JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2024, 75, 1, 3-9
www.jpp.krakow.pl | DOI: 10.26402/jpp.2024.1.01

Review article

L. ROMANO[1,2], L. NAPOLITANO[2], F. CROCETTO[2], C. SCIORIO[3], K. PRIADKO[4], M. FONTICELLI[4], A. FEDERICO[4], M. ROMANO[4], A.G. GRAVINA[4]

THE POTENTIAL THERAPEUTIC ROLE OF *HERICIUM ERINACEUS* EXTRACT IN PATHOLOGIC CONDITIONS INVOLVING THE UROGENITAL-GUT AXIS: INSIGHTS INTO THE INVOLVED MECHANISMS AND MEDIATORS

[1]Department of Neurosciences, Sciences of Reproduction, and Odontostomatology, University of Naples 'Federico II', Naples, Italy; [2]Unit of Urology, Department of Woman, Child and General and Specialized Surgery, University of Campania 'Luigi Vanvitelli', Naples, Italy; [3]Division of Urology, A. Manzoni General Hospital, Lecco, Italy; [4]Department of Precision Medicine and Hepatogastroenterology Unit, University of Campania 'Luigi Vanvitelli', Naples, Italy

In this review we focused on the putative therapeutic effect of *Hericium erinaceus* extract in the treatment of pathologic conditions of the lower urinary tract in which intestinal inflammation may play a role. To this aim we reviewed the available evidence on pelvic cross-organ sensitization as a possible mechanism through which intestinal inflammation and dysbiosis may affect the lower urinary tract. Also, we reviewed the clinical and experimental evidence supporting the role of *Hericium erinaceus* extract as an anti-inflammatory agent highlighting the role of a number of putative mediators and mechanisms which might make this nutraceutical suitable for the management of 'difficult to treat' lower urinary tract disorders.

Key words: *urogenital-gut axis, medicinal mushroom, Hericium erinaceus extract, lower urinary tract, intestinal inflammation, dysbiosis, inflammatory bowel disease, gut microbiota*

INTRODUCTION

Lower urinary tract symptoms (LUTS) refer to different symptoms divided into voiding, storage, or postvoiding including urinary hesitancy, straining, nocturia, increased urination frequency, and dysuria. They are frequent in the general population and approximately a third of individuals experience LUTS during their lifetime with a negative impact on patients' health-related quality of life. There are several causes of LUTS such as benign prostate enlargement, detrusor muscle weakness or overactivity, prostate inflammation (prostatitis), urinary tract infection, prostate cancer, and neurological disease (1). Several studies highlighted the concept that inflammatory conditions affecting the gastrointestinal tract may at least in part contribute to occurrence of genito-urinary disorders, thus being a putative target of intervention (2-4). *Hericium erinaceus* (*H. erinaceus*) is an ancient medicinal mushroom from China whose extract main biologicaly activities are neuroprotective and anti-cancer (5, 6). However, *H. erinaceus* extracts have also shown to exert beneficial effects in a number of pathological conditions due to its anti-inflammatory properties (7, 8). In particular, an *H. erinaceus*-derived nutraceutical has been demonstrated to be effective in decreasing intestinal inflammation probably, at least in part, due to its prebiotic activity similar to that of other edible mushrooms (8).

In this review we therefore analyze the mechanisms underlying the pathophysiological connection between the urogenital and the gastrointestinal tract. Also, we review the scientific evidence which supports the beneficial effects of *H. erinaceus* in the gut highlighting the involved mechanisms and mediators. Finally we discuss the potential role of *H. erinaceus* in the treatment of genito-urinary tract conditions in which the involvement of intestinal inflammation might play a role.

METHODOLOGY

We conducted a narrative review in the Medline (US National Library of Medicine, Bethesda, MD, USA), Scopus (Elsevier, Amsterdam, The Netherlands), and Web of Science Core Collection (Thomson Reuters, Toronto, ON, Canada) databases up to November 2023. The following terms were combined to capture relevant publications: 'lower urinary tract symptoms', OR 'chronic prostate inflammation', OR 'urinary tract infection' AND 'microbiota' OR 'intestinal microbiota' OR 'gut microbiota' OR *Hericium erinaceus*. Retrospective and prospective studies, both comparative and non-comparative; narrative reviews; systematic reviews; and meta-analysis were included. Reference lists of included studies were searched for additional relevant articles. Letters, editorial comments, replies from authors, case reports, meeting abstracts, and non-human and non-English language articles were excluded. Data were extracted, and the results were qualitatively described, as reported in primary studies.

LOWER URINARY TRACT SYMPTOMS AND THE GASTROINTESTINAL TRACT

Lower urinary tract symptoms (LUTS), mainly due to recurrent urinary tract infections (rUTI), have a significant epidemiological burden in the general population and may negatively affect patients quality of live. Moreover, they represent a therapeutic challenge and require management with both antibiotic-based and behavioural strategies (9). Gut is a well known reservoir of uropathogenic bacteria and therefore it has been regarded to as a possible source of rUTI. In recent years. In recent years, the concept of the 'gut-bladder axis', identified by the complex interactions between the gastrointestinal and genitourinary digestive systems, is increasingly emerging (10). This relationship is often expressed by the co-occurrence of LUTS and intestinal disease (11). Indeed, it is well known, that women who suffer from fecal incontinence also frequently suffer from urinary incontinence and that in patients with irritable bowel syndrome, urinary symptoms such as voiding frequency and urgency coexist (12). In this regard, we have recently evaluated the prevalence of LUTS in a large cohort of 301 patients with inflammatory bowel disease (IBD) through standardised questionnaires (*i.e.* Bristol female lower urinary tract symptoms (BFLUTS), NIH-chronic prostatitis symptom index (NIH-CPSI), and international prostate symptom score (IPSS)).

Our study demonstrated that women had an increased prevalence of LUTS as determined by BFLUTS total score, high age at diagnosis being a significant predictor of worse filling symptoms and a worse quality of life (13). Similarly, in men 67.1% had mild, 28.5% moderate, and 4.4% severe LUTS as assessed by IPSS with an overall NIH-CPSI prevalence of chronic prostatitis-like symptoms as high as 26.8% (13).

The pathophysiological link between diseases of the urogenital tract and intestinal tract is well explained by the concept of cross-organ sensitization which refers to the ability of a given organ to influence the homeostasis of an adjacent or distant organ by the transmission of noxious stimuli. In particular, the pathophysiology of a number of chronic urogenital conditions such as interstitial cystitis/bladder pain syndrome or chronic prostatitis/chronic pelvic pain syndrome has been attributed to a cross-organ sensitization between the genito-urinary tract and the gut (14). Pelvic cross-organ sensitization has also been demonstrated between experimentally-induced colitis and bladder overactivity and painful sensation in a murine experimental model (15). Indeed, in animal models of experimental colitis, increased neuronal activity with amplification of bladder sodium ion current in the intestinal microenvironment was demonstrated when urinary bladder distension occurred (15).

Intestinal microbiome and its ability to modulate intestinal permeability may represent a putative link between genito-urinay tract and gastrointestinal tract since these two microenvironments share a wide range of bacterial and fungal species (*e.g.*, *Firmicutes*, *Bacteroidetes*, *Proteobacteriae*, *Actinobacteria*) (10, 16-18). In particular, short chain fatty acids produced by gut bacteria, are capable of affecting gut permeability by strengthening tight junctions, stimulating mucus production and IgA synthesis (16). Short chain fatty acids, in particular acetic acid and propionic acid, have also been found in higher concentrations in the saliva of patients with gastro-esophageal reflux disease compared witth control subjects (19). Also, *E. coli*-derived indole stimulates the synthesis of proteins present in tight and adherence junctional complexes of intestinal epithelial cells (16). It has therefore been hypothesized that a quali-quantitative modification of gut microbiota may induce a leaky gut syndrome (*i.e.*, a syndrome associated to increased intestinal permeability) which may then favour the transmission of noxious agents, such as bacteria or bacterial products, to the genito-urinary tract (18). Other mechanisms of cross-organ - sensitization in the pelvis may also occur through shared sensory neural pahways at different prespinal, spinal and supraspinal levels (20), thus causing an impairment of sensory pathways of the bladder (17). Another mechanism underlying cross-organ sensitization may be represented by glutamate and glutamate receptors, as well as capsaicin and its receptor, TRPV1 (21). To support the relevance of intestinal microbiota in the occurrence of urinary-tract disorders, Worby *et al*. in a study conducted in women with and without rUTI, found that women with a history of rUTI had significantly decreased microbial richness and depleted butyrate-producing bacteria compared to controls (22). Interestingly in a recent study, Thanert *et al*. analyzed whole genome sequences of uropathogenic *E. coli* (UPEC) in the stool and urine of a large cohort of men and women and found 119 lineages of antibiotic-resistant UPEC. Some of these were found only in urine, some only in the stools some in both. Interestingly dual colonizers (*i.e*., present in both urine an stools) UPEC had higher genetic diversity due to the presence of genetic adaptations favouring successful establishment in both niches (23). Altogether, experimental and clinical evidence strengthen the concept of the role of the urinary-intestinal axis in a number of genito-urinary pathologic conditions with a direct impact of gut microbiota composition (18, 24).

HERICIUM ERINACEUS AND ITS BENEFICIAL EFFECTS IN THE GUT

Mounting evidence accumulated over the past decades strongly supports the concept that products isolated or purified by foods (in our case an edible mushroom) may exert a biologically activity with a physiological benefit and/or protection against chronic diseases (25). When these products are in a medicinal form such as a pill, a powder or a suppository, they are named nutraceuticals (*i.e.* naturally bioactive products which cover the gap between nutrition and pharmaceutical) (26). In other words a nutraceutical gives the opportunity to deliver, under a medicinal form, the biologically active component of a given food in a concentration higher than that you might deliver by simply eating that particular food. In this respect, *H. erinaceus*, also known in Japan as Yamabushitake and in China as Houtou, is an edible mushroom belonging to the class *Basidiomycota*, subclass *Holobasidiomycetidae*, order *Hericiales*, and family *Hericiaceae* (27). *H. erinaceus* has a number of bioactive metabolites and the main biologically active constituents are erinacines, steroids, alkaloids, and lactones such as vitamin B12-c-lactone (7, 8). Moreover, *H. erinaceus* contains numerous endopolysaccharides such as the β-glucans and chitin, in the fungal cell wall, which exert a marked anti-inflammatory and anti-cancer effect being also able to positively modify the gut microbiota (28). Wang *et al*. have demonstrated that *H. erinaceus*-derived polysaccharides inhibit the secretion of a number pro-inflammatory cytokines and promote the secretion of interleukin-10 (IL-10) thus favouring an anti-inflammatory cytokine pattern in an *in vitro* model consisting of a co-culture of cancer colon 2 (CaCo-2) cells and Caco-2/RAW264.7 cells under bacterial lipopolysaccharide stimulation (29). Because of its potent anti-inflammatory effects, *H. erinaceus* has been studied as a potential therapeutic agent in inflammatory conditions involving the gut, such as inflammatory bowel disease (*i.e* ulcerative colitis (UC) and Crohn's disease (CD)). Diling *et al*. (8) in a model of trinitrobenzene-sulfonic acid (TNBS)-induced colitis showed that treatment with mixed extracts of *H. erinaceus*

(polysaccharide, ethanol extracts, and cumulative fractions) for 14 days led to a significant clinical and histological improvement with a reduced neutrophil infiltration and a recovery of the pro-inflammatory/anti-inflammatory cytokine balance. This beneficial effect was also confirmed in a different experimental colitis model (*i.e*. dextran sulphate sodium-induced colitis) and, in this case, was associated to a significant anti-oxidant activity (30). More recently, in an *ex-vivo* model consisting of biopsy specimens obtained from the intestine of patients with IBD, we evaluated the anti-inflammatory potential of a nutraceutical compound consisting of *H. erinaceus*, berberine, and quercetin (*i.e*., HBQ-Complex®). Incubation for up to 180 minutes with HBQ-Complex® of biopsies obtained from inflamed intestinal areas resulted in a progressive decrease in the gene and protein expression of the proinflammatory cyclo-oxygenase-2 (COX-2) and tumor necrosis factor-alpha (TNF-α) compared to base-line, control values. On the other hand, the anti-inflammatory IL-10 showed an opposite trend, with a progressive increase of mRNA and protein expression compared with base-line values (31). The anti-inflammatory effect of *H. erinaceus* might be contributed to by its potent anti-oxidant effect (32).

Another mechanism whereby *H. erinaceus* extracts from fruiting bodies or mycelia may promote beneficial effects in the gut might be through the modulation of gut microbiota, which seems to play a crucial role in the development and progression of IBD, as well as in the treatment of several gastrointestinal pathological conditions, including IBD (33) Mounting evidence suggests that *H. erinaceus* extract is capable of favouring a healthy phenotype of the gut microbiota, both quantitatively and qualitatively by selecting certain beneficial bacterial strains at the expense of pathogenic strains (8, 34-36). Xie *et al*. (36) studied the effect of fourteen days administration of 1 g of *H. erinaceus* powder containing polysaccharides, peptides, crude fat, and trace elements in 13 healthy young volunteers and showed an increase in the alpha diversity of the gut microbiota with an increase in *Bifidobacterium* and *Bacteroides*, an increase in short-chain fatty acid (SCFAs) production, and a reduction in the relative abundance of pathogenic bacteria (*Streptococcus thermophilus*, *Roseburia intestinalis*, *Bacteroides caccae*, and *Anaerostipes hadrus*). SCFA-producing bacteria are known to be able to regulate lymphocyte chemotaxis and phagocytosis and to possess anti-inflammatory and anti-tumourigenic properties (37) and are associated with a reduced risk of IBD and IBD-associated dysbiosis (38) Also, Yang *et al*. (39) studied the impact of a polysaccharide from *H. erinaceus* on the quality of murine gut microbiota and found a change in the relative abundance of different bacteria depending on the age of the mice used for the microbiota analysis. In particular, they demonstrated an increase in the relative abundance of *Lachnospiraceae*, *Ruminococcaceae*, which, among other bacteria, are the most important butyrate-producing bacteria. Butyrate is an SCFA used as an energy source by the intestinal mucosa to promote gut health and protect against colorectal cancer (40-43). *Fig. 1* shows *H. erinaceus* contituents, their effects and putative mechanisms of action.

HERICIUM ERINACEUS AS A POTENTIAL THERAPEUTIC AGENT IN EXTRAINTESTINAL PATHOLOGIC CONDITIONS AND IN DISORDERS OF THE LOWER URINARY TRACT

H. erinaceus has shown beneficial effects in a number of clinical conditions, besides IBD, due to its anti-inflammatory and anti-tumorigenic effect. In particular, extracts from *H. erinaceus* have proven efficacy as anti-depressant agent and this is mainly due to the modulation of monoamine neurotransmitters as well as pro-inflammatory cytokines (44) and to stimulation of nerve growth factor release (45). *H. erinaceus* extract from mycelia has also been demonstrated to inhibit TNF-α-induced angiogenesis and generation of reactive oxygen species through the suppression of matrix metalloproteinase-9- and nuclear factor-κB signalling pathways (46). Moreover *H. erinaceus* up-regulated gene expressions of heme oxygenase-1 (HO-1), γ-glutamylcysteine synthetase (γ-GCLC), and glutathione levels,

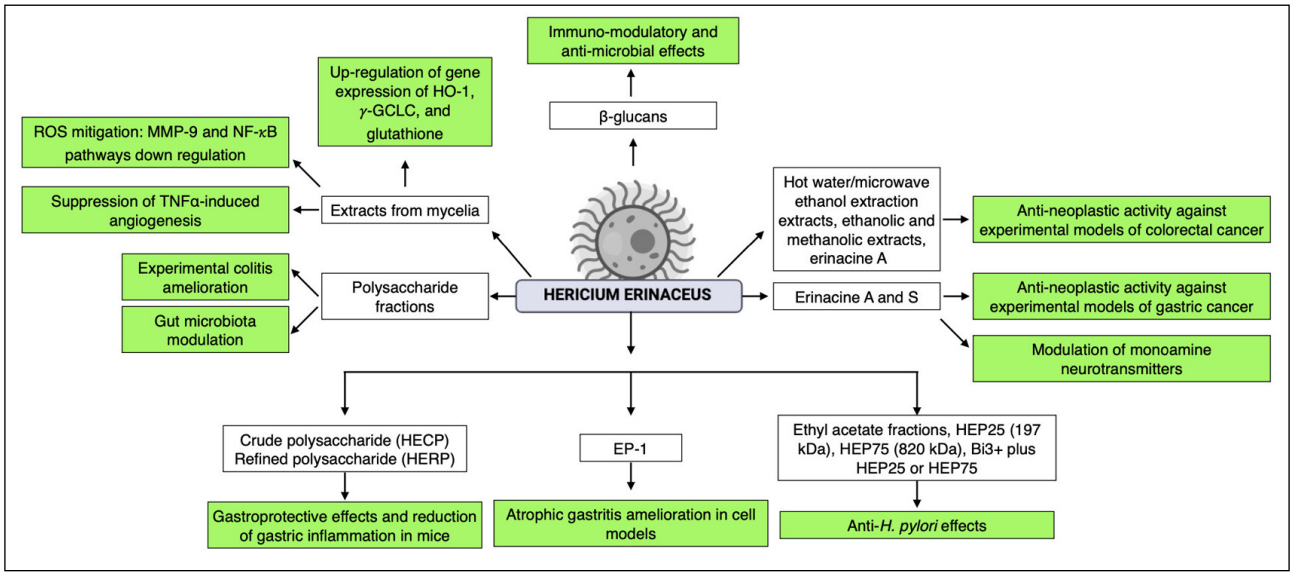

Fig. 1. *Hericium erinaceus* constituents, their effects, and putative mechanisms of action. HECP, *H. erinaceus* crude polysaccharide; HERP, *H. erinaceus* refined polysaccharide; EP-1, purified unique polysaccharide isolated from *H. erinaceus* mycelium 1; HEP25, purified polysaccharides from *H. erinaceus*, ethanol 25%; HEP75, purified polysaccharides from *H. erinaceus*, ethanol 75%; ROS, reactive oxygen species; MMP-9, matrix metalloproteinase-9; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; HO-1, heme oxygenase-1; γ-GCLC, gamma-glutamylcysteine synthetase.

Table 1. Summary of studies showing positive outcome of *Hericium erinaceus* in the intestinal tract.

Reference	Experimental Model	Outcome
Diling C., *et al*. (Ref. 8)	TNBS-induced colitis in rats	Clinical and histological improvement. Recovery of pro-inflammatory/anti-inflammatory cytokine balance. Prebiotic effect on intestinal microbiota. Improvement of host immunity
Wang D., *et al*. (Ref. 29)	CaCo-2 cells	Inhibition of pro-inflammatory cytokines and secretion of anti-inflammatory IL-10
Qin M., *et al*. (Ref. 30)	Dextran sulphate sodium-induced colitis in mice	Histological improvement associated to anti-oxidant activity
Gravina A.G., *et al*. (Ref. 31)	Ex-vivo experimental model with human intestinal biopsy specimens	Decreased expression of pro-inflammatory COX-2 and TNF-α and increase in anti-inflammatory IL-10 at the mRNA and protein levels
Ren Y., *et al*. (Ref. 32)	Experimental colitis in C57BL/6 mice	Decrease in colitis through regulation of oxidative stress, inflammation-related signaling pathways and modulation of the composition of the gut microbiota
Yang Y., *et al*. (Ref 34)	Simulated gastric and intestinal digests	Positive, qualitative and quantitative regulation of intestinal microbiota
Diling C., *et al*. (Ref. 35) Yang Y., *et al*. (Ref 39)	Mice	Immuno-modulatory effect and positive regulation of intestinal microbiota
Xie X.Q. *et al*. (Ref. 36)	Humans	Positive regulation of diversity and abundance of intestinal microbiota

thus contributing to inhibition of reactive oxygen species (ROS) (46). Also, *H. erinaceus* was found to exert chrondroprotective activities both in *in vitro* and *in vivo* models thus showing a potential in the treatment of osteo-arthritis conditions (47). Interestingly, Hetland *et al*. outlined the potential anti-infectious activity of *H. erinaceus* which showed antimicrobial activity against viral agents, Gram negative and Gram positive bacteria and parasites. Because this effect is not accounted for by an antibiotic-like effect but is rather due to its immunomodulatory capabilities, *H. erinaceus* should be effective also against multi-resistant agents (48). In this regard, *H. erinaceus* has proven effective against faecal Gram negative bacteria (49) and enterovirus 71 (50), which might be responsible of rUTI. The immunomodulation exerted by *H. erinaceus* is mainly due to the β-glucans which are the main constituent of the cell wall in fungi (28). Finally, erinacine A from *H. erinaceus* mycelia has proven to be neuroprotective against neurodegenerative diseases (51). *Table 1* summarizes the studies which show positive outcomes of *H. erinaceus* in the intestine.

Because of its anti-inflammatory and anti-oxidant effects, well documented in the gastrointestinal tract, due to its ability to positively affect the gut microbiota, because of its immunomodulatory action, and also due to its ability of modulating neurotransmission, we hypothesize that *H. erinaceus* extract might represent a novel therapeutic agent capable of ameliorating symptoms and or inflammation in the lower urinary tract, mainly in those cases arising from an altered gut microbiota, intestinal inflammation and/or increased intestinal permeability (52, 53). In partial support of this hypothesis we tested the efficacy of an *H. erinaceus*-derived nutraceutical (*i.e*. HBQ complex) in a small pilot study involving 20 patients suffering from chronic prostatitis. Int his proof-of concept pilot study, we found a significant decrease in the IPSS after 1 month of treatment, thus supporting the concept of a possible therapeutic role of *H. erinaceus* in the treatments of LUTS (M. Romano, unpublished observation). Should this be confirmed in a prospective study with a larger series of patients, one might envision the use of this nutraceutical, alone or in combination with conventional therapies or other nutraceuticals, such as those containing lycopene (54) to efficiently treat chronic prostatitis, which is a condition predisposing to prostate cancer (55). A schematic diagram on the putative targets of intervention of *H. erinaceus* in urogenital conditions linked to inflammation of the gut is presented in *Fig. 2*.

In this narrative review we have provided evidence that a pathophysiological link exists between the low urinary tract and the gastrointestinal tract. Cross-organ sensitization seems to play a major role and, in this respect, data from the literature suggest that an altered gut microbiota is crucial in driving increased gut inflammation and permeability which may favor the transmission of noxious stimuly/agents to pelvic organs. We have also shown that *H. erinaceus*, a chinese traditional medicinal mushroom, has proven efficacy in a number of clinical conditions, including those affecting the gastrointestinal tract. In details, it has been shown to exert anti-inflammatory, immunomodulatory, anti-oxidant and anti-angiogenetic effects also being able to positively modulate intestinal microbiota serving as a prebiotic. In a small pilot study preliminar to a prospective study in a larger cohort of

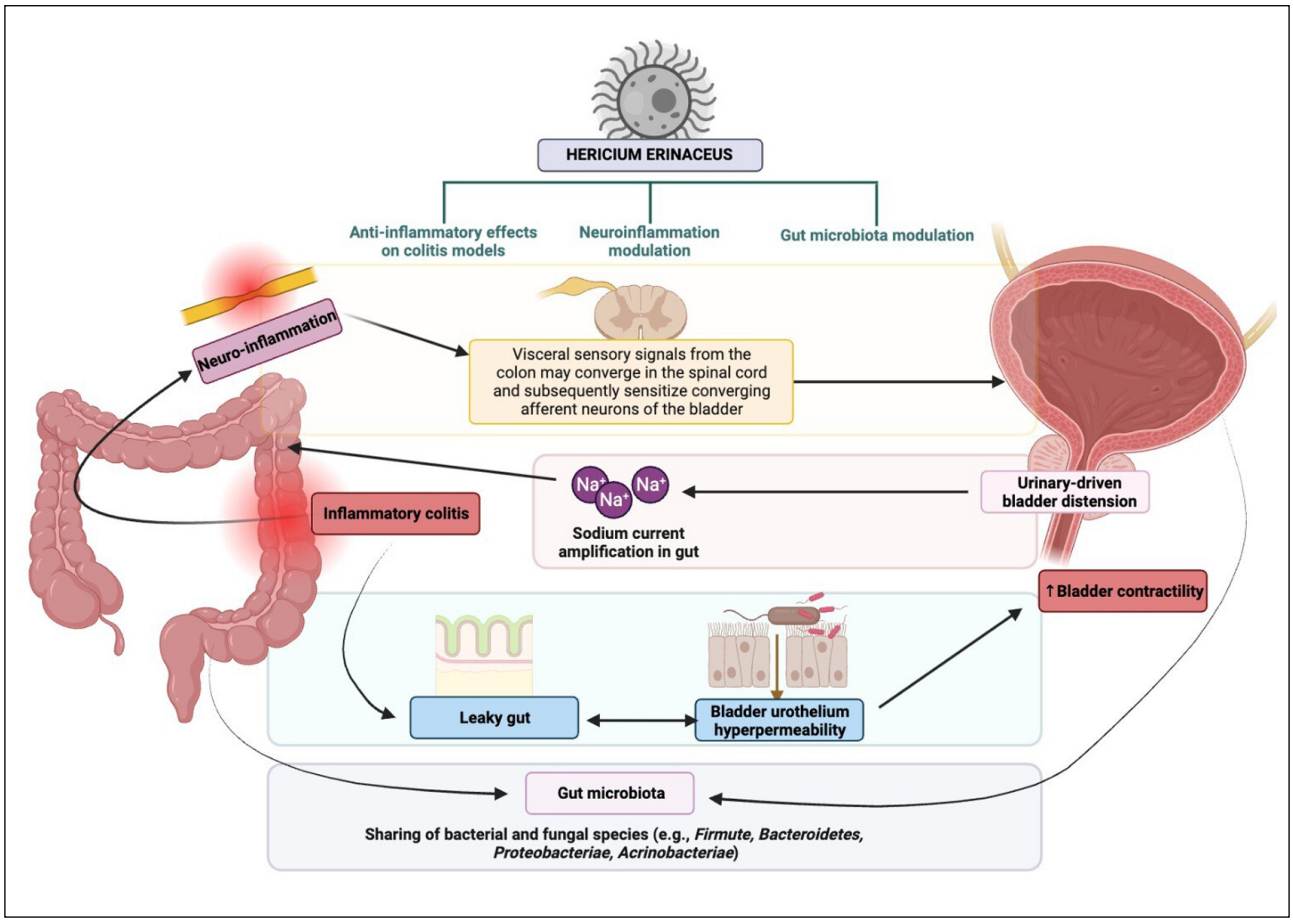

Fig. 2. Schematic representation of cross-organ sensitization between the colon and lower urinary tract and the mechanisms of potential beneficial effects of *Hericium erinaceus*. The colon and bladder interact with each other through several mechanisms that emerged during fundamental preclinical studies in mouse models. In detail, the central nervous system mediates the transmission of visceral sensory signals between these two organs. Inflammatory phenomena in one organ (*e.g.*, colitis) can affect the other organ and *vice versa*. This is the case, for example, of inflammatory colitis, which can result in afferent neuroinflammation, potentially affecting bladder function. In addition, the leaky gut syndrome can also indirectly result in hyperpermeability of the bladder urothelium and positively or negatively regulate bladder motility. In addition, through its motility, the bladder may increase the transmission of sodium currents into the colon and modulate its function. Finally, the colon and bladder share several bacterial species in their microbiota, which may be an additional point of contact between these two organs. *H. erinaceus* is a fungus with known anti-inflammatory, neuromodulatory and prebiotic properties and may, as a proof-of-concept, be a potential beneficial agent in such pathophysiological phenomena. This figure was created using the BioRender program (© 2023 BioRender).

patients, we have shown that an *H. erinaceus*-derived nutraceutical containing *H. erinaceus* polysaccharides was effective in ameliorating LUTS in subjects with chronic prostatitis. Based on these premises, we hypothesize that *H. erinaceus*-derived nutraceuticals, in combination with conventional drugs or other nutraceuticals, might be considered a putative therapeutic agent to be used in chronic inflammatory conditions of the low urinary tract to ameliorate inflammation, decrease symptoms and eventually prevent cancer.

Contribution information: two senior authors (L. Romano and l. Napolitano) selected the most relevant studies for design, sample size and level of evidence, according to their knowledge and experience. Other authors reviewed and approved the study selection.

Conflict of interests: None declared.

REFERENCES

1. Anderson DJ, Aucoin A, Toups CR, *et al*. Lower urinary tract symptoms in depression: a review. *Health Psychol Res* 2023; 11: 81040. doi: 10.52965/001c.81040
2. Romano L, Pellegrino R, Sciorio C, *et al*. Erectile and sexual dysfunction in male and female patients with celiac disease: a cross-sectional observational study. *Andrology* 2022; 10: 910-918.
3. Romano L, Gravina AG, Dajti E, *et al*. Sexual dysfunction in patients with gastroenterological disorders: do gastroenterologists care enough? A national survey from the Italian Society of Gastroenterology. *Dig Liver Dis* 2022; 54: 1194-1501.
4. Romano L, Granata L, Fusco F, *et al*. Sexual dysfunction in patients with chronic gastrointestinal and liver diseases: a neglected issue. *Sex Med Rev* 2022; 10: 620-631.

5. Xie G, Tang L, Xie Y, Xie L. Secondary metabolites from Hericium erinaceus and their anti-inflammatory activities. *Molecules* 2022; 27: 2157. doi: 10.3390/molecules27072157
6. Kim S. Biochemical characterization and cytotoxicity of polylactosamine-extended N-glycans binding isolectins from the mushroom Hericium erinaceus. *Int J Biol Macromol* 2023; 226: 1010-1020.
7. Friedman M. Chemistry, nutrition, and health-promoting properties of Hericium erinaceus (Lion's Mane) mushroom fruiting bodies and mycelia and their bioactive compounds. *J Agric Food Chem* 2015; 63: 7108-7123.
8. Diling C, Xin Y, Chaoqun Z, *et al*. Extracts from Hericium erinaceus relieve inflammatory bowel disease by regulating immunity and gut microbiota. *Oncotarget* 2017; 8: 85838-85857.
9. Hughes T, Juliebo-Jones P, Saada L, Saeed K, Somani BK. Recurrent urinary tract infections in adults: a practical guide. *Br J Hosp Med* (*Lond*) 2021; 82: 1-11. doi: 10.12968/hmed.2021.0337
10. Jung J, Kim A, Yang SH. The innovative approach in functional bladder disorders: the communication between bladder and brain-gut axis. *Int Neurourol J* 2023; 27: 15-22.
11. Malykhina AP, Wyndaele JJ, Andersson KE, De Wachter S, Dmochowski RR. Do the urinary bladder and large bowel interact, in sickness or in health? ICI-RS 2011. *Neurourol Urodyn* 2012; 31: 352-358.
12. Monga AK, Marrero JM, Stanton SL, Lemieux MC, Maxwell JD. Is there an irritable bladder in the irritable bowel syndrome? *Br J Obstet Gynaecol* 1997; 104: 1409-1412.
13. Romano L, Pellegrino R, Arcaniolo D, *et al*. Lower urinary tract symptoms in patients with inflammatory bowel diseases: a cross-sectional observational study. *Dig Liver Dis* 2023; Oct 23: S1590-8658(23)00998-2. doi: 10.1016/j.dld.2023.10.010
14. Qin C, Malykhina AP, Akbarali HI, Foreman RD. Cross-organ sensitization of lumbosacral spinal neurons receiving urinary bladder input in rats with inflamed colon. *Gastroenterology* 2005; 129: 1967-1978.
15. Yokishawa S,Kawamorita N, Oguchi T, *et al*. Pelvic organ cross-sensitization to enhance bladder and urethral pain behaviors in rats with experimental colitis. *Neuroscience* 2015; 284: 422-429.
16. Priadko K, Romano L, Olivieri S, *et al*. Intestinal microbiota, intestinal permeability and the urogenital tract: is there a pathophysiological link? *J Physiol Pharmacol* 2022: 73: 575-585.
17. Grundy L, Brierley SM. Cross-organ sensitization between the colon and bladder: to pee or not to pee? *Am J Physiol Gastrointest Liver Physiol* 2018; 314: G301-G308.
18. Salazar AM, Neugent ML, De Nisco NJ, Mysorekar IU. Gut-bladder axis enters the stage: Implication for recurrent urinary tract infections. *Cell Host Microbe* 2022; 30: 1066-1069.
19. Szczeklik K, Krzysciak W, Osiewicz M, *et al*. Short-chain fatty acids in the saliva of patients with gastroesophageal reflux disease. *J Physiol Pharmacol* 2022; 73: 521-530.
20. Malykhina AP. Neural mechanisms of perlvic organ cross-sensitization. *Neuroscience* 2007; 149: 660-672.
21. Brumovsky PR, Gebhart GS. Visceral organ cross-sensitization- an integrated perspective. *Auton Neurosci* 2010; 153: 106-115.
22. Worby CJ, Schreiber HL 4th, Straub TJ, *et al*. Longitudinal multi-omics analyses link gut microbiome dysbiosis with recurrent urinary tract infections in women. *Nat Microbiol* 2022; 7: 630-639.
23. Thanert R, Choi J, Reske KA, *et al*. Persisting uropathogenic Escherichia coli lineages show signatures of niche-specific within-host adaptation mediated by mobile genetic elements. *Cell Host Microbe* 2022; 30: 1034-1047.
24. Schembri MA, Nhu NTK, Phan MD. Gut-bladder axis in recurrent UTI. *Nat Microbiol* 2022; 7: 601-602.
25. Zaiac M, Muszynska B, Kala K, Sikora A, Opoka W. Popular species of edible mushrooms as a good source of zinc to be released to artificial digestive juices. *J Physiol Pharmacol* 2015; 66: 763-769.
26. Kalra EK. Nutraceutical - definition and introduction 2003. *AAPS PharmSci* 2003; 5(3): E25. doi: 10.1208/ps050325
27. Thongbai B, Rapior S, Hyde KD, Wittstein K, Stadler M. Hericium erinaceus, an amazing medicinal mushroom. *Mycol Progress* 2015; 14: 91. doi: 10.1007/s11557-015-1105-4
28. Jayachandran M, Chen J, Chung SSM, Xu B. A critical review on the impacts of β-glucans on gut microbiota and human health. *J Nutr Biochem* 2018; 61: 101-110.
29. Wang D, Xu D, Zhang Y, Zhao D, Wang M. A novel oligosaccharide isolated from Hericium erinaceus and its protection against LPS-induced Caco-2 cells via the TLR4/NF-κB pathway. *J Food Biochem* 2020; 44: e13135. doi: 10.1111/jfbc.13135
30. Qin M, Geng Y, Lu Z, *et al*. Anti-Inflammatory effects of ethanol extract of Lion's Mane medicinal mushroom, Hericium erinaceus (Agaricomycetes), in mice with ulcerative colitis. *Int J Med Mushrooms* 2016; 18: 227-234.
31. Gravina AG, Pellegrino R, Palladino G, *et al*. Hericium erinaceus, in combination with natural flavonoid/alkaloid and B_3/B_8 vitamins, can improve inflammatory burden in inflammatory bowel diseases tissue: an ex vivo study. *Front Immunol* 2023; 14: 1215329. doi: 10.3389/fimmu.2023.1215329
32. Ren Y, Geng Y, Du Y, *et al*. Polysaccharide of Hericium erinaceus attenuates colitis in C57BL/6 mice via regulation of oxidative stress, inflammation-related signaling pathways and modulating the composition of the gut microbiota. *J Nutr Biochem* 2018; 57: 67-76.
33. Hills RD Jr, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR. Gut microbiome: profound implications for diet and disease. *Nutrients* 2019; 11: 1613. doi: 10.3390/nu11071613
34. Yang Y, Zhao C, Diao M, *et al.* The prebiotic activity of simulated gastric and intestinal digesta of polysaccharides from the Hericium erinaceus. *Molecules* 2018; 23: 3158. doi: 10.3390/molecules23123158
35. Diling C, Chaoqun Z, Jian Y, *et al*. Immunomodulatory activities of a fungal protein extracted from Hericium erinaceus through regulating the gut microbiota. Front Immunol 2017; 8: 666. doi: 10.3389/fimmu.2017.00666
36. Xie XQ, Geng Y, Guan Q, *et al*. Influence of short-term consumption of Hericium erinaceus on serum biochemical markers and the changes of the gut microbiota: a pilot study. *Nutrients* 2021; 13: 1008. doi: 10.3390/nu13031008
37. Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. *Adv Immunol* 2014; 121: 91-119.
38. Sun M, Wu W, Liu Z, Cong Y. Microbiota metabolite short chain fatty acids, GPCR, and inflammatory bowel diseases. *J Gastroenterol* 2017; 52: 1-8. doi: 10.1007/s00535-016-1242-9
39. Yang Y, Ye H, Zhao C, *et al*. Value added immunoregulatory polysaccharides of Hericium erinaceus and their effect on the gut microbiota. *Carbohydr Polym* 2021; 262: 117668. doi: 10.1016/j.carbpol.2021.117668
40. Dmitrieva-Posocco O, Wong AC, Lundgren P, *et al*. β-Hydroxybutyrate suppresses colorectal cancer. *Nature* 2022; 605: 160-165.

41. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol* 2014; 12: 661-672.
42. Bultman SJ. Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer. *Mol Nutr Food Res* 2017; 61: 10.1002/mnfr.201500902. doi: 10.1002/mnfr.201500902
43. Louis P, Flint HJ. Formation of propionate and butyrate by the human colonic microbiota. *Environ Microbiol* 2017; 19: 29-41.
44. Chiu C-H, Chyau C-C, Chen C-C, *et al*. Erinacine A-enriched Hericium erinaceus mycelium produces antidepressant-like effects through modulating BDNF/PI3K/Akt/GSK-3-b signaling in mice. *J Mol Sci* 2018; 19: 341. doi:10.3390/ijms19020341.
45. Szucko-Kociuba I, Trzeciak-Ryczek A, Kupnicka P, Chlubek D. Neurotrophic and neuroprotective effects of Hericium erinaceus. *Int J Mol Sci* 2023; 24: 15960. doi: 10.3390/ijms242115960
46. Chang HC, Yang H-L, Pan J-H, *et al*. Hericium erinaceus inhibits TNF-α-induced angiogenesis and ROS generation through suppression of MMP-9/NF-κB signaling and activation of Nrf2-mediated antioxidant genes in human EA.hy926 endothelial cells. *Oxid Med Cell Longev* 2016; 2016: 8257238. doi: 10.1155/2016/825723847
47. Rahman MM, Kim HK, Kim SE, Kim MJ, Kim DH, Lee HS. Chondroprotective effects of a standardized extract (KBH-JP-040) from Kalopanax pictus, Hericium erinaceus, and Astragalus membranaceus in experimentally induced in vitro and in vivo osteoarthritis models. *Nutrients* 2018; 10: 356. doi:10.3390/nu10030356
48. Hetland G, Tangen J-M, Mahmood F, *et al*. Antitumor, anti-inflammatory and antiallergic effects of Agaricus blazei mushroom extract and the related medicinal Basidiomycetes mushrooms, Hericium erinaceus and Grifola frondosa: a review of preclinical and clinical studies *Nutrients* 2020; 12: 1339. doi:10.3390/nu12051339
49. Bernardshaw S, Hetland G, Grinde B, Johnson E. An extract of the mushroom Agaricus blazei Murill protects against lethal septicemia in a mouse model of faecal peritonitis. *Shock* 2006; 25: 420-425.
50. Zhao C, Gao L, Wang C, Liu B, Jin Y, Xing Z. Structural characterization and antiviral activity of a novel heteropolysaccharide isolated from Grifola frondosa against enterovirus 71. *Carbohydr Polym* 2016; 144: 382-389.
51. Lee SL, Hsu JY, Chen TC, Huang CC, Wu TY, Chin TY. Erinacine A prevents lipopolysaccharide-mediated glial cell activation to protect dopaminergic neurons against inflammatory factor-induced cell death in vitro and in vivo. *Int J Mol Sci* 2022; 23: 810. doi: 10.3390/ijms23020810
52. Romano L, Napolitano L, Crocetto F, *et al*. Prostate and gut: any relationship? A narrative review on the available evidence and putative mechanisms. *Prostate* 2024; Feb 14. doi: 10.1002/pros.24675
53. Holland B, Karr M, Delfino K, *et al*. The effect of the urinary and faecal microbiota on lower urinary tract symptoms measured by the International Prostate Symptom Score: analysis utilising next-generation sequencing. *BJU Int* 2020; 125: 905-910.
54. Moran NE, Thomas-Ahner JM, Lei Wan L, Zuniga KE, Erdman JW Jr, Clinton SK. Tomatoes, lycopene, and prostate cancer: what have we learned from experimental models? *J Nutr* 2022; 152: 1381-1403.
55. Jung G, Kim JK, Kim H, Lee J, Hong SK. The association between prostatitis and risk of prostate cancer: a national health insurance database study. *World J Urol* 2022; 40: 2781-2787.

Received: December 19, 2023
Accepted: February 29, 2024

Author for correspondence: Prof. Marco Romano, Department of Precision Medicine, University of Campania “L. Vanvitelli”, Naples, Italy.
E-mail: marco.romano@unicampania.it