional polysaccharide protein extracted from the fermented mycelia of *H. erinaceus* (HEG-5) was studied in SGC-7901 gastric cancer lines. Again, positive regulation of apoptosis and the cell cycle appears to be the mechanisms underlying this antineoplastic action. Indeed, it seems that HEG-5 blocks the development of SGC-7901 cells in the S phase of the cell cycle by promoting the opposite regulation of anti- and pro-apoptotic genes. That is, predictably, the downregulation of anti-apoptotic molecules (such as Bcl-2, PI3K, and AKT) and, conversely, by upregulating caspases 3,8, p53, the bcl-2-associated X-protein, and the bcl-2-associated death promoter. Thus, caspase 3,8-dependent, p53-dependent, and PI3K/AKT-mediated apoptotic pathways are activated<sup>[75]</sup>.

A synergy between doxorubicin and *H. erinaceus* was also observed in their pro-apoptotic action toward SGC-7901 cells via ROS-induced stress and caspase activation<sup>[76]</sup>.

Moreover, two extracts of *H. erinaceus* (i.e., HTH5 and HTJ5A) have been shown in an experiment conducted in NCI-87 gastric carcinoma cells to possess both *in vitro* and *in vivo* (in xenograft models including severe combined immunodeficient bearing mice) concentration-dependent cytotoxicity toward such cells, lower toxicity, and more efficacy than 5-fluorouracil<sup>[77]</sup>.

Finally, *H. erinaceus* (via the EP-1 polysaccharide) targets not only cancer cells but also precancerous cell lines by promoting their arrest in the G<sub>0</sub>/G<sub>1</sub> phase of the cell cycle<sup>[78]</sup>.

## H. ERINACEUS IN LOWER GASTROINTESTINAL TRACT DISEASES: THE EVIDENCE

### *H. erinaceus* and IBD

IBD is a chronic digestive disease that results in sustained gastrointestinal inflammation and consists mainly of ulcerative colitis (UC) and Crohn's disease<sup>[79]</sup>.

Available evidence related to *H. erinaceus* primarily focuses on UC. Wang *et al*<sup>[80]</sup> evaluated three polysaccharides (*i.e.*, wHEP-1, wHEP-2, and wHEP-3) and proposed the third as the one showing the greatest anti-inflammatory action in a UC-like model in Caco-2 cells inflamed by bacterial lipopolysaccharide.

A more complete *in vivo* model has been reported by Diling *et al*<sup>[81]</sup>. The authors experimentally induced UC-like colitis in mice using trinitrobenzene-sulfonic acid enemas. They were then treated with mixed extracts of *H. erinaceus* (polysaccharide, alcoholic, and cumulative fractions) for 14 d. Significant clinical improvements were observed in the treated mice compared with the untreated control mice. Also, histologically, the treated group had significantly less severe lesions. They recorded reduced MPO levels in the treated mice to verify tissue infiltration of neutrophils. This was accompanied by a modulation of cytokines in the treated group with the restoration of proinflammatory and anti-inflammatory cytokines to pre-treatment levels with trinitro-benzene-sulfonic acid.

Further study has confirmed the anti-UC properties of ethanolic extracts of *H. erinaceus* in C57BL/6 mice exposed to dextran sulphate sodium orally to induce experimental UC-like colitis. The dosage used by the authors was 250/500 mg/kg/d<sup>[82]</sup>. This study showed as much clinical improvement as histologic (including neutrophil infiltration by MPO dosing) and cytokine improvement. However, these authors also stigmatised antioxidant potential by upregulating NO, malondialdehyde, and SOD. Wang *et al*<sup>[83]</sup> also focused on the antioxidant potential of *H. erinaceus* polysaccharides as a therapeutic mechanism in UC experimental colitis and discovered the positive regulation of SOD and reduced ROS production. It is no coincidence that combating oxidative stress is part of the therapeutic proposals for IBD<sup>[84]</sup>.

UC pathogenesis remains largely unclear, but bowel inflammation and oxidative stress are considered fundamental mechanisms underlying its pathophysiology. During the active phase of UC, activated leukocytes generate many proinflammatory cytokines

and pro-oxidative stress reactions. The joint deterioration caused by inflammation and oxidative stress significantly alters the redox balance within the intestinal mucosa, which accelerates the apoptosis of intestinal epithelial cells<sup>[85,86]</sup>. Excessive ROS production directly leads to tissue damage and induces an inflammatory cascade<sup>[87]</sup>. When mitochondria are damaged by oxidative stress, they enter a vicious cycle in which the loss of respiration disrupts redox homeostasis and, in turn, increases intracellular oxygen availability, resulting in increased ROS formation and subsequent oxidative damage to DNA<sup>[88]</sup>. Several studies have shown that UC onset and course are related to changes in mitochondrial structure and function<sup>[89,90]</sup>.

Finally, in the context of *H. erinaceus* polysaccharides, Ren *et al*<sup>[91]</sup> confirmed this finding in C57BL/6 mice with experimental UC-like colitis induced by dextran sulphate sodium. Furthermore, the authors recorded (as also done by Diling *et al*<sup>[81]</sup>) an anti-inflammatory downregulation of nuclear factor kappa B (NF- $\kappa$ B).

NF- $\kappa$ B is part of several pathways (*i.e.*, the canonical and noncanonical pathways) that have been extensively studied in IBD, upon which the mainstay of biological therapy for IBD, namely anti-TNF- $\alpha$  agents, has been built<sup>[92]</sup>.

However, another mechanism by which the anti-IBD effect of *H. erinaceus* has been studied is the modulation of the gut microbiota, as described in the last section of this review.

### ***Colonic diverticulosis and H. erinaceus***

Diverticular disease has acquired several modifications of its nomenclature over time, including the concept of symptomatic uncomplicated diverticular disease (SUDD) in its gnoseological entity. SUDD is characterised by colonic diverticulosis associated with chronic abdominal pain without signs, symptoms, or evidence of underlying diverticulitis or colitis<sup>[93]</sup>. Several pathogenetic mechanisms have been implicated, including visceral hypersensitivity and a reduction in the interstitial Cajal cells, resulting in slowed colonic motility<sup>[94]</sup>. SUDD therapy includes poorly absorbable antibiotics (such as rifaximin<sup>[95]</sup>), mesalamine<sup>[96]</sup>, or probiotics<sup>[97]</sup>, as well as modification



of habits with increased physical activity<sup>[94]</sup>. However, definitive medical therapy for SUDD has not yet been defined.

Paradoxically, in the case of diverticular disease, the *H. erinaceus* research trend was reversed with the availability of clinical studies and the absence of preclinical studies. Brandimarte *et al*<sup>[98]</sup>, in a single study, evaluated a combination nutraceutical compound mainly consisting of polysaccharide extracts of *H. erinaceus* in 305 patients with SUDD. The authors recorded clinical remission rates (defined by them as the disappearance of all symptoms) of 9.34% and 17.64% at three and six months of treatment, respectively. Beyond clinical remission, it is interesting to note that the clinical response rate (defined as symptom reduction) was > 90% at three months and approximately 85% at six months. Furthermore, at three and six months, the authors recorded a significant decrease in faecal calprotectin values from baseline. However, these data should be interpreted within the limitations of a single study and the lack of clarification regarding the actual mechanism underlying this clinical improvement.

Nevertheless, it is clear how <sup>4</sup> the inflammatory process plays a role in the pathogenesis of diverticular disease<sup>[99]</sup>. In addition, TNF- $\alpha$  levels appear to increase progressively with the severity of diverticular disease in both diverticulitis and SUDD<sup>[100]</sup>. Therefore, as in the other gastrointestinal disorders already discussed in this review, *H. erinaceus* might potentially intervene in diverticular disease through the regulation of the local inflammatory load; however, as already mentioned, there is currently no evidence.

#### ***H. erinaceus and irritable bowel syndrome: A potential ally in this brain-gut interaction disorder?***

Unlike IBD, where *H. erinaceus* has been extensively studied in preclinical models, no evidence is available regarding its role in irritable bowel syndrome (IBS). However, it is becoming increasingly clear that IBS is coded within functional gastrointestinal disorders and how ROME IV has now defined these disorders as “disorders of brain-gut interaction”, stigmatising the decisive role that the gut-brain axis has acquired in



the pathogenesis and clinical features of IBS and other similar functional disorders<sup>[101]</sup>. Indeed, it is also clear how many brain-derived factors (from neurotransmitters to psychological disorders) are directly involved in IBS pathogenesis<sup>[101]</sup>. Patients with IBS experience a notably higher prevalence of anxiety-depressive disorders than the healthy population<sup>[102]</sup>. *H. erinaceus* has been widely studied in clinical settings in patients with anxiety and depression. One randomised controlled trial provided results in favour of positive regulation of psychiatric disorders<sup>[103]</sup>. Moreover, several pathogenic mechanisms have been suggested in studies on mood disorders. In mice, *H. erinaceus* appears to exert anti-inflammatory effects (negative regulation of proinflammatory cytokines and positive regulation of anti-inflammatory cytokines), stimulate hippocampal neurogenesis, and increase neurotransmitters such as 5-hydroxytryptamine, dopamine, and noradrenaline. However, in humans, it appears to increase salivary levels of free 3-methoxy-4-hydroxyphenylethylene glycol and circulating levels of pro-brain-derived neurotrophic factor. These molecular changes are associated with an improved anxiety-depressive effect<sup>[104-107]</sup>.

Beyond that, the potential of *H. erinaceus* to intervene in the gut-brain axis could also be explored in patients with IBD, where the prevalence and impact on the disease course of anxiety-depressive disorders are not negligible<sup>[108,109]</sup>. In addition, factors leading to anxiety-depressive disorders can impact therapeutic adherence, as observed during the COVID-19 pandemic<sup>[110,111]</sup>.

IBS therapy is challenging, and much more needs to be added to the research field<sup>[112]</sup>. In addition, naturally derived substances have repeatedly been considered possible therapies for IBS<sup>[113-115]</sup>. Ultimately, despite the interesting prospect of the impact of *H. erinaceus* on the dysregulation of the gut-brain axis in IBS, studies evaluating the effects of this fungus on both the gastrointestinal clinical features and the impact of modulation of anxiety and depression on the latter are still awaited.

### *H. erinaceus and the colorectal cancer*

As observed for gastric cancer, even in the case of colorectal cancer, studies have been conducted regarding the antineoplastic potential of *H. erinaceus*. Table 2 summarises the main pathophysiological mechanisms identified.

Liu *et al*<sup>[116]</sup> focused on two polysaccharides from the fruiting body of *H. erinaceus* extracted by hot water and ferrocyanide-zinc acetate (HEFP-1 and HEFP-2). These polysaccharides showed the ability in their assay to selectively inhibit the growth of colonic cancer cells (*i.e.*, HCT-116) while sparing normal colonic cells. Furthermore, the HEFP polysaccharide 2b fraction (HEFP-2b) was determined to be responsible for this action. In other words, HEFP-2b induced S-phase cell cycle arrest of such cells through the downregulation of CDK1,2 and cyclin A2 and concomitant inhibition of minichromosomal maintenance protein 5 (MCM5), a protein essential for the transition from the S-phase to the M-phase<sup>[117]</sup>.

Using the exact extraction mechanism, Hou *et al*<sup>[118]</sup> obtained and characterised another polysaccharide fraction of the mushroom fruiting body with antineoplastic properties in colonic cancer. The model was similar to the cellular model employing both the same cells as the previous authors (*i.e.*, HCT-116) but with the addition of the DLD1 cell group. They showed an upregulation of cleaved caspase-9 and cleaved caspase-3 without a change in the cleavage of caspase-8, confirming that the apoptotic mechanism was mitochondrial and not extrinsic with relative inhibition of the Bcl-2 protein and stimulation of the pro-apoptotic Bax protein. Confirming this evidence, the authors identified that ROS production might be one of the triggers of this apoptotic phenomenon.

Another study examined fungal extracts obtained by boiling water, microwave extraction in ethanol, and acid or alkaline extracts with hydrochloric acid or sodium hydroxide, respectively<sup>[119]</sup>. These extracts specifically demonstrated inhibitory effects on implanted tumours in mice (using CT-26 murine cancer cells). Furthermore, intraperitoneal administration of the extracts obtained by boiling water and microwaving in ethanol reduced tumour growth by 38% and 41%, respectively. These

extracts increased the cytolytic activity of natural killer cells and phagocytic activity of macrophages and blocked tumour angiogenesis.

In addition, as in gastric cancer, HTJ5 and HTJ5A extracts were shown to block the growth of HT-29 colon cancer cell implants in mice with severe combined immunodeficiency<sup>[77]</sup>. Another study also confirmed the antineoplastic action of *H. erinaceus* in HT-29 cells by evaluating its anti-tyrosinase and  $\alpha$ -glucosidase activities<sup>[120]</sup>.

As previously described, erinacines are the principal antineoplastic components of *H. erinaceus* in gastric cancer. However, erinacine A showed marked antineoplastic effects against colon cancer. In detail, Lee *et al*<sup>[65]</sup> highlighted this in HCT-116 and DLD-1 cells by demonstrating how erinacine A was able to exert its cytotoxic action similar to that observed in gastric cancer by increasing ROS production and decreasing cancer cell proliferation through upregulation of the PI3K/mTOR/p70S6K pathway.

## H. ERINACEUS AND GUT MICROBIOTA MODULATION

*H. erinaceus* may promote a shift in the gut microbiota phenotype toward the increased selection of short-chain fatty acids-producing bacteria

The gut microbiota, although not fully detailed and understood, plays a crucial role in the development, progression, and treatment of several gastrointestinal pathological conditions, including IBS and IBD<sup>[121]</sup>.

*H. erinaceus* is closely related to the modulation of the gut microbiota. In general, it seems to be able to change the gut microbiota's quantitative and qualitative phenotypes in a health-promoting manner. Therefore, it has often been defined as a prebiotic or probiotic<sup>[81,122-124]</sup>. It appears that *H. erinaceus* selects certain beneficial bacterial strains from the gut microbiota at the expense of pathogenic strains. For example, Xie *et al*<sup>[124]</sup> studied the fourteen days administration of 1 g of *H. erinaceus* dry powder in submerged cultures in 13 healthy young volunteers and recorded an increase in the alpha diversity of the gut microbiota. They recorded an increase in *Bifidobacterium* and *Bacteroides* and an increase in short-chain fatty acid (SCFAs) production (i.e., *Roseburia*

*faecis*, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Fusicatenibacter saccharivorans*, *Kineothrix alysoides*, *Gemmiger formicilis*, and *Dorea longicatena*). Confirming the modulation of the microbiota, in addition to this whole series of beneficial bacterial species, *H. erinaceus* resulted in a reduction in the relative abundance of pathogenic bacteria (*Streptococcus thermophilus*, *Roseburia intestinalis*, *Bacteroides caccae*, and *Anaerostipes hadrus*).

SCFA-producing bacteria may intervene in immune homeostasis through the regulation of lymphocyte chemotaxis and phagocytosis and possess anti-inflammatory and anti-tumourigenic properties<sup>[125]</sup>. In addition, SCFAs produced mainly in the colon from indigestible polysaccharides are associated with a reduced risk of IBD and IBD-associated dysbiosis<sup>[126]</sup>. Not surprisingly, they regulate the immune response by suppressing TNF- $\alpha$  production in neutrophils, contributing to intestinal barrier integrity by inducing secretion of IL-18, mucin, and antimicrobial peptides by intestinal epithelial cells and impacting the ability of dendritic cells to bind to T lymphocytes<sup>[126]</sup>.

Moreover, the authors posited the impact of such changes in the gut microbiota with a shift in several hematochemical parameters by observing a beneficial correlation with several analytes (*i.e.*, alkaline phosphatase, low-density lipoprotein, creatinine, and uric acid). These data suggest a possible clinical impact of *H. erinaceus*-driven modulation of the gut microbiota.

A further study recreated some experimental conditions of digestion to evaluate whether some polysaccharides of *H. erinaceus* could overcome the digestive barrier of the upper digestive tract and influence gut microbiota composition.

Following this experimental model, several *H. erinaceus* polysaccharides obtained by alcohol precipitation (*i.e.*, HEP30, HEP50, and HEP70) increased the relative abundance of SCFA-producing bacteria and reduced pathobiont concentrations (*i.e.*, *Escherichia-Shigella*, *Klebsiella*, and *Enterobacter* in this experience), stigmatised the role of such polysaccharides as possible functional foods<sup>[127]</sup>. Therefore, they set up an experimental *in vitro* digestion model, as previously described. First, they suggested the likely passage of polysaccharides through the gastrointestinal tract without being digested by



the saliva of healthy donors or gastric and small intestinal juices (simulated in the laboratory). Therefore, they may reach the distal tract of the intestine. Second, at that level, the authors demonstrated how the gut microbiota utilised HEP50 for fermentation by increasing the levels of SCFAs and decreasing the pH of the faecal fermentation broth.

Furthermore, Yang *et al*<sup>[127]</sup> examined the impact of a polysaccharide from the mycelium of *H. erinaceus* on the quality of murine gut microbiota. The authors observed a change in the relative abundance of different bacteria depending on the age of the mice used for the microbiota analysis. In both the control and experimental groups of adult and middle-aged mice, there was an increase in the relative abundance of *Lachnospiraceae*, *Ruminococcaceae*, and *Akkermansiaceae* and a decrease in the relative abundance of *Muribaculaceae*, *Rikenellaceae*, *Lactobacillaceae*, and *Bacteroidaceae*. On the other hand, only the treated adult mice showed an increase in *Erysipelotrichaceae*, *Enterobacteriaceae*, *Christensenellaceae*, and *Coriobacteriaceae* and a decrease in *Bifidobacteriaceae* and *Peptostreptococcaceae*. Finally, in the group of middle-aged and old mice, the increased bacterial species were *Rhizobiaceae*, *Desulfovibrionaceae*, and *Lachnospiraceae*, while the decreased species were *Corynebacteraceae* and *Rikenellaceae*. Among the many modified families of bacteria, the relevant ones are the butyrate-producing bacteria (*i.e.*, *Lachnospiraceae* and *Ruminococcaceae*). Butyrate is an SCFA used as an energy source by the intestinal mucosa to promote gut health and protect against colorectal cancer<sup>[128-130]</sup>. These two species of bacteria are among the leading producers of butyrate<sup>[131]</sup>. Further *in vitro* studies have shown the beneficial effects of *H. erinaceus* in modulating SCFA-producing bacteria<sup>[132]</sup>. Positive *H. erinaceus*-driven modulation of the gut microbiota has also been confirmed in elderly dogs, with ameliorative effects on immunity and obesity<sup>[133]</sup>.

***H. erinaceus* in restoring the gut microbiota after dysbiosis induced by antineoplastic drug therapy: The evidence**



Cancer therapy is associated with significant adverse events, including gastrointestinal complications. The latter includes dysbiosis induced by antineoplastic treatments<sup>[134]</sup>. However, while the microbiota may be impacted by antineoplastic therapy, it is also true that several reports suggest an opposite mechanism whereby the gut microbiota may modulate the response to treatment, specifically immunotherapy<sup>[135]</sup>. In this context, *H. erinaceus* showed some preclinical results, demonstrating its potential in cancer therapy-induced toxicity. For this purpose, an investigation based on polysaccharides was conducted in mice treated with cyclophosphamide<sup>[136]</sup>. This brought the composition of the gut microbiota of chemotherapy-treated mice closer to that of control and healthy mice through increased alpha and beta diversity. Similar results were reported in another study<sup>[123]</sup>. Moreover, these data are also available for 5-fluorouracil toxicity. Wang *et al*<sup>[137]</sup> examined the proteins of *H. erinaceus* in a xenograft cancer model in mice successfully treated with 5-fluorouracil and revealed an anti-dysbiosis action.

#### ***H. erinaceus may intervene in IBD through the gut microbiota***

Although a therapy based on the direct modification of the gut microbiota is not yet recommended in the current guidelines for managing IBD, it is clear that the potential of this option has been extensively studied and is currently under investigation<sup>[138-141]</sup>.

Ren *et al*<sup>[142]</sup> studied whether the administration of *H. erinaceus* to Cynomolgus monkeys affected the clinical features of spontaneous UC by exerting an anti-inflammatory effect through modulation of the gut microbiota. They recorded an increase in the abundance of bacteria, such as *Lactobacillus reuteri* (already implicated in improving the clinical features of IBS, acute gastrointestinal infections, and IBD in children and adults). In contrast, *Streptococcus lutetiensis* is negatively modulated and is known to cause sepsis in newborns<sup>[143]</sup>.

In addition, Diling *et al*<sup>[81]</sup>, in the above cited model of murine colitis induced by trinitro-benzene-sulfonic acid, demonstrated how the administration of extracts (*i.e.*, polysaccharide, alcoholic extracts, and whole extracts) of *H. erinaceus* improved both the

clinical and histological picture but, more importantly, the gut microbiota by promoting a switch to a microbial composition similar to that of the controls. In other words, a reduction in proinflammatory strains (*Corynebacterium*, *Staphylococcus*, *Ruminococcus*, *Roseburia*, *Dorea*, and *Sutterella*) and an increase in anti-inflammatory strains (*Bacteroides*, *Bifidobacterium*, *Prevotella*, *Parabacteroides*, *Coprococcus*, *Desulfovibrio*, and *Lactobacillus*) were observed.

In a similar study, in an acetic acid-induced murine colitis model, the mycelium polysaccharide EP-1 drastically improved the gut microbiota of mice by increasing SCFA-producing populations while suppressing the expression of G protein-coupled receptor 41 (GPR41) and GPR43<sup>[144]</sup>. SCFAs can bind to GPR41 and GPR43 and increase the production of inflammatory cytokines and chemokines in the intestine<sup>[145]</sup>.

Finally, positive microbiota modulation was observed in mice with dextran sulphate sodium-induced colitis<sup>[91]</sup>.

Despite the possibility that *H. erinaceus* may have intervened in the pathogenesis of IBD through the gut microbiota, studies conducted in humans as well as those exploring the clinical impact of such microbiota modification, are still awaited, especially with clinical tools and scores that are widely validated and used in clinical and IBD research practise<sup>[146,147]</sup>.

## CONCLUSION

*H. erinaceus* is a mushroom with a long tradition of use as a medicinal product. Numerous preclinical studies have probed its gastrointestinal anti-inflammatory and antineoplastic properties and its impact on the composition of the intestinal microbiota (Figure 3). In the face of a large body of evidence, there is a strong need for clinical studies conducted on humans, especially considering the promising results of previous studies. Furthermore, it is necessary to determine whether this fungus can represent an excellent nutritional supplement in gastrointestinal pathologies, the patients who may benefit from it, and whether there is a possible therapeutic role for the compounds extracted from *H. erinaceus*. Finally, various technical processes for such fungi yield

many extracts and fractions. Therefore, it is essential to understand which of these presents the best safety and efficacy profiles.

### Figure Legends

**Figure 1 Several constituents can be obtained from *Hericium erinaceus* by different means of extraction (for example, by alcohol, chloroform, or petroleum).** However, fractions such as erinacins and polysaccharides are those most commonly used in studies conducted in the gastrointestinal setting.

**Figure 2 Main antineoplastic molecular mechanisms of erinacines S and A from *H. erinaceus* in gastric cancer cell models.** Erinacine S (in AGS gastric cancer cells) can activate a pathway (red arrows) with reactive oxygen species (ROS) mediated phosphorylation of focal adhesion kinase (FAK)/protein kinase B (also known as AKT)/p21-activated kinase 1 (PAK1). Subsequently, by trimethylation of histone H3, the latter pathway can induce the increased expression of TNF-related apoptosis-inducing ligand T and Fas ligand receptors by the cancer cell with the subsequent activation of apoptosis by initiating caspases 3, 8, and 9. Erinacine A (in TSGH9201 gastric cancer cells), once activated (blue arrows), the FAK/AKT/PAK1 pathway, in a similar manner as previously described, upregulates microtubule-associated scaffold protein 2/14-3-3 protein sigma proteins with subsequent activation of caspases-mediated apoptosis. In addition, erinacines can also modulate cell cycle regulation by preventing cell cycle continuation through the blockade at checkpoints, *i.e.*, blocking cyclin-dependent kinases. ROS: Reactive oxygen species; FAK: Focal adhesion kinase; PAK: Activated kinase 1; MTUS2: Microtubule-associated scaffold protein 2; TRAIL: TNF-related apoptosis-inducing ligand T; Fas-L: Fas ligand; CDKs: Cyclin-dependent kinases; 1433S: 14-3-3 protein sigma.

**Figure 3 The potential of *Hericium erinaceus* in upper and lower gastrointestinal tract diseases.** *Hericium erinaceus* is a promising candidate as a therapeutic modality or

functional food in the treatment of various diseases of the gastrointestinal tract. This evidence stems from several experiences, largely preclinical, that have shown that this mushroom possesses anti-inflammatory and antineoplastic capabilities concerning the gastrointestinal tract.

**Table 1** Preclinical studies evaluating the antimicrobial activity of several *Hericium erinaceus* fraction toward *Helicobacter pylori*

Ref.	<i>H. erinaceus</i> fraction employed	Extraction method	Anti- <i>H. pylori</i> MIC (µg/mL)
Shang <i>et al</i> <sup>[50]</sup> , 2013	Ethyl acetate fractions		62.5-250.0 <sup>1</sup>
Zhu <i>et al</i> <sup>[51]</sup> , 2014	HEP25 (197 kDa)	Ethanol precipitation (ethanol concentration 25%)	320 <sup>2</sup>
	HEP75 (20 kDa)	Ethanol precipitation (ethanol concentration 75%)	160 <sup>2</sup>
	Bi <sup>3+</sup> plus HEP25	Complexation of peptides with bismuth <sup>[54]</sup>	20 <sup>2</sup>
	Bi <sup>3+</sup> plus HEP75		20 <sup>2</sup>
Liu <i>et al</i> <sup>[52]</sup> , 2016	PE2s (4 g)	Petroleum ether extract	250-500 <sup>3</sup>
	II-14-18 (311.000 mg)	Methyl alcohol elution from PE2s	12.5-50 <sup>3</sup>
	II-19-30 (355.100 mg)		12.5-25 <sup>3</sup>
	II-10-13 (306.100 mg)		25-100 <sup>3</sup>
	II-54-58 (96.000 mg)		100-400 + <sup>3</sup>
	II-31-45 (363.900 mg)		25-50 <sup>3</sup>
	II-46-53 (184.500 mg)		25-100 <sup>3</sup>
	II-59-63 (78.100 mg)		50-100 <sup>3</sup>



II-64-78 (425.400 mg)		100-400 + <sup>3</sup>
<sup>9</sup> II-1-6 (215.700 mg)		50-200 <sup>3</sup>
II-7-9 (319.900 mg)		25-200 <sup>3</sup>
<sup>18</sup> 1-(5-chloro-2-hydroxyphenyl)-3-methyl-1-butanone)	Recrystallized from II-10-13 and II-54-58	12.5-50 <sup>3</sup>
2,5-bis(methoxycarbonyl)terephthalic acid	Recrystallized from II-10-13 and II-54-58	6.25-25 <sup>3</sup>
Thi My Ngan <i>et al</i> <sup>[53]</sup> , fEtOAc (11.040 g)	Culture filtrate-derived ethyl acetate fraction	1.25 <sup>4</sup>
2021 mEtOAc (0.091 g)	Mycelium-derived Ethyl acetate fraction	1.5 <sup>4</sup>
mHexane (0.162 g)	Mycelium-derived hexane fraction	7.5 <sup>4</sup>
PS (26.400 g)	Culture filtrate-derived polysaccharide	7.5 <sup>4</sup>
fHexane (0.120 g)	Culture filtrate-derived hexane fraction	10 <sup>4</sup>
mWater (0.509 g)	Mycelium-derived water fraction	10 + <sup>4</sup>
fWater (72.480 g)	Culture filtrate-derived water fraction	10 + <sup>4</sup>

<sup>1</sup>Nine clinical isolates are the employed strain of *Helicobacter pylori* (*H. pylori*).

<sup>2</sup>Colloidal bismuth subcitrate with a minimum inhibitory concentration (MIC) of 20 µg/mL was used as the comparison reference. NTCC11637 is the employed strain of *H. pylori*.

<sup>3</sup>The comparison references were metronidazole (MIC range 0.7800-1.5625 µg/mL) and tetracycline (MIC range 0.780-3.125 µg/mL). In addition, different isolates of *H. pylori* were used (*i.e.*, ATCC 43504, SS1, *H. pylori* Wz504, *H. pylori* 9, *H. pylori* 64, *H. pylori* 78, and *H. pylori* 83). Therefore, the results are presented as MIC ranges.

<sup>4</sup>The reference comparison was amoxicillin, with a MIC of 0.032 <sup>37</sup> µg/mL.

ATCC43504 is the employed strain of *H. pylori*. Bi<sup>3+</sup>; Bismuth, *H. pylori*: *Helicobacter pylori*; MIC: Minimum inhibitory concentration.

**Table 2 Main studies examining antineoplastic mechanisms of *Hericium erinaceus* against colorectal cancer**

Ref.	<i>H. erinaceus</i> fraction employed	Colonic cancer model	Identified mechanism
Kim <i>et al</i> <sup>[119]</sup> , 2011	Hot water/ ethanol extraction	microwave extracts CT-26 cancer cells graft in mice	NK cells activity ↑; macrophages activity ↑; angiogenesis ↓
Li <i>et al</i> <sup>[77]</sup> , 2014	Polysaccharides	HT-29 cancer cells graft in mice	-
Lee <i>et al</i> <sup>[65]</sup> , 2017	Erinacine A	Cancer cells (HCT-116, DLD1)	PI3K/AKT/mTOR/ p70S6K pathway; ROS ↑
Sharif <i>et al</i> <sup>[120]</sup> , 2018	Ethanolic and methanolic extracts	Cancer cells (HT-29)	α-glucosidase activity ↑; anti-tyrosinase activity ↓
Liu <i>et al</i> <sup>[116]</sup> , 2020	Polysaccharides	Cancer cells (HCT-116)	CDK1 ↓; CDK2 ↓; Cyclin A2 ↓; MCM5 ↓
Hou <i>et al</i> <sup>[118]</sup> , 2020	Polysaccharides	Cancer cells (HCT-116, DLD1)	Clived caspases 3,9 ↑; ROS ↑; Bax ↑; Bcl-2 ↓

NK: Natural killer; PI3K: Phosphatidylinositol 3-Kinase; AKT: Protein kinase B; mTOR: Mechanistic target of rapamycin; p70S6K: Ribosomal protein S6 kinase beta-1; CDK: Cyclin-dependent kinase; MCM5: Mini-chromosomal maintenance protein 5; ROS: Reactive oxygen species; Bax: Bcl-2-like protein 4; Bcl-2: B-cell lymphoma 2.

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