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Review

Remedies

The analgesic effect of several edible mushrooms

H Wang†, Y Liu†, C Han*

Abstract

Introduction

Edible mushrooms, a valuable source of bioactive compounds and nutrients, have been consumed as part of the diet in some countries for thousands of years. They are quite high in protein, carbohydrate and fibre and low in fat content with low trans-isomers of unsaturated fatty acids. In addition, they also have many components such as triterpenes, phenolic compounds, chitosan, eritadenine, sterols (such as ergosterol), triterpenes, etc., which are considered momentous agents for some hitherto unknown healthy properties. Recently, edible mushrooms have become increasingly attractive as functional foods and medicines to treat diseases including cancer, diabetes, inflammation and ache due to the presence of these active components. Pain is an unpleasant sensation, which is a typical response to an untoward event associated with tissue damage, such as injury and inflammation. The aims of this review are to report the positive analgesic effect of several edible mushrooms on pain and its relevant active constituents.

Conclusion

In our review, the edible mushrooms including *Pleurotus pulmonarius, Agaricus brasiliensis, Agaricus bisporus var. hortensis, Agaricus macrosporus, Coriolus versicolor* and *Cordyceps sinensis* have been investigated that possess antinociceptive and anti-inflammatory effects owing to their bioactive components such as β-glucan, agaricoglyceride A, polysaccharopeptide and cordymin as well as other active components. What is more, there are barely any side effects caused by the toxicity of edible mushrooms in vitro and in vivo. However, further research is required with clinical trials and applications.

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Introduction

Pain is a physiologically relevant sensation necessary to detect and/or prevent injury; it is sometimes useful to us[1,2]. Typically, it is a direct response to an untoward event associated with tissue damage, such as injury and inflammation, but severe pain can arise independently of any obvious redisposing cause, or precipitate healing after injury for a relatively long time. It can also occur as a consequence of brain or nerve injury. Pain signalling to the central nervous system is initiated when harmful excitement and primary afferent nociceptive C and A fibres are frequently caused by activation of several types of ionotropic channels and etabotropic receptors[3,4]. In fact, transient receptor potential and acid-sensing ion channels participate in generating nociceptive signals in response to various specific noxious stimuli[4–6]. Activity of some of these channels and other proteins implicated in nociceptive signalling pathways can be upregulated by protein kinase C[7–9]. Thus, pain is generated.

Edible mushrooms are the fleshy and edible fruiting bodies of several species of fungi, typically produced above ground on soil or on its food source[10]. They have been used as delicious foods and as healthy nutritional supplements for several centuries. For the Chinese, some mushrooms are especially regarded as medical substances that boost health and increase longevity, which is attributed to their far-ranging functions, for example antinociceptive, anti-inflammatory, immunity, anti-tumour, ascorbic and so on. Mushrooms are quite high in protein (19–35%) and low in fat. Miles et al. concluded that mushrooms also contain relatively large amounts of carbohydrate and fibre, ranging from 51% to 88% and from 4% to 20%, respectively (dry weight). In addition, mushrooms contain significant amounts of vitamins, namely thiamin, ascorbic acid, riboflavin and vitamin D2, as well as minerals[11,12]. In addition to their nutritional value, some mushrooms may also have a medicinal value: anti-tumour, antiviral and hypolipidemic effects have been reported[11–13]. They form a huge, but largely untapped powerful source of new pharmaceutical products[14,15]. They are low-calorie foods with very little fat and are highly suitable for obese persons[16]. Their consumption is widespread in China, Japan, Korea, Taiwan, Italy and Spain, among other countries[17–19].

In this review, we intend to discuss the result of research on the antinociception effect of edible mushrooms over the past two decades, emphasising animal studies as well as supporting mechanistic studies. We selected several typical edible fungi which result in pain relief. Our goals are to evaluate the analgesic effect of edible fungus, identify some putative bioactive compounds involved in the effect and stimulate further work in the field.

Discussion

The authors have referenced some of their own studies in this review. The protocols of these studies have been

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approved by the relevant ethics committees related to the institution in which they were performed. Animal care was in accordance with the institution guidelines.

Analgesic effect of several edible mushrooms

Oyster mushrooms

Pleurotus is a genus of gilled mushrooms, one of the most widely eaten mushrooms. Species of *Pleurotus* are commonly known as oyster mushrooms and are some of the most commonly cultivated edible mushrooms in the world. The genus *Pleurotus* include edible and medicinal species, most of them being currently commercialised in China[20]. The fungi are rich in proteins, vitamins, carbohydrates, minerals and dietary fibres. Basidiomycetes have been widely studied over the past 30 years in the light of their polysaccharide composition and therapeutic application[21,22].

Pleurotus pulmonarius

Pleurotus pulmonarius, also known as oyster mushroom, is a common edible mushroom consumed worldwide due to its several polysaccharides, besides high amount of proteins, essential amino acids and vitamins[23,24]. A variety of biological effects have been ascribed to β-glucans, such as anti-inflammatory, antioxidant, anti-tumoural, immunomodulatory and antinociceptive properties[25–28]. There have been some literature research showing that *P. pulmonarius* have analgesic effects[29–32]. Smiderle et al.[29] isolated β-glucan (GL) with hot water from the basidiomycete *P. pulmonarius* and found the glucan had potent anti-inflammatory and antinociceptive activities in mice. Animals treated with β-glucan showed a reduction of 85 ± 5% of writhes induced by acetic acid and the significant inhibition of both the early (neurogenic pain) and the late (inflammatory pain) phases of formalin-induced licking in 43 ± 5% and 96 ± 4%, respectively. Then, the results showed that *P. pulmonarius* had notable analgesic and anti-inflammatory effects due to the inhibition of pro-inflammatory cytokines[29]. The structure of β-D-glucan was characterised using mono- and two-dimensional NMR spectroscopy, methylation analysis and a controlled Smith degradation[20,29]. And the dates showed that it had a main chain of (1 → 6)-linked α-D-galactopyranosyl and 3-*O*-methyl-α-D-galactopyranosyl units, both of which are partially substituted at *O*-2 by β-D-mannopyranosyl non-reducing ends (Figure 1).

In order to evaluate the involvement of transient receptor potential (TRP) channels and protein kinase C (PKC) on antinociceptive effect of a (1 → 3), (1 → 6)-linked β-D-glucan (GL), Baggio et al.[30] isolated GL from *P. pulmonarius* to treat it with intraperitoneal administration in mice. In this study, nociceptive responses, induced by intraplantar injections of capsaicin, cinnamaldehyde, menthol, acidified saline and phorbol myristate acetate (PMA), were significantly inhibited by GL. The results demonstrated that GL displayed pronounced systemic antinociceptive properties in chemical models of nociception in mice as a result of the inhibition of PKCε[30]. In addition, GL isolated from *P. pulmonarius* could dramatically inhibit acute and neuropathic pain in mice through mechanisms that involve the inhibition of ionotropic glutamate receptors and the interleukin-1β pathway[31].

Pleurotus florida

Pleurotus florida, an American oyster mushroom, has been reported to possess antioxidant, immunostimulator, anti-tumour and anti-inflammatory activities[32,33]. The analgesic and anti-inflammatory activity of *P. florida* was evaluated using a hot plate method, tail flick method, acetic acid-induced writhing, formalin-induced pain and carrageenan-induced inflammation in rats[34]. Animals treated orally with hydroethanolic extract (HEE) of *P. florida* in a dose-dependent manner were tested for nociceptive response with these methods. Then, results demonstrated *P. florida* exerted excellent analgesic and anti-inflammatory activity in rats on account of myoconstituents like flavonoids, phenolics, polysaccharides and polysaccharopeptides[34]. Simultaneously, the antinociceptive activity of HEE of *P. florida* is related to the activation of the opioid system.

Pleurotus eous and Pleurotus ostreatus

Pleurotus mushrooms are the second most important mushrooms in terms of production in the world. Furthermore, this species has been of interest to researchers because its phytochemical constituents are similar to those of *P. pulmonarius, P. florida, Pleurotus eous and Pleurotus ostreatus,* which are popularly used in medicines. The ethyl acetate, methanol and aqueous extracts of *P. eous* mushroom were investigated to evaluate

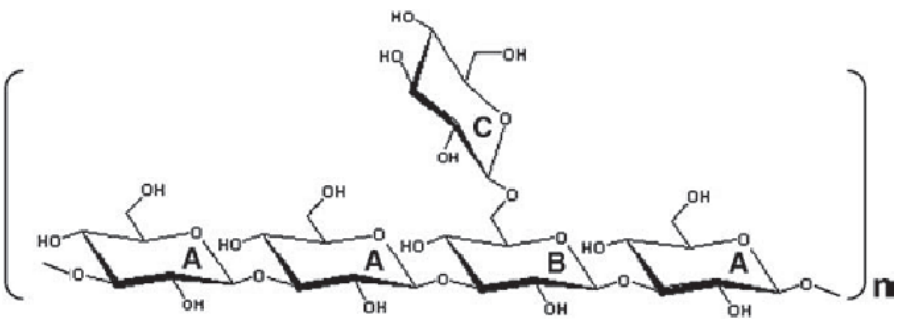

Figure 1: Chemical structure of β-glucan isolated from *Pleurotus pulmonarius*.

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the analgesic activity using acetic acid-induced writhing, hot-plate, tail immersion and tail-clip tests[35]. The dates showed that these extracts of *P. eous* produced significant reduction in the number of writhes and markedly raised the pain threshold at different times of observation in comparison with the control ($p < 0.05$). The extracts also caused a notable inhibition of pain in the tail-clip test. Thus, the results of this study revealed that extracts of *P. eous* possessed potent analgesic property and could serve as a base for future drugs[35].

Similarly, the antinociceptive potential of *P. ostreatus* was also investigated in rats through the hot-plate, tail-flick and formalin tests[36]. The reaction times on hot-plate and tail-flick tests were significantly prolonged and pain was significantly suppressed in both phases in the formalin test. The research results showed that *P. ostreatus* had antinociception against neurogenic and continuous inflammatory pain possibly by opioid mechanisms[36].

In summary, oyster mushrooms have shown potent antinociceptive and anti-inflammatory properties in several animal model studies and no side effects. However, further studies are needed to investigate the antinociceptive mechanisms in vivo, and human intervention studies of oyster mushrooms alone or in combination with conventional chemotherapy are also demanded to establish efficacy in humans.

Agaricus

Agaricus is the most common eubacterium among the whole macrofungi. The species number admitted by taxonomists is more than 200. It is a large family, which is named *Psalliota Kummer* in the early days, including *Agaricus bisporus, Agaricus bitorquis, Agaricus blazei, Agaricus silvaticus, Agaricus macrospors* and so on. We select three typical species (*A. brasiliensis, A. bisporus var. hortensis* and *A. macrosporus*) in order to elaborate the antinociceptive properties of *Agaricus*.

Agaricus rasiliensis and Agaricus bisporis var. hortensis

Fucogalactans from *A. brasiliensis* (EPF-Ab) and *A. bisporus var. hortensis* (EPF-Ah) have antinociceptive action, which is related to their structures. Fucogalactans play a positive role in antinociceptive, anti-inflammatory and anti-sepsis. Besides, they possess activities even after extraction[37]. The active ingredients are attained by their aqueous extraction and a series of purification. According to methylation analysis[38] and GC–MS, Komuraa et al.[37] concluded that EFP-Ab (Mw = 19.4 × 10^3 g/mol) had a (1 → 6)-linked α-D-Galp main-chain partially substituted in O-2 by non-reducing end-units of α-L-Fucp. EPF-Ah (Mw = 31.1 × 10^3 g/mol) had a similar main-chain with O-2 substitution, but was partially methylated at HO-3, as well as having 2.5% non-reducing end-units of β-D-Gal substitution (Figure 2). Analgesic activity was determined using the hot-plate method, acetic acid-induced writhing, formalin-induced pain in rats and many other classic methods[37,39]. There are different modes of action among different experiments. Above all, EFP-Ab and EFP-Ah prefer to cure inflammatory nociception and act at a central and peripheric level. These results showed that the structure determines the function; it is the (1 → 6)-linked α-D-galactopyranosyl main-chain that determines the analgesic property of *A. brasiliensis* and *A. bisporus var. hortensis*. Many articles have reported that a lot of other basidiomycetes' fruiting bodies or cultivated mycelium such as *P. pulmonarius, Lentinus edodes, Coprinus comatus* and *Hericium erinaceus,* which have the main-chain, also can inhibit nociception[20,40–42].

Agaricus macrosporus

Agaricus macrosporus is another species which has obvious analgesic effect by inhibiting neurolysin. The active ingredient of *A. macrosporus* is agaricoglycerides, which is a new class of fungal secondary metabolites that constitute esters of chlorinated 4-hydroxy benzoic acid and glycerol[43]. They are produced in cultures of the edible mushroom, which is different from the two species described above. There are seven structures of agaricoglycerides in cultures according to reports, and agaricoglyceride A is the main active principle of the crude extract of *A. macrosporus* (Figure 3). Neurolysin inhibitors are likely to enhance the analgesic properties of neurotensin and/or dynorphin A by inhibiting cleavage and inactivation of these peptides[44,45].

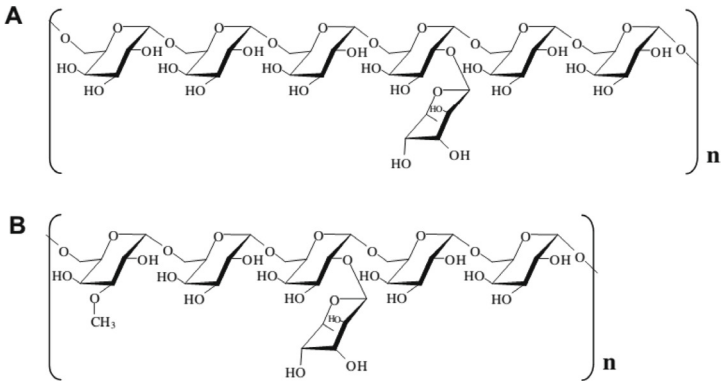

Figure 2: Structure of the fucogalactans EPF-Ab and EPF-Ah, obtained respectively from *A. brasiliensis* (A) and *A. bisporus var. hortensis* (B).

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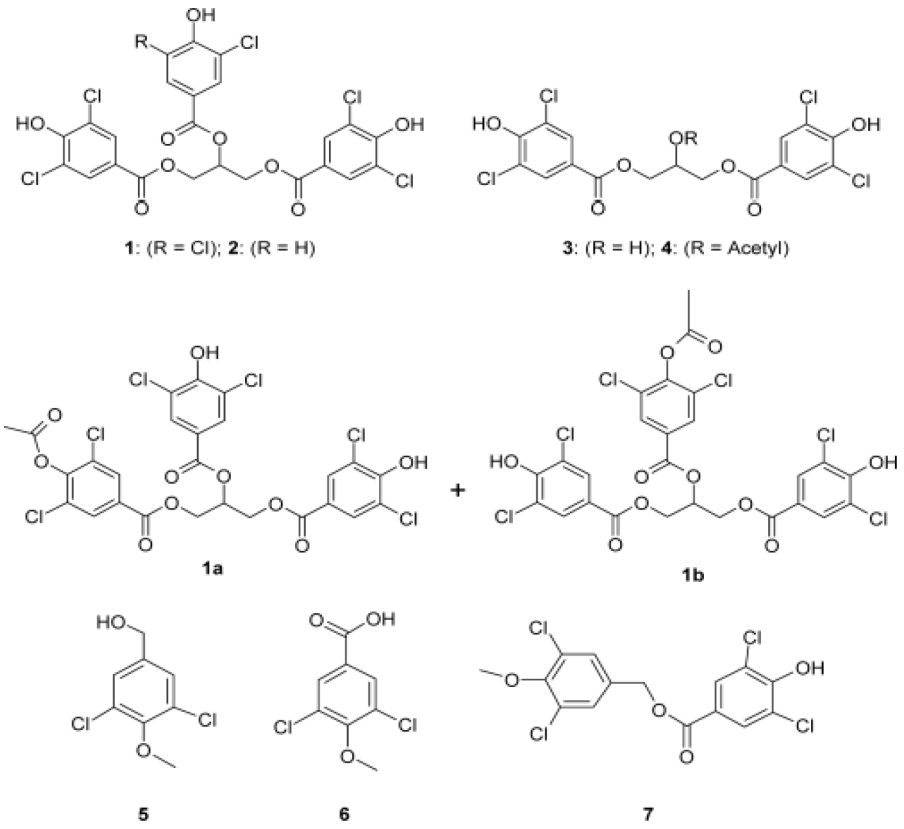

Figure 3: Chemical structures of metabolites isolated from *Agaricus macrosporus*. 1: Agaricoglyceride A; 2: Agaricoglyceride B; 1a/b: Monoacetyl-agaricoglycerides A (isolated as inseparable mixture); 3: Agaricoglyceride C; 4: Agaricoglyceride D; 5: DCMB; 6: 3,5-Dichloro-4-anisic acid; 7: Agaricic ester.

The agaricoglyceride A just shows strong activities against neurolysin. Many studies suggested that the production of agaricoglycerides and related metabolites in culture is widespread in the genus *Agaricus*[46–48] and other genera and families, such as *Triticum, Psathyrella, Hypholoma*[49,50] and *Stropharia,* are able to synthesise these aromatic triglycerides.

The genus *Agaricus* generally has an analgesic effect in spite of the kinds of effective ingredients and the different modes of action.

Coriolus versicolor

Coriolus versicolor, also referred to as the turkey-tail mushroom, contains large quantities of β-glucans that act to stimulate the immune system. *Coriolus* can dramatically regenerate and rejuvenate the body. Its most active medicinal components are biological response modifiers called protein-bound polysaccharides. Both extracellular and intracellular polysaccharopeptides of *C. versicolor* are physiologically active as biological response modifiers. The best known commercial polysaccharopeptide preparations of *C. versicolor* are polysaccharopeptide Krestin (PSK) and polysaccharopeptide (PSP). What is more, PSP and PSK have been investigated for possessing anticancer, anti-inflammatory and antinociceptive activities and immunopotentiation[51–55].

The PSP from the mushroom *C. versicolor* has immunomodulatory and anti-tumour activities, which has been used as a drug for cancer patients[56,57]. Ng et al.[54] studied the analgesic activity of PSP in the hot-plate test upon intraperitoneal administration to ICR mice and found that its analgesic activity would add to its attribute as an immunomodulatory and anti-tumour drug. Pain response in mice was significantly suppressed after receiving an intraperitoneal injection of *C. versicolor* PSP. Then, it was demonstrated that *C. versicolor* PSP possesses analgesic activity, which is beneficial for cancer patients as an immunomodulatory and anti-tumour drug[54]. In addition to this, one study shows that the analgesia produced by PSP is mediated by IL-2, which is activated by PSP and interacts with IL-2 receptors in the mediobasal hypothalamus (MBH)[55]. Rats were divided at random into different groups to test and the degree of analgesic effect of PSP was evaluated by the pain threshold (mA) or by the percentage increase from baseline pain threshold. The experiment results demonstrated that the analgesia appeared only 1 h after PSP administration and began to decrease after another hour. The phenomenon suggested that PSP-produced analgesia might be mediated by some intermediary substances activated by PSP[55].

On the whole, *C. versicolor* as a medicinal mushroom is widely used to treat cancer and enhance the immune system. Its PSK and PSP are the main bioactive components possessing anti-tumour, antimicrobial, hepato-protective and analgesic effects. Even so, the clinical applications need further study.

Cordyceps

Among the whole macrofungi family, *Cordyceps* is a special genus of entomogenous fungi that forms a fruiting body mainly on pupae or larvae[58]. The most typical species is *Cordyceps sinensis* (CS, caterpillar fungus). It is named Dong-Chong-Xia-Cao in Chinese, which translates as winter worm and summer grass. CS has many pharmacological actions such as modulation of immune response,

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inhibition of tumour growth, induction of cell apoptosis, antinociception and so on[59–62]. The effective constituent of antinociception in CS is cordymin, a peptide purified from its culture and fruiting bodies. Some studies have shown that cordymin inhibits the acetic acid-induced abdominal constriction in mice in a dose-dependent manner, which shows that cordymin had a peripheral antinociceptive effect. In addition to the results of the hot-plate test which is used for the assessment of the central antinociceptive effect, cordymin significantly inhibited the reaction time to thermal stimuli[63,64]. In brief, cordymin has antinociceptive effect in both peripheral and central aspects. Cordymin-1, cordymin-2 and cordymin-4 inhibited neurolysin in a dose-dependent manner and neurolysin has been reported to have analgesic properties in animal models[65]. As a result, cordymin is a potent anti-inflammatory and analgesic medicine and CS is an effective analgesic.

Table 1 Bioactive components/extracts from edible mushrooms with analgesic effect

Edible mushrooms	Bioactive components/extracts of analgesic effect	References
Pleurotus pulmonarius	β-Glucans	[25–32]
Pleurotus florida	Hydroethanolic extract	[34]
Pleurotus eous	Methanol and aqueous extracts	[35]
Agaricus brasiliensis	Fucogalactan (EPF-Ab)	[37]
Agaricus bisporus var. hortensis	Fucogalactan (EPF-Ah)	[37]
Agaricus macrospores	Agaricoglycerides	[43–48]
Coriolus versicolor	Polysaccharopeptides	[51–57]
Cordyceps	Cordymin	[63–65]
Termitomyces albuminosus	Crude saponin extract Crude polysaccharide extract	[66]
Inonotus obliquus	Methanol extract	[67]
Phellinus linteus	EtOH extract	[68]
Lactarius rufus	Soluble β-D-glucan	[69]
Grifola frondosa	Agaricoglycerides	[70]

Others

Not only the four genuses described above but also many others have the effect of analgesia. Lu et al.[66] concluded that the dry matter of culture broth (DMCB) of *Termitomyces albuminosus* in submerged culture, its crude saponin extract (CSE) and crude polysaccharide extract (CPE) inhibited the mouse ear swelling by 61.8%, 79.0% and 81.6%, respectively. Then the dates illustrated that *T. albuminosus* possessed the analgesic activity owing to saponins and polysaccharides, which are its major active constituents[66]. One study, designed by Park et al., demonstrated that the methanol extract from *Inonotus obliquus* had analgesic activity due to the inhibition of iNOS and COX-2 expression via the down-regulation of NF-κB binding activity[67]. In addition, Kim et al.[68] found that the EtOH extract of *Phellinus linteus* (PLE) could significantly reduce the numbers of writhing induced by acetic acid in mice. The results indicated that PLE had potent antinociceptive effect, which might be mediated by its anti-inflammatory action[68]. Moreover, Ruthes et al.[69] studied and found that *Lactarius rufus* had the anti-inflammatory and antinociceptive potential of their polysaccharides evaluated using the formalin model. Soluble β-D-glucan isolated from fruiting bodies of *L. rufus* produced potent inhibition of inflammatory pain caused by formalin when compared with the insoluble one[69]. Furthermore, a recent study stated that *Grifola frondosa* has important and antinociceptive effects in acetic acid-induced pain and formalin-induced inflammatory pain at the dose level of 500 mg/kg in mice[70]. Therefore, *G. frondosa* may be used as an alternative medicine for inflammatory pain.

Conclusion

Edible mushrooms have been widely used in some cultures as traditional medicines to treat diseases including diabetes and cancer, and to stimulate the immune system. Pain is intuitive for feelings of these diseases such as cancer, inflammation and injuries. As a result, the analgesic effects of edible fungi have a wide range of applications. The active components in many mushrooms with analgesic effects are very clear. In our review, edible mushrooms including *P. pulmonarius, A. brasiliensis, A. bisporus var. hortensis, A. macrosporus, C. versicolor* and CS have been investigated that possessed antinociceptive and anti-inflammatory effects owing to their bioactive components such as β-glucan, agaricoglyceride A, polysaccharopeptide and cordymin as well as other active components (Table 1). What is more, there are barely any side effects caused by toxicity of edible mushrooms in vitro and in vivo. However, further research is required with clinical trials and applications.

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Abbreviations list

CPE, crude polysaccharide extract; CS, *Cordyceps sinensis*; CSE, crude saponin extract; DMCB, dry matter of culture broth; HEE, hydro-ethanolic extract; MBH, mediobasal hypothalamus; PKC, protein kinase C; PMA, phorbol myristate acetate; PSK, polysaccharopeptide Krestin; PSP, polysaccharopeptide; TRP, transient receptor potential.

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