

The use of *Hericium erinaceus* and *Trametes versicolor* extracts in supportive treatment in oncology

MATEUSZ WINDER*
WERONIKA BULSKA-BĘDKOWSKA
JERZY CHUDEK

Department of Internal Medicine and
Oncological Chemotherapy
Medical University of Silesia
Katowice 40-027, Poland

Substances available in nature with potential therapeutic effects are the subject of research that raises tremendous hopes for new challenges in medicine. Fungi are the most common organisms in the ecosystem and the most interesting in this respect. This review discusses two species of edible fungi, used for centuries in Eastern natural medicine, with the best-documented effect – *Hericium erinaceus* (He) and *Trametes versicolor* (Tv). The results of *in vivo* and *in vitro* studies conducted on mice and human cell lines demonstrate immunomodulatory, potentially, anticancer, anti-inflammatory and neuroregenerative effects of substances isolated from these fungi. The substances contained in the extracts of He and Tv seem to have immunomodulatory effects that may support chemotherapy. The use of these extracts is justified stronger than the other supportive treatments based on supplements.

Accepted March 24, 2020
Published online April 21, 2020

Keywords: *Hericium erinaceus*, *Trametes versicolor*, oncology, fungi, immunomodulation

INTRODUCTION

The healing properties of substances available in nature have been known for centuries. Medical practices using extracts and infusions from plants have been described in detail by various civilizations. Many of the medicines currently in use are of natural origin. These include acetylsalicylic acid, salicylate derivative obtained from willow bark (*Salix*, 1853), digoxin, an alkaloid of digitalis (*Digitalis lanata*, 1925), morphine, poppy alkaloid (*Papaver somniferum*, 1803) or the first anti-malarial drug – cinchona alkaloid quinine (*Cinchona*, 1820) (1, 2). One of the best-known natural medicines is penicillin. It was discovered by Ernest Duchesne, author of the work *Contribution to the Study of the Vital Competition in Microorganisms: Antagonism Between Moulds and Microbes* (1897), and then isolated from fungus mold *Penicillium notatum* in 1929 by the later Nobel laureate Alexander Fleming (1). We also remind on the discovery of other antibiotics, e.g. vancomycin (*Amycolaptosis orientalis*, 1955) and erythromycin (*Saccharopolyspora erythraea*, 1952) from fungi (1). The research on modern antibacterial drugs produced by fungi, including cetromycin, is being continued. In oncology, derivatives of camptothecin alkaloid from the *Camptotheca acuminata* tree

* Correspondence, e-mail: mwinder@sum.edu.pl

(topotecan and irinotecan) and amrubicin – generation 3 anthracycline derived from the *Streptomyces peucetius* are used (1, 3).

It is estimated that less than 10 % of the world's biodiversity has been assessed for potential biological activity so far. This means that many potentially useful natural medicines are still waiting to be discovered (4). At the same time, numerous dietary supplements based on natural products containing substances with unproven or unconfirmed biological properties are available on the market. Their use during anticancer treatment, without doctors' knowledge, may cause drug interactions and life-threatening complications.

This review article discusses two species, among many edible fungi, with the most documented immunomodulatory effect – *Hericium erinaceus* (He) and *Trametes versicolor* (Tv).

HERICIUM ERINACEUS

Hericium erinaceus (He) of Herinaceae family is a widespread, edible fungus popular in Asian countries, such as China (*houtou*, *monkey head mushroom*), Korea or Japan (*yama-bushitake*). It is traditionally used to treat peptic ulcers and acute gastritis. Its extracts are attributed to antineoplastic, neuroregenerative, cardio-, hepato- and nephroprotective effects, as well as improvement in glycemic and lipid profile control (5, 6).

As in the case of some other species of fungi, He extract has an antibacterial effect. It was demonstrated in an *in vitro* study of human gastric cells and *in vivo* research in mice infected with *Helicobacter pylori* (7). As a result of using an alcohol extract (2 mg mL⁻¹) in the *in vitro* study, a shortened *Helicobacter pylori* survival in phosphate-buffered saline (PBS), in the absence of effects on *Escherichia coli*, and a decreased bacterial ability to adhere to gastric cells was demonstrated. In addition, a reduction in the *H. pylori* bacterial count was observed in the mouse organisms in the *in vivo* study.

He extract (in mice) exerted a protective effect on the chemically damaged mucous membrane of the stomach and intestines. The study showed that it prevented further damage to the mucosa and promoted its regeneration by regulating the activity of neutrophils and lymphocytes, inhibiting the production of inflammatory mediators, such as TNF alpha, interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and releasing substances that reduce oxidative stress (NO, malondialdehyde, peroxide dismutase) (8, 9).

Several biologically active ingredients have been detected in the He extract, including hericerones (meroterpenoids) obtained from the fruiting body (hericerin, hericerin A, hericenone J, isohericenone J, isoericerine, *N*-De-phenylethyl-isohericerin and 4-(3',7'-dimethyl-2',6'-octadienyl)-2-formyl-3-hydroxy-5-methoxybenzylalcohol), erinacines (cyathane diterpenoids) from the mycelium (erinacin A to K and P to S), He polysaccharide (HEP) and lectins (10). Fig. 1a gives the chemical structures of the components.

The effect of hericerin and hericerin A was investigated on human blast cells of acute promyelocytic leukaemia (HL60). Both substances inhibited the proliferation of leukemic cells and induced their apoptosis (10). Similar results were obtained by the authors of the study comparing the effect of various solutions obtained from the powdered fruit body of He on human leukemic cells MOLT-4 and U-937. Hot water extract (HWE) and microwave-assisted 50 % ethanol extract (MWE) from powdered He fruit body in concentrations of 500 mg mL⁻¹ suppressed the growth of leukemic cells by inducing the apoptosis without affecting the normal human fibroblasts (HGF-1). The cytotoxic activity of HWE and MWE

extract was compared with the effect of a solution containing RNase and propidium iodide (according to the performance-based standards, PBS) and it resulted in 47 and 44 % decrease, resp. (11). In the same study, the authors compared the effect of the He extracts on the decrease of the mitochondrial membrane potential of human leukemic U-937 cells associated with the cytochrome c release. As in the previous observations, HWE and MWE extracts showed higher efficiency in decreasing the mitochondrial membrane potential in U-937 cells of 62.3 and 59.8 %, resp., as compared to the effect of etoposide used as a control.

The purified polysaccharide, named EP-1, extracted from He showed a selective pro-apoptotic effect on human stomach pre-cancerous cells (MC), without damaging healthy cells (GES-1) (12). A more accurate study using HEG-5 polysaccharide performed on human stomach cancer cells (SGC-7901) proved the dose-dependent inhibitory effect of this substance on the cancer cell proliferation, which reached 93.4 % at a concentration of 200 $\mu\text{g mL}^{-1}$ after 48 hours of incubation (13).

The results of the studies on the effect of He agglutinin (HEA) presented by Li *et al.* (14) show its inhibitory effect not only on human hepatocellular carcinoma and breast cancer cells but also on HIV-1 reverse transcriptase.

The apoptosis of tumour cells is dependent on the induction of nitric oxide (NO) production in macrophages and the activation of mitochondrial caspases (caspase 9 and caspase 3) (11). Additionally, the extracts from He increased the concentrations of pro-apoptotic proteins (p53, Bax, Bad, Bid) and at the same time reduced the concentrations of anti-apoptotic proteins (Bcl-2, PI3K, CDK4, Akt).

A summary of the results on cell lines studies is presented in Table I.

Anticancer effects of M8 extract from 8 species of fungi including He, were tested in mice with intravenously administered adenocarcinoma cells colon 26-L5, showing a significant dose-dependent (50–200 mg kg^{-1} daily) inhibition of the tumour cell dissemination to the lungs (15). Cytometric analysis of the blood of the tested mice showed a dose-dependent increase of CD3, CD19, CD4 and CD8 cells, without affecting NK1.1 and Mac-1 cell numbers. Increased production of IFN- γ and IL-4 by splenocytes was also found in the treated mice compared to the control group.

It is suggested that the immune effect of the He polysaccharide (HEP) is associated with the activation of mitogen-activated protein kinases (MAPK) – ERK, JNK, p38, AKT (16). As a result, it strengthens the innate and acquired immune response by increasing the activity of NK cells and macrophages and increasing the production of lymphocytes in the spleen. In addition, the mice receiving HEP also had increased levels of intestinal IgA.

Apart from the potential anticancer properties, the most widely commented effect of the He extracts is the effect on the nervous system. There are reports of neuroprotective and neuroregenerative effects of erinacins contained in the He. Erianacin A administered to mice at a dose of 19 mg g^{-1} resulted in an increased proliferation of neural progenitor cells and the number of new neurons around the dentate gyrus and stimulation of nerve growth factor (NGF), blocking the kappa opioid receptor, reducing β -amyloid deposition and increasing expression of the insulin-degrading enzyme (IDE) (17).

It has been shown that oral supplementation of He extracts improved cognitive processes in mice and improved their locomotor functions (18). A detailed analysis of biochemical processes allowed to specify the suppressing effect of the He extracts on the activity of ATP-dependent calcium conductance in rat PC12 neuron-differentiation cells and

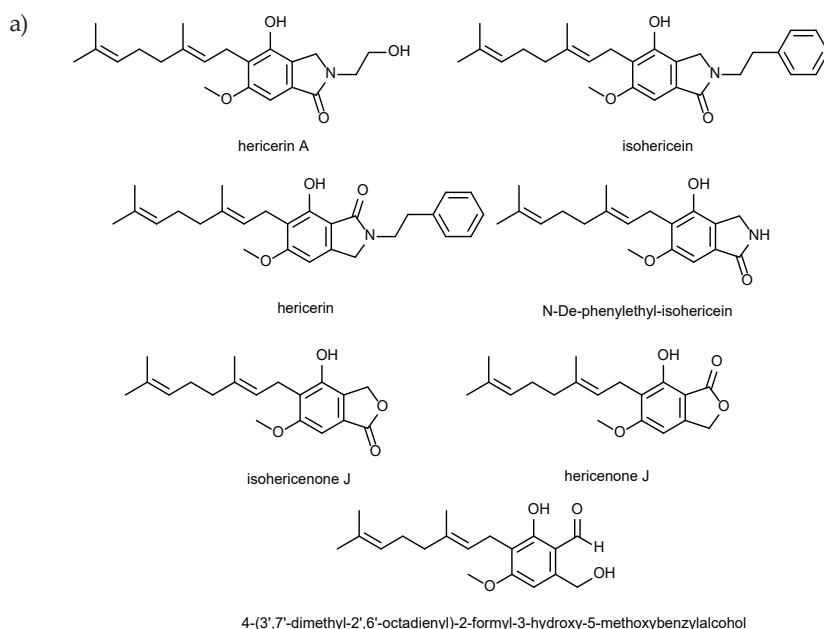
Table 1. The activity of *Herichium erinaceus* components in in vitro studies

<i>Herichium erinaceus</i> component	Cancer cell line Control cell line	IC_{50}	Units	Reference
Hericerin A	HL-60	3.06 ± 0.56	$\mu\text{mol L}^{-1}$	10
	HEL-299	64.61 ± 3.82	$\mu\text{mol L}^{-1}$	
Isohericerin	HL-60	59.74 ± 0.19	$\mu\text{mol L}^{-1}$	10
	HEL-299	–		
Hericerin	HL-60	5.47 ± 0.32	$\mu\text{mol L}^{-1}$	10
	HEL-299	> 100	$\mu\text{mol L}^{-1}$	
N-De phenylethyl isohericerin	HL-60	62.24 ± 0.70	$\mu\text{mol L}^{-1}$	10
	HEL-299	–		
Isohericenon J	HL-60	4.10 ± 0.21	$\mu\text{mol L}^{-1}$	10
	HEL-299	5.79 ± 0.60	$\mu\text{mol L}^{-1}$	
Hericenon J	HL-60	4.13 ± 0.20	$\mu\text{mol L}^{-1}$	10
	HEL-299	5.07 ± 0.60	$\mu\text{mol L}^{-1}$	
4-(3',7'-Dimethyl-2',6'-octa- dienyl)-2-formyl-3-hydroxy- 5-methoxy-benzyl alcohol	HL-60	4.28 ± 0.19	$\mu\text{mol L}^{-1}$	10
	HEL-299	8.46 ± 0.61	$\mu\text{mol L}^{-1}$	
Polysaccharide EP-1	MC	Induction of apoptosis		12
	GES-1	No effect		
Lectin HEA	HepG2	56.1	$\mu\text{mol L}^{-1}$	14
Lectin HEA	MCF7	76.5	$\mu\text{mol L}^{-1}$	14
Lectin HEA	Inhibition of HIV-1 reverse transcriptase	31.7	$\mu\text{mol L}^{-1}$	14
HWE	U-937	67.9 ± 1.4	%	11
	MOLT-4	47.1 ± 4.8		
	HGF-1	5.8 ± 1.6	%	
MWE	U-937	69.6 ± 1.3	%	11
	MOLT-4	44.2 ± 0.8		
	HGF-1	4.5 ± 2.2	%	
HEG-5	SGC-7901	107.4 (24 h)	$\mu\text{g mL}^{-1}$	13
		46.7 (48 h)		

GES-1 – human stomach cells, HEA – *Herichium erinaceus* agglutinin, HEG-5 – polysaccharide-protein, HEL-299 – human embryonic lung cells, HepG2 – human hepatocellular carcinoma cells, HGF-1 – human fibroblasts, HL-60 – human leukemia line, HWE – hot water eluate, IC_{50} – half maximal inhibitory concentration, MC – human pre-cancerous stomach cells, MCF7 – human breast cancer cells, MWE – microwave water-ethanol eluate, MOLT-4 and U-937 – human leukemia cells, SGC-7901 – human stomach cancer cells

human HOS cells. The effect of this action is to slow down the conduction of stimuli dependent on P2R purinoreceptors which, in the animal model, resulted in the weakening of the sensation of pain stimuli caused by the heat (19). Zhang *et al.* (20) isolated eleven compounds from the fruiting bodies of He including one previously unknown – hericin K, and analysed their neurotrophic activity *in vitro*. The rest of the compounds were ergosterol peroxide, cerevisterol, $3\beta,5\alpha,9\alpha$ -trihydroxy-ergosta-7,22-dien-6-one, inoterpene A, astradoric acid C, betulin, oleanolic acid, ursolic acid, hemisceramide, 3,4-dihydro-5-methoxy-2-methyl-2-(40-methyl-20-oxo-30-pentenyl)-9(7*H*)-oxo-2*H*-furo[3,4-*H*]benzopyran. The identification of these compounds was achieved by purification of ethyl acetate soluble portion of an ethanol extract of dried fruiting bodies of He. PC12 cells were incubated with each of the latter compounds in non-toxic concentrations of 10 and 20 $\mu\text{mol L}^{-1}$, in the presence and the absence of NGF (20 ng mL^{-1}) as a control. The data showed that 3,4-dihydro-5-methoxy-2-methyl-2-(40-methyl-20-oxo-30-pentenyl)-9(7*H*)-oxo-2*H*-furo[3,4-*H*]benzopyran exhibited high neurite outgrowth-promoting activity in NGF-induced PC12 cell, while ergosterol peroxide, cerevisterol and $3\beta,5\alpha,9\alpha$ -trihydroxy-ergosta-7,22-dien-6-one had weak neuroactive activity. Fig. 1b shows the structures of isolated compounds.

Studies conducted among people aged 50–80 years with mild cognitive impairment showed that the use of orally administered powdered He fruit body at a dose of 250 mg 3× per day improved their cognitive function compared to the placebo group, and this effect persisted for 4 weeks after discontinuation of the tested supplement (21). In another study, a reduction in the severity of depression and anxiety was observed in women after 4 weeks of taking 500 mg of the powdered He fruiting body 4× per day compared to the placebo group (22). Both quoted experiments involving humans were double-blind, and the groups



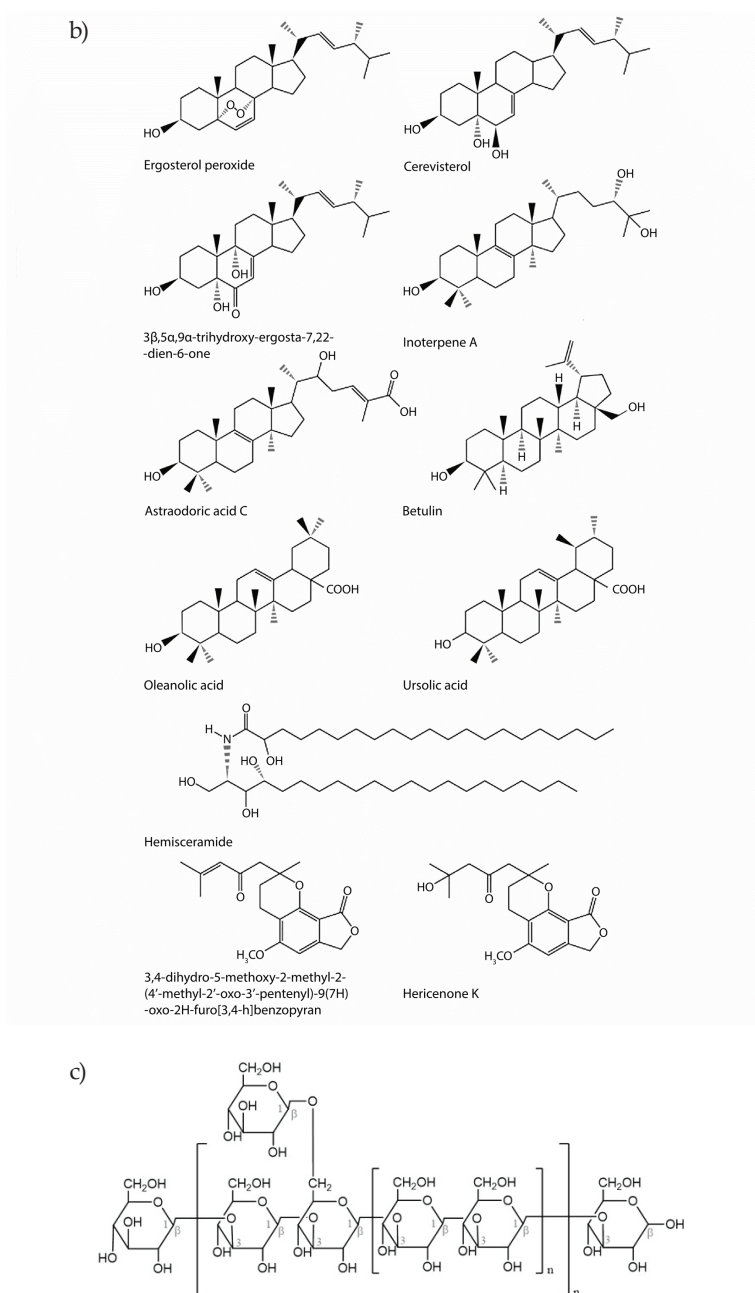


Fig. 1. Chemical structures of *Herichium erinaceus* and *Trametes versicolor* components: a) identified in the MeOH extract of He fruiting body (10), b) identified in the ethanol extract of He fruiting body (20), c) β -glucan (15, 35, 54).

of women in the second experiment were randomized. However, it should be noted that the above-mentioned studies were carried out on small groups of 30 people in both cases. A summary of the results of study performed *in vivo* is presented in Table II.

A toxicological analysis indicated that even large doses of He extracts do not cause side-effects in rats. Doses of He mycelium enriched with erinacine A administered orally in the mentioned studies were 3–5 g kg⁻¹ (17). A teratogenic effect of a 2625 mg kg⁻¹ dose in rats was excluded. Furthermore, the mutagenic effect of He extract was not demonstrated on bacterial cells in the Ames test (5 mg), *in vitro* in the chromosomal aberration test (2.5 mg mL⁻¹) and *in vivo* in the micronucleus test in erythrocytes (5 mg kg⁻¹). The mitogenic effect of He lectins on lymphocytes was also excluded (14). The few studies that described the use of He extracts in humans have also proven the absence of adverse effects and proved their good tolerance (21, 22).

The conclusions from these observations as well as the lack of reports on adverse effects suggest possible benefits of using He in the treatment of chronic pain caused by cancer as well as complications of chemotherapy such as peripheral polyneuropathy. In order to confirm the described properties of He, it is necessary to conduct randomized studies on large cohorts of patients receiving chemotherapy and to exclude possible drug interactions that could adversely affect the results of evidence-based medicine (EBM) therapy. Due to immunomodulatory effects, He extracts should not be used in allograft recipients, because of the potential risk of rejection and the development of graft-*versus*-host disease (GvHD).

TRAMETES VERSICOLOR

Trametes versicolor (Tv, also known as *Coriolus versicolor*, *Polyporus versicolor*, *yun-Zhi*, *kawaratake*, *Turkey tail mushroom*) is a species of fungus (Polyporaceae family) used in Asian medicine for thousands of years, but the immunomodulatory activity of Tv was first discovered in 1965 in Japan (23, 24). Tv contains two proteoglycan fractions with anticancer properties: K – krestin polysaccharide (PSK) and polysaccharidopeptides (PSP). In Japan, PSK is routinely used in oncology in patients during and after treatment. PSK was approved as an anticancer drug by the Japanese National Health Registry in 1977 (in China in 1987) (24). Gastric cancer was the first cancer in which PSK was used in adjuvant therapy (25). It is worth noting that the results of the treatment of stomach cancer in Asian countries are more satisfying than in Western countries. In the meta-analysis of patients with colorectal cancer, it was shown that the addition of PSK to adjuvant therapy improved overall survival (OS) and disease-free survival (DFS) (26). Recent studies have raised the role of Tv in supportive therapy of breast cancer (24). In the studies on the Asian population, an increase in 5-year survival was observed in patients with recurrent breast cancer after adding of PSK to standard oncological treatment (27). Moreover, the prognosis in patients with early breast cancer with pathological features of angioinvasion has been improved (28). During the three decades of Asian studies, the components of Tv were used as supportive therapy in cancers of the stomach, oesophagus, nasopharynx, colon, rectum and lung (29). With the development of immunomodulatory therapy, interest in PSK and PSP appeared in the last decade also in Western countries.

The immunological activity of the components of Tv extracts is the result of enhanced innate and acquired immune response through agonistic effects on TLR (toll-like receptor),

especially TLR2 and TLR4 (30–33). TLR are membrane proteins of immune cells (dendritic cells, macrophages), which are the first to react with antigens, triggering the release of pro-inflammatory cytokines and subsequent activation of T and B lymphocytes.

PSP and PSK contain the common, most biologically active component – β -glucan (34). TLR2 and TLR4 are immune receptors for β -glucans (32, 35). Thus, β -glucans activate a series of immune cells, such as monocytes, macrophages, NK cells, dendritic cells. Additionally, the results of breast cancer research suggest the effect of β -glucan obtained from a Tv on a potential increase in the anticancer activity of lymphocytes by reacting with the complement iC3b receptor (36). Monoclonal antibodies, such as trastuzumab combined with β -glucan have been shown to induce a greater regression of breast tumours in the mouse model compared to trastuzumab alone (24). It is also suggested that other monoclonal antibodies known to activate complements, such as cetuximab or rituximab, would be more effective if combined with the β -glucan polysaccharide (37–39) (see Fig. 1c).

PSK induces the production of many cytokines, including TNF- α , IL-2, IL-6, IL-8, IL-12 (40–42). The increase in IL-8 and IL-12 concentration after PSK induction confirms the effect on lymphocytes, monocytes and macrophages circulating in the peripheral blood, most probably as a result of increased expression of IL-8 genes in mononuclear cells and IL-12 in monocytes and macrophages (24, 42). The immunomodulatory effect of PSK is associated with the IL-12-dependent increase in the CD4 + Th1 cell response to tumour cells (43). Maintaining the advantage of Th1 responses to Th2 is perceived as beneficial in cancer therapy.

PSK also stimulates T $\gamma\delta$ lymphocytes, which are a small but significant population of T lymphocytes in the anti-tumour immune response. In *in vitro* studies, PSK increased the expression of CD25, CD69, CD107a and activation of T $\gamma\delta$ lymphocytes in tumour-infiltrating lymphocytes (TILs), the higher percentage of which is associated with a better prognosis for survival (44). Additionally, in response to PSK stimulation, T $\gamma\delta$ lymphocytes produce significant amounts of IFN- γ , which plays an important role in the anti-tumour response. The presence of activated T $\gamma\delta$ lymphocytes in both a direct and indirect way also affects the population of DC cells, which, in turn, enhance the response of T and NK cells by reinforcing the production of IL-12 (44).

Furthermore, PSK is believed to stimulate NK cells and increase antibody-dependent cell cytotoxicity (ADCC), a leading mechanism in the control of cancer cells through TLR-2 agonistic effects (30). Torkelson *et al.* (45) showed a relationship between an increase in the dose of Tv extract and an increase in the activity of NK cells, lymphocytes and the number of T cells (CD8 +) and B (CD19 +), without changes in NK cell numbers.

PSP, due to the structure similar to that of PSK, shows similar immunological activity. It stimulates the expression of TLR4 and TRAF6, and induces the synthesis of cytokines such as IL-1 β , IL-6, TNF- α (33, 35). Sekhon *et al.* (46) observed an increase in the number of monocytes (CD14+/CD16-) under the influence of PSP in the absence of a direct effect on the proliferation of T, B and NK lymphocytes.

Both PSP and PSK will antagonize the decrease in cell counts and their immunological activity, contributing to the reduction of adverse effects associated with cancer treatment. This hypothesis was confirmed by studies conducted in animals and humans. Weneer *et al.* (47) observed a smaller decrease in leukocytes in mice after attaching PSK to docetaxel. Hu *et al.* (48) showed that adding PSP to chemotherapy based on cyclophosphamide

Table II. The activity of *Herichium erinaceus* in vivo studies

Studied He extract	Main component disclosed	Extract (main component) concentration	Study focus	Group size	Dominant effect	Reference
Ethanol extract	N/A	2 mg mL ⁻¹ (N/A)	Human stomach cells infected with <i>H. pylori</i>	–	Shortening the bacterial survival, decrease in adherence of bacteria to stomach cells	7
Ethanol extract	N/A	2 mg mL ⁻¹ (N/A)	Mice infected with <i>H. pylori</i>	–	A decrease in the number of bacteria	7
Ethanol extract	N/A	250 mg kg ⁻¹ daily 500 mg kg ⁻¹ daily (N/A)	Mice with chemically damaged intestine mucous membrane	–	Prevention of mucosal damage and improvement of regeneration	8
Ethanol extract from dried mycelium	Erinacin A	300 mg kg ⁻¹ daily (19 mg g ⁻¹)	APP ^{swe} /PS1ΔE9 mice	–	Increasing the proliferation of neuron progenitor cells and the number of new neurons in the dentate gyrus, decreasing β-amyloid deposition, increasing IDE and NGF expression	17
Hot water M8 extract	β-glucan, 1,3-β-D-glucan	50–200 mg kg ⁻¹ daily (N/A)	Mice injected with adenocarcinoma cells colon 26-L5	–	Inhibiting the spread of tumour cells to the lungs	15
Powdered dry fruiting body	N/A	3 × 250 mg daily (N/A)	People with mild cognitive impairment	30	Improvement of cognitive functions	21
Powdered dry fruiting body	N/A	4 × 500 mg daily (N/A)	Women with affective disorders	30	Reducing the feeling of depression and anxiety	22

IDE – insulin-degrading enzyme, NA – not applicable, NGF – nerve growth factors

Table III. Studies on the cytotoxic activity of *Trametes versicolor* extracts on tumour cell lines

<i>Trametes versicolor</i> extract	Identified component	Tumor cell line	IC ₅₀ (mg mL ⁻¹)	Reference
Fruiting body ethanol extract	N/A	HeLa	168.5 ± 28.9	51
		LS174	> 200	
		A549	> 200	
Mycelium ethanol extract	N/A	HeLa	42.4 ± 0.7	51
		LS174	86.1 ± 12.3	
		A549	65.6 ± 7.7	
Fruiting body ethanol-water extract	Polysaccharides and triterpenoids (30 %)	Raji	253.8 ± 60.7	43
		NB-4	269.3 ± 12.4	
		HL-60	147.3 ± 15.2	
Fruiting body ethanol extract	N/A	MCF-7	134.3 ± 4.3	52
		HepG2	123.5 ± 3.7	
Fruiting body ethanol-water extract	Polysaccharides and triterpenoids (30 %)	MCF-7	271.7 ± 20.5	53
		BT-20	> 800	
		MDA-MB-231	514.0 ± 42.0	
Fruiting body water extract	α-glucans (8.7 %) β-glucans (65.6 %)	T47-D	233.3 ± 21.9	54
		LoVo	224	

IC₅₀ – half-maximal inhibitory concentration, N/A – not applicable

reduced some of the side-effects of CTX, whereas Xu *et al.* (49) observed a lower rate of bone marrow suppression in patients receiving oxaliplatin-based chemotherapy after using PSP. The minimization of the frequency of side-effects of oncological therapies contributes to better overall survival by maintaining the rhythm of chemotherapy and improves the quality of life of oncological patients. Recent data suggest that Tv extract may also improve immune status in patients during radiotherapy, which causes specific immunodeficiency disorders, including lymphopenia and low NK cell activity (45). Randomized studies have demonstrated the benefits of using PSK not only related to the improvement in immune status, but also fitness status, stable body mass or reduction of symptoms associated with cancer, such as fatigue and malnutrition (50).

Apart from immunomodulatory activity, the antitumor activity of both components of the Tv was also observed. In recent experimental studies, the simultaneous use of PSK with docetaxel was associated with a greater regression of prostate cancer in the mouse model, including increased inhibition of tumour cell proliferation and intensification of their apoptosis in comparison with the use of taxanes alone (47).

In vitro studies have demonstrated the inhibitory effect of Tv extract on the proliferation of HeLa tumor cell lines (cervical cancer), LS174 (colorectal cancer), A549 (lung cancer) (51), Raji (Burkitt's lymphoma), NB-4 and HL-60 (acute promyelocytic leukemia) (43), MCF-7,

MDA-MB-231, T47-D (breast cancer) (52, 53), HepG-2 (hepatocarcinoma) (52) and LoVo (colorectal cancer) (54) (Table III). Several studies have shown that the cytotoxic effect was dose-dependent and selective only for cancer cells. However, no cytotoxic activity of Tv extract was observed against the normal cell lines – IEC-6, Vero, WRL (23, 43) and tumour cell lines BT-20 (breast cancer) (53) and JCA-1 (prostate cancer) (55). Interestingly, both tumour cell lines BT-20 and JCA-1 are hormone-dependent. The hypothesis of the importance of the hormonal status may be confirmed by studies on the inhibitory effect of Tv on the androgen-sensitive prostate cancer cell line LNCaP (55).

It is suggested that high doses of the extract of Tv fruiting bodies could achieve comparable cytotoxic efficacy as commonly used oncological drugs, with a lesser impact on healthy cells. Lau *et al.* (43) observed a comparable cytotoxic effect with more than 90 % growth suppression of the acute promyelocytic leukaemia cell lines (HL60, NB-4) and Burkitt's lymphoma B cell line (Raji) using mitomycin C at a dose of 20 $\mu\text{g mL}^{-1}$ and extract of Tv fruiting bodies at doses exceeding 3.5–4 fold the IC_{50} value for HL60, NB-4, Raji cells. In their study, cell death ELISA was used for the detection of cell death based on which half-maximal inhibitory concentration (IC_{50}) for Tv extract was determined. These results confirm that Tv extract dose-dependently inhibits the proliferation of lymphoma and leukemic cells possibly *via* an apoptosis-dependent pathway. However, recent studies have shown that mycelium extract shows a much stronger cytostatic effect than the extract obtained from Tv fruiting bodies (basidiocarps) (51).

Due to the fact that PSP and PSK are obtained from the mycelium of Tv, it is expected that Tv proteoglycans may also be responsible for antitumor activity related to the cytotoxic activity. Hirahara *et al.* (56) showed that isolated PSK effectively inhibited the proliferation of HL60 (leukaemia) cell lines, and, to a lesser extent, HT29, SW480 (colorectal cancer); however, increase in the dose did not enhance the cytotoxic effect, unlike in the study on the extract from Tv fruiting bodies or mycelium. In turn, Hattori *et al.* (57) did not observe any PSK effect on the HL-60 cell line, not even at a dose exceeding 30 times the dose used in the previous study. The discrepancies in the results may be due to the differences in experimental conditions. Moreover, the results of the above studies may suggest the presence of another unknown substance in the Tv mycelium with a dose-dependent cytostatic effect.

We do not know the molecular mechanisms of Tv activity well enough to determine whether the visible antitumor effect is mainly associated with a direct cytotoxic activity or immunomodulatory properties of Tv extract. A direct comparison of the results of experimental studies is difficult due to differences in the methodology. Previous studies have suggested that the antitumor effect may be dependent on the modulation of the major histocompatibility complex (MHC) and the inhibition of the nuclear factor-kappa ($\text{NF-}\kappa\text{B}$) (58–60). Heish *et al.* (55) suggested that the anti-proliferative activity of Tv extract is based on the arrest of the cell cycle in the G1/S phase. In turn, Jiménez-Medina *et al.* (61) demonstrated the suppression of the tumour cell proliferation in the G0/G1 phase. Hirahara *et al.* (56) suggested that the activation of caspase 3 by PSK may be partially responsible for antitumor activity against leukemic cells. These mechanisms might be synergistic and probably different depending on the type of cancer.

Because of the existing discrepancies, the mechanisms of cytotoxic activity of the extracts obtained from Tv, the assessment of their applicability in oncological patients in supportive therapy remains open and requires further research.

CONCLUSIONS

The commercially available He and Tv supplements contain between 100 and 1000 mg of the fruiting body or mycelium powder per dose depending on the pharmaceutical manufacturer. Extracts are composed mainly of polysaccharides but also beta-glucans, palmitic acid, minerals and are dedicated to the treatment of gastrointestinal, neurological (He) and oncological (Tv) diseases. Daily doses of He and Tv supplements have not been officially established. Manufacturers' recommendations on the daily He and Tv doses are up to 2 g. They are contraindicated in pregnant and lactating women and children before the age of 3.

Hericium erinaceus and *Trametes versicolor* give rise to high hopes as sources of substances potentially useful in medicine. The substances existing in the extracts of *Hericium erinaceus* and *Trametes versicolor* may exhibit chemotherapy-supporting and immunomodulatory effects in oncological patients. Their use is more justified than that of other supplements used by patients.

REFERENCES

1. W. Sneader, *Drug Discovery. A History*, John Wiley & Sons, Chichester 2005.
2. D. T. Courtwright, *Forces of Habit – Drugs and the Making of the Modern World*, Harvard University Press, Cambridge (MA) 2002.
3. M. Hanada, *Case Studies in Modern Drug Discovery and Development*, John Wiley & Sons, Hoboken (NJ) 2012.
4. D. A. Dias, S. Urban and U. Roessner, A historical overview of natural products in drug discovery, *Metabolites* **2** (2012) 303–336; <https://doi.org/10.3390/metabo2020303>
5. M. Friedman, 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.* **63** (2015) 7108–7123; <https://doi.org/10.1021/acs.jafc.5b02914>
6. X. He, X. Wang, J. Fang, Y. Chang, N. Ning, H. Guo, L. Huang, X. Huang and Z. Zhao, Structures, biological activities, and industrial applications of the polysaccharides from *Hericium erinaceus* (Lion's mane) mushroom: A review, *Int. J. Biol. Macromol.* **97** (2017) 228–237; <https://doi.org/10.1016/j.ijbiomac.2017.01.040>
7. G. Wang, X. Zhang, S. E. Maier, L. Zhang and R. J. Maier, In vitro and in vivo inhibition of *Helicobacter pylori* by ethanolic extracts of Lion's mane medicinal mushroom, *Hericium erinaceus* (Agaricomycetes), *Int. J. Med. Mushrooms* **21** (2019) 1–11; <https://doi.org/10.1615/IntJMedMushrooms.2018029487>
8. M. Qin, Y. Geng, Z. Lu, H. Xu, J. S. Shi, X. Xu and Z. H. Xu, Antiinflammatory effects of ethanol extract of Lion's mane medicinal mushroom, *Hericium erinaceus* (Agaricomycetes), in mice with ulcerative colitis, *Int. J. Med. Mushrooms* **18** (2016) 227–234; <https://doi.org/10.1615/IntJMedMushrooms.v18.i3.50>
9. M. Wang, T. Konishi, Y. Gao, D. Xu and Q. Gao, Anti-gastric ulcer activity of polysaccharide fraction isolated from mycelium culture of Lion's mane medicinal mushroom, *Hericium erinaceus* (higher Basidiomycetes), *Int. J. Med. Mushrooms* **17** (2015) 1055–1060; <https://doi.org/10.1615/intjmedmushrooms.v17.i11.50>
10. W. Li, W. Zhou, E. J. Kim, S. H. Shim, H. K. Kang and Y. H. Kim, Isolation and identification of aromatic compounds in Lion's Mane Mushroom and their anticancer activities, *Food Chem.* **170** (2015) 336–342; <https://doi.org/10.1016/j.foodchem.2014.08.078>

11. S. P. Kim, M. Y. Kang, Y. H. Choi, J. H. Kim, S. H. Nam and M. Friedman, Mechanism of *Hericium erinaceus* (yamabushitake) mushroom-induced apoptosis of U937 human monocytic leukemia cells, *Food Funct.* **2** (2011) 348–356; <https://doi.org/10.1039/c1fo10030k>
12. M. Wang, Y. Zhang, X. Xiao, D. Xu, Y. Gao and Q. Gao, A polysaccharide isolated from mycelia of the Lion's mane medicinal mushroom *Hericium erinaceus* (Agaricomycetes) induced apoptosis in precancerous human gastric cells, *Int. J. Med. Mushrooms* **19** (2017) 1053–1060; <https://doi.org/10.1615/IntJMedMushrooms.2017024975>
13. X. Zan, F. Cui, Y. Li, Y. Yang, D. Wu, W. Sun and L. Ping, *Hericium erinaceus* polysaccharide-protein HEG-5 inhibits SGC-7901 cell growth via cell cycle arrest and apoptosis, *Int. J. Biol. Macromol.* **76** (2015) 242–253; <https://doi.org/10.1016/j.ijbiomac.2015.01.060>
14. Y. Li, G. Zhang, T. B. Ng and H. Wang, A novel lectin with antiproliferative and HIV-1 reverse transcriptase inhibitory activities from dried fruiting bodies of the monkey head mushroom *Hericium erinaceum*, *J. Biomed. Biotechnol.* **2010** (2010) Article ID 716515 (9 pages); <https://doi.org/10.1155/2010/716515>
15. S. S. Han, C. K. Cho, Y. W. Lee and H. S. Yoo, Antimetastatic and immunomodulating effect of water extracts from various mushrooms, *J. Acupunct. Meridian Stud.* **2** (2009) 218–227; [https://doi.org/10.1016/S2005-2901\(09\)60058-3](https://doi.org/10.1016/S2005-2901(09)60058-3)
16. X. Sheng, J. Yan, Y. Meng, Y. Kang, Z. Han, G. Tai, Y. Zhou and H. Cheng, Immunomodulatory effects of *Hericium erinaceus* derived polysaccharides are mediated by intestinal immunology, *Food Funct.* **8** (2017) 1020–1027; <https://doi.org/10.1039/c7fo00071e>
17. I.-C. Li, L.-Y. Lee, T.-T. Tzeng, W.-P. Chen, Y.-P. Chen, Y.-J. Shiao and C.-C. Chen, Neurohealth properties of *Hericium erinaceus* mycelia enriched with erinacines, *Behav. Neurol.* **2018** (2018) 5802634 (10 pages); <https://doi.org/10.1155/2018/5802634>
18. P. Rossi, V. Cesaroni, F. Brandalise, A. Occhinegro, D. Ratto, F. Perrucci, V. Lanaia, C. Girometta, G. Orrù and E. Savino, Dietary supplementation of Lion's mane medicinal mushroom, *Hericium erinaceus* (Agaricomycetes), and spatial memory in wild-type mice, *Int. J. Med. Mushrooms* **20** (2018) 485–494; <https://doi.org/10.1615/IntJMedMushrooms.2018026241>
19. P. S. Liu, S. H. Chueh, C. C. Chen, L. Y. Lee and L. Y. Shiu, Lion's mane medicinal mushroom, *Hericium erinaceus* (Agaricomycetes), modulates purinoceptor-coupled calcium signaling and murine nociceptive behavior, *Int. J. Med. Mushrooms* **19** (2017) 499–507; <https://doi.org/10.1615/IntJMedMushrooms.v19.i6.20>
20. C.-C. Zhang, X. Yin, C.-Y. Cao, J. Wei, Q. Zhang and J.-M. Gao, Chemical constituents from *Hericium erinaceus* and their ability to stimulate NGF-mediated neurite outgrowth on PC12 cells, *Bioorg. Med. Chem. Lett.* **25** (2015) 5078–5082; <https://doi.org/10.1016/j.bmcl.2015.10.016>
21. K. Mori, S. Inatomi, K. Ouchi, Y. Azumi and T. Tsuchida, Improving effects of the mushroom yamabushitake (*Hericium erinaceus*) on mild cognitive impairment: a double-blind placebo-controlled clinical trial, *Phytother. Res.* **23** (2009) 367–372; <https://doi.org/10.1002/ptr.2634>
22. M. Nagano, K. Shimizu, R. Kondo, C. Hayashi, D. Sato, K. Kitagawa and K. Ohnuki, Reduction of depression and anxiety by 4 weeks *Hericium erinaceus* intake, *Biomed. Res.* **31** (2010) 231–237; <https://doi.org/10.2220/biomedres.31.231>
23. A. Blagodatski, M. Yatsunskaya, V. Mikhailova, V. Tiasto, A. Kagansky and V. L. Katanaev, Medicinal mushrooms as an attractive new source of natural compounds for future cancer therapy, *Oncotarget* **9** (2018) 29259–29274; <https://doi.org/10.18632/oncotarget.25660>
24. L. J. Standish, C. A. Wenner, E. S. Sweet, C. Bridge, A. Nelson, M. Martzen, J. Novack and C. Torkelson, *Trametes versicolor* mushroom immune therapy in breast cancer, *J. Soc. Integr. Oncol.* **6** (2008) 122–128.
25. K. Oba, S. Teramukai, M. Kobayashi, T. Matsui, Y. Kodera and J. Sakamoto, Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curative resections of gastric cancer, *Cancer Immunol. Immunother.* **56** (2007) 905–911; <https://doi.org/10.1007/s00262-006-0248-1>

26. J. Sakamoto, S. Morita, K. Oba, T. Matsui, M. Kobayashi, H. Nakazato and Y. Ohashi, Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curatively resected colorectal cancer: a meta-analysis of centrally randomized controlled clinical trials, *Cancer Immunol. Immunother.* **55** (2006) 404–411; <https://doi.org/10.1007/s00262-005-0054-1>
27. K. Sugimachi, K. Inokuchi and H. Matsuura, Hormone conditioned cancer chemotherapy for recurrent breast cancer prolongs survival, *Jpn. J. Surg.* **14** (1984) 217–221.
28. Y. Iino, T. Yokoe, M. Maemura, J. Horiguchi, H. Takei, S. Ohwada and Y. Morishita, Immunotherapies versus chemotherapy as adjuvant treatment after curative resection of operable breast cancer, *Anticancer Res.* **15** (1995) 2907–2911.
29. L. Zhong, P. Yan, W. C. Lam, L. Yao and Z. Bian, *Coriolus versicolor* and *Ganoderma lucidum* related natural products as an adjunct therapy for cancers: A systematic review and meta-analysis of randomized controlled trials, *Front. Pharmacol.* **10** (2019) 703 (14 pages); <https://doi.org/10.3389/fphar.2019.00703>
30. H. Lu, Y. Yang, E. Gad, C. Inatsuka, C. A. Wenner, M. L. Disis and L. J. Standish, TLR2 agonist PSK activates human NK cells and enhances the antitumor effect of HER2-targeted monoclonal antibody therapy, *Clin. Cancer Res.* **17** (2011) 6742–6753; <https://doi.org/10.1158/1078-0432.CCR-11-1142>
31. H. Lu, Y. Yang, E. Gad, C. A. Wenner, A. Chang, E. R. Larson, Y. Dang, M. Martzen, L. J. Standish and M. L. Disis, Polysaccharide krestin is a novel TLR2 agonist that mediates inhibition of tumor growth via stimulation of CD8 T cells and NK cells, *Clin. Cancer Res.* **17** (2011) 67–76; <https://doi.org/10.1158/1078-0432.CCR-10-1763>
32. K. Quayle, C. Coy, L. Standish and H. Lu, The TLR2 agonist in polysaccharide-K is a structurally distinct lipid which acts synergistically with the protein-bound β -glucan, *J. Nat. Med.* **69** (2015) 198–208; <https://doi.org/10.1007/s11418-014-0879-z>
33. Z. Wang, B. Dong, Z. Feng, S. Yu and Y. Bao, A study on immunomodulatory mechanism of polysaccharopeptide mediated by TLR4 signaling pathway, *BMC Immunol.* **16** (2015) Article ID 34 (9 pages); <https://doi.org/10.1186/s12865-015-0100-5>
34. H. Dou, Y. Chang and L. Zhang, *Coriolus versicolor* polysaccharopeptide as an immunotherapeutic in China, *Prog. Mol. Biol. Transl. Sci.* **163** (2019) 361–381; <https://doi.org/10.1016/bs.pmbts.2019.03.001>
35. Y. Chang, M. Zhang, Y. Jiang, Y. Liu, H. Luo, C. Hao, P. Zeng and L. Zhang, Preclinical and clinical studies of *Coriolus versicolor* polysaccharopeptide as an immunotherapeutic in China, *Discov. Med.* **23** (2017) 207–219.
36. F. Hong, R. Hansen, J. Yan D. Allendorf, J. Baran, G. Ostroff and G. Ross, Beta-glucan functions as an adjuvant for monoclonal antibody immunotherapy by recruiting tumoricidal granulocytes as killer cells, *Cancer Res.* **63** (2003) 9023–9031; <https://cancerres.aacrjournals.org/content/63/24/9023.long>
37. S. Modak, G. Koehne, A. Vickers, R. O'Reilly and N.-K. V. Cheung, Rituximab therapy of lymphoma is enhanced by orally administered (1→3),(1→4)-D- β -glucan, *Leuk. Res.* **29** (2005) 679–683; <https://doi.org/10.1016/j.leukres.2004.10.008>
38. M. Thomas, P. Sadjadian, J. Kollmeier, J. Lowe, P. Mattson, J. R. Trout, M. Gargano, M. L. Patchen, R. Walsh, M. Beliveau, J. F. Marier, N. Bose, K. Gorden and F. Schneller III, A randomized, open-label, multicenter, phase II study evaluating the efficacy and safety of BTH1677 (1,3-1,6 beta glucan; Imprime PGG) in combination with cetuximab and chemotherapy in patients with advanced non-small cell lung cancer, *Invest. New Drugs* **35** (2017) 345–358; <https://doi.org/10.1007/s10637-017-0450-3>
39. N. H. Segal, P. Gada, N. Senzer, M. Gargano, M. Patchen and L. Saltz, A phase II efficacy and safety, open-label, multicenter study of imprime PGG injection in combination with cetuximab in patients with stage IV KRAS-mutant colorectal cancer, *Clin. Colorectal Cancer* **15** (2016) 222–227; <https://doi.org/10.1016/j.clcc.2016.02.013>

40. H. Asai, H. Iijima, K. Matsunaga, Y. Oguchi, H. Katsuno and K. Maeda, Protein-bound polysaccharide K augments IL-2 production from murine mesenteric lymph node CD4⁺ T cells by modulating T cell receptor signaling, *Cancer Immunol. Immunother.* **57** (2008) 1647–1655; <https://doi.org/10.1007/s00262-008-0498-1>
41. A. L. Engel, G. C. Sun, E. Gad, L. R. Rastetter, K. Strobe, Y. Yang, Y. Dang, M. L. Disis and H. Lu, Protein-bound polysaccharide activates dendritic cells and enhances OVA-specific T cell response as vaccine adjuvant, *Immunobiology* **218** (2013) 1468–1476; <https://doi.org/10.1016/j.imbio.2013.05.001>
42. M. Kato, K. Hirose, M. Hakozaiki, M. Ohno, Y. Saito, R. Izutani, J. Noguchi, Y. Hori, S. Okumoto, D. Kuroda, H. Nomura, S. Nishimatsu and H. Ohyanagi, Induction of gene expression for immunomodulating cytokines in peripheral blood mononuclear cells in response to orally administered PSK, an immunomodulating protein-bound polysaccharide, *Cancer Immunol. Immunother.* **40** (1995) 152–156.
43. C. B. Lau, C. Y. Ho, C. F. Kim, K. N. Leung, K. P. Fung, T. F. Tse, H. H. Chan and M. S. Chow, Cytotoxic activities of *Coriolus versicolor* (yunzhi) extract on human leukemia and lymphoma cells by induction of apoptosis, *Life Sci.* **75** (2004) 797–808; <https://doi.org/10.1016/j.lfs.2004.04.001>
44. C. Inatsuka, Y. Yang, E. Gad, L. Rastetter, M. L. Disis and H. Lu, Gamma delta T cells are activated by polysaccharide K (PSK) and contribute to the anti-tumor effect of PSK, *Cancer Immunol. Immunother.* **62** (2013) 1335–1345; <https://doi.org/10.1007/s00262-013-1436-4>
45. C. J. Torkelson, E. Sweet, M. R. Martzen, M. Sasagawa, C. A. Wenner, J. Gay, A. Putiri and L. J. Standish, Phase 1 clinical trial of *Trametes versicolor* in women with breast cancer, *ISRN Oncol.* **2012** (2012) 251632 (7 pages); <https://doi.org/10.5402/2012/251632>
46. B. K. Sekhon, D. M. Sze, W. K. Chan, K. Fan, G. Q. Li, D. E. Moore and R. H. Roubin, PSP activates monocytes in resting human peripheral blood mononuclear cells: immunomodulatory implications for cancer treatment, *Food Chem.* **138** (2013) 2201–2209; <https://doi.org/10.1016/j.foodchem.2012.11.009>
47. C. A. Wenner, M. R. Martzen, H. Lu, M. R. Verneris, H. Wang and J. W. Slaton, Polysaccharide-K augments docetaxel-induced tumor suppression and antitumor immune response in an immunocompetent murine model of human prostate cancer, *Int. J. Oncol.* **40** (2012) 905–913; <https://doi.org/10.3892/ijo.2011.1292>
48. Q. Y. Hu, H. Wang, W. M. Shen, X. R. Chen and M. Zou, Promoting effects of polysaccharide of *Polysticus versicolor* (L) FR. in C57BL/6J mice bearing melanoma B16, *Chin. J. Antibiot.* **6** (1988) 425–431.
49. S. Xu, Y. H. Song, H. Li and H. B. Cai, Curative effect observation on advanced colorectal cancer by the treatment with PSP combined with XELOX regimen, *Acta Univ. Med. Nanjing* **12** (2008) 1616–1618.
50. H. Fritz, D. A. Kennedy, M. Ishii, D. Fergusson, R. Fernandes, K. Cooley and D. Seely, Polysaccharide K and *Coriolus versicolor* extracts for lung cancer: A systematic review, *Integr. Cancer Ther.* **14** (2015) 201–211; <https://doi.org/10.1177/1534735415572883>
51. A. Knežević, M. Stajić, I. Sofrenić, T. Stanojković, I. Milovanović, V. Tešević and J. Vukojević, Antioxidative, antifungal, cytotoxic and antineurodegenerative activity of selected *Trametes* species from Serbia, *PLoS ONE* **13** (2018) e0203064 (18 pages); <https://doi.org/10.1371/journal.pone.0203064>
52. L. Janjušević, B. Pejin, S. Kaišarević, S. Gorjanović, F. Pastor, K. Tešanović and M. Karaman, *Trametes versicolor* ethanol extract, a promising candidate for health-promoting food supplement, *Nat. Prod. Res.* **32** (2018) 963–967; <https://doi.org/10.1080/14786419.2017.1366484>
53. C. Y. Ho, C. F. Kim, K. N. Leung, K. P. Fung, T. F. Tse, H. Chan and C. B. Lau, Differential anti-tumor activity of *coriolus versicolor* (yunzhi) extract through p53- and/or Bcl-2-dependent apoptotic pathway in human breast cancer cells, *Cancer Biol. Ther.* **4** (2005) 638–644; <https://doi.org/10.4161/cbt.4.6.1721>

54. D. Roca-Lema, O. Martínez-Iglesias, C. Fernández de Ana Portela, A. Rodríguez-Blanco, M. Valadares-Ayerbes, A. Díaz-Díaz, A. Casas-Pais, C. Prego and A. Figueroa, In vitro anti-proliferative and anti-invasive effect of polysaccharide-rich extracts from *Trametes versicolor* and *Grifola frondosa* in colon cancer cells, *Int. J. Med. Sci.* **16** (2019) 231–240; <https://doi.org/10.7150/ijms.28811>
55. T.-C. Hsieh, J. Kunicki, Z. Darzynkiewicz and J. M. Wu, Effects of extracts of *Coriolus versicolor* (Im-Yunity™) on cell-cycle progression and expression of interleukins-1 β , -6, and -8 in promyelocytic HL-60 leukemic cells and mitogenically stimulated and nonstimulated human lymphocytes, *J. Altern. Complement. Med.* **8** (2002) 591–602; <https://doi.org/10.1089/107555302320825101>
56. N. Hirahara, M. Fujioka, T. Edamatsu, A. Fujieda, F. Sekine, T. Wada and T. Tanaka, Protein-bound polysaccharide-K (PSK) induces apoptosis and inhibits proliferation of promyelomonocytic leukemia HL-60 cells, *Anticancer Res.* **31** (2011) 2733–2738.
57. T. S. Hattori, N. Komatsu, S. Shichijo and K. Itoh, Protein-bound polysaccharide K induced apoptosis of the human Burkitt lymphoma cell line, Namalwa, *Biomed. Pharmacother.* **58** (2004) 226–230; <https://doi.org/10.1016/j.biopha.2004.02.004>
58. C. Iguchi, Y. Nio, H. Takeda, K. Yamasawa, N. Hirahara, T. Toga, M. Itakura and K. Tamura, Plant polysaccharide PSK: cytostatic effects on growth and invasion; modulating effect on the expression of HLA and adhesion molecules on human gastric and colonic tumor cell surface, *Anticancer Res.* **21** (2001) 1007–1013.
59. S. F. Yang, T. F. Zhuang, Y. M. Si, K. Y. Qi and J. Zhao, Coriolus versicolor mushroom polysaccharides exert immunoregulatory effects on mouse B cells via membrane Ig and TLR-4 to activate the MAPK and NF- κ B signaling pathways, *Mol. Immunol.* **64** (2015) 144–151; <https://doi.org/10.1016/j.molimm.2014.11.007>
60. H. Zhang, T. Morisaki, C. Nakahara, H. Matsunaga, N. Sato, F. Nagumo, J. Tadano and M. Katano, PSK-mediated NF-kappaB inhibition augments docetaxel-induced apoptosis in human pancreatic cancer cells NOR-P1, *Oncogene* **22** (2003) 2088–2096; <https://doi.org/10.1038/sj.onc.1206310>
61. E. Jiménez-Medina, E. Berruguilla, I. Romero, I. Algarra, A. Collado, F. Garrido and A. Garcia-Lora, The immunomodulator PSK induces *in vitro* cytotoxic activity in tumor cell lines *via* arrest of cell cycle and induction of apoptosis, *BMC Cancer* **8** (2008) Article ID 78 (10 pages); <https://doi.org/10.1186/1471-2407-8-78>