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Significance of Mushrooms in Urological Diseases and Disorders

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ABSTRACT

Background: Since a number of medicinal mushrooms have various pharmacological properties, we have been studying them mainly for urological diseases/disorders over 24 years. Among them, we present herein the interesting study of anticancer effect of a mushroom on urological cancers to illustrate the significance of mushrooms in urology.
Materials and Methods: Anticancer effect of maitake mushroom extract (PDF) on prostate cancer PC-3 cells *in vitro* was assessed by cell viability assay, and its synergistic potentiation with vitamin C (VC) was also demonstrated. Whether oxidative stress (OXS) may play a significant role in the anticancer mechanism was also explored. In addition, a possible chemosensitizing effect of PDF, capable of enhancing anticancer activity of chemotherapeutic drugs, was examined.
Results: PDF alone led to a significant reduction in PC-3 cell viability, which became even greater when combined with VC, exhibiting <10% cell viability. Such a profound cell viability reduction was primarily attributed to apoptosis induced by OXS. Moreover, anticancer activity of certain drugs against prostate and bladder cancer cells was also improved when combined with PDF, indicating a chemosensitizing effect of PDF.
Conclusion: This study demonstrates anticancer effect of PDF on urological cancer cells, and the PDF/VC combination is highly effective, ultimately leading to apoptosis. A chemosensitizing effect of PDF demonstrated here implies its possible clinical use as an adjuvant agent in current chemotherapy. Therefore, this study represents only anticancer effect of a mushroom but the significance of mushrooms in urological diseases/disorders can be yet understood.

Keywords: Mushrooms, Maitake, Anticancer, Medicinal properties, Urological diseases, Chemosensitization.

INTRODUCTION

Although a wide variety of mushrooms have been consumed by Chinese, Korean, and Japanese people for hundreds of years, many Europeans and Americans did not know much about them. One of the reasons for such public setback comes from misunderstandings or misconceptions about mushrooms. For example, many people think mushrooms as "fungi" with no nutritional values, or some people even believe that eating mushrooms could make you vulnerable to certain fungal infections (Candida or yeast). As is now clearly known, neither view is valid. On the contrary, most mushrooms, except for poisonous ones, are rich in vitamins, minerals, amino acids, and fibers but low in fat, cholesterol, and

calories.[1] In addition, extensive scientific and clinical research on mushrooms over 40 years revealed and demonstrated their medicinal or pharmacological properties, which might provide us with the remarkable health benefits. As mushrooms appears to be finally recognized by the public, several types of edible mushrooms are sold in supermarkets today, while the mushroom supplements are also available at the dietary or health food stores.

We have been studying various mushrooms on urological diseases, especially urological cancers, such as prostate, bladder, and renal cell carcinomas, for the past 24 years. In particular, we were interested in medicinal mushrooms, such as Maitake (*Grifola frondosa*), Reishi (*Ganoderma lucidum*), *Poria cocos*, *Phellinus linteus*, *Abrocybe chaxingu*, Lion's mane (*Hericium erinaceus*) etc. (Figure 1). Although these and other mushrooms have also shown potent anticancer effect on other cancers, including breast, lung, stomach, liver, colorectal, brain, and leukemia,[2,3] we will mainly describe the study of anticancer effect of *maitake* extract against urological cancers herein.

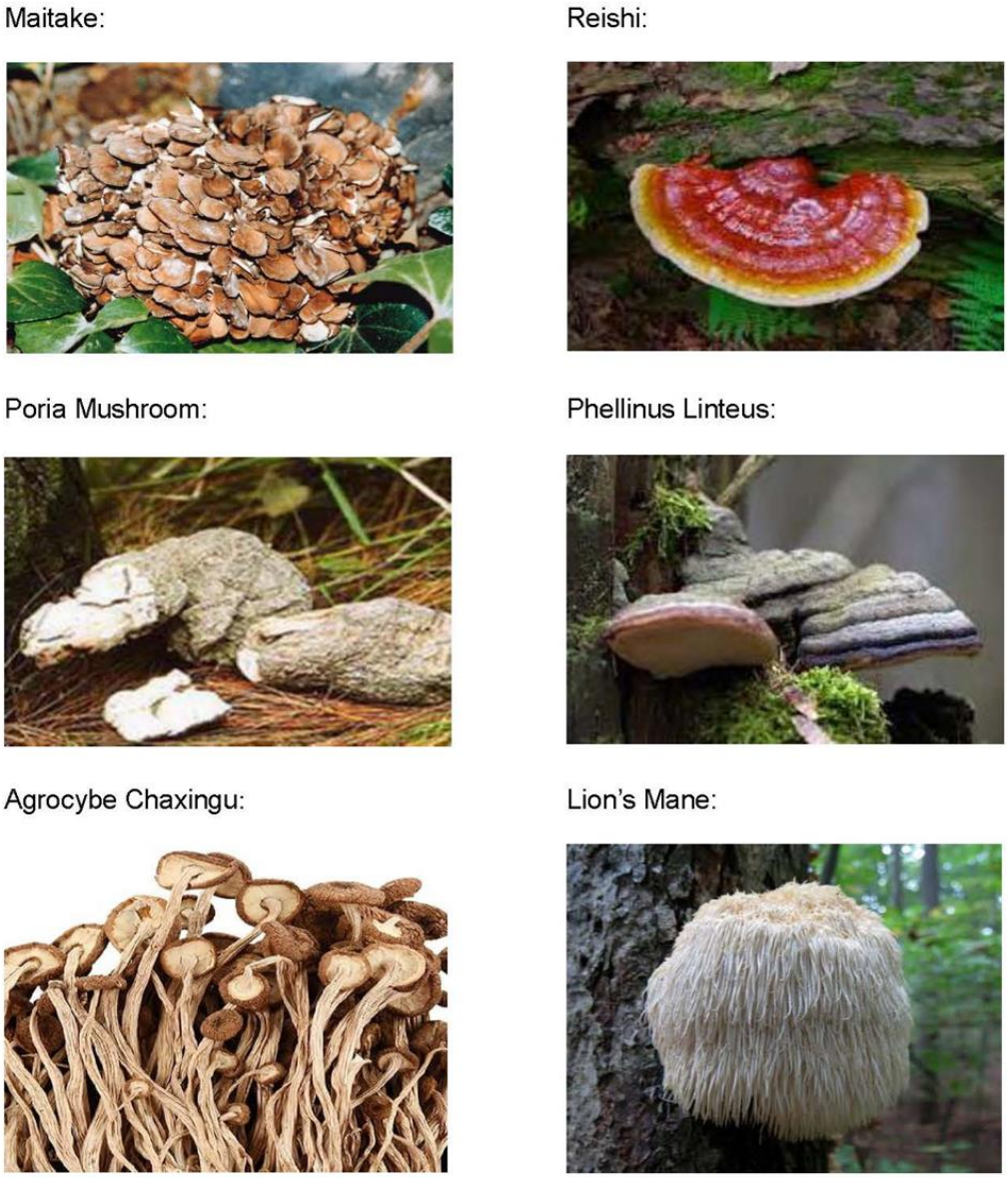

Figure 1. Medicinal mushrooms. Photos of six different mushrooms are shown.

"Maitake" literally means "dancing mushroom" but the origin of its name is unclear, although it is believed that people who found the mushroom deep in the mountains (of Japan) *danced with joy* because of its delicious taste and remarkable health benefits. It is also documented that in the feudal era, this mushroom could be exchanged for its weight in silver. Characteristically, maitake is a giant mushroom that often reaches 20 inches in diameter and may weigh up to 100 pounds. Because of such unique physical features and potential health benefits, maitake still is one of the most valuable and praised mushrooms in Japan as it is commercially sold in many grocery stores.

The medicinal properties of this mushroom were claimed in anecdotes and folklore, while a number of medical and scientific studies revealed numerous physiological and pharmacological properties, including antitumor, anticancer, anticarcinogenic, anti-metastatic, immunomodulatory, hypotensive, anti-diabetic, hypoglycemic, antioxidant, anti-inflammatory, antiviral effects etc.[4-9] It is also worth mentioning that the US National Cancer Institute (NCI) has confirmed antiviral activity of maitake against human immunodeficiency virus (HIV) in 1992.[10] Hence, we were interested in studying maitake as it appeared to have certain therapeutic and clinical implications.

We then obtained the bioactive extract of maitake called "Maitake D-Fraction (PDF)" from the manufacturer (Mushroom Wisdom, Inc.) over 20 years ago. We initiated studying anticancer effect of PDF on prostate cancer cells *in vitro* and a potentiation of PDF with vitamin C (VC). The anticancer mechanism was also explored, focusing on oxidative stress (OXS) and apoptosis. A possible chemosensitizing effect of PDF, capable of improving/enhancing anticancer activity of (chemotherapeutic) drugs, was further examined. Additionally, various pharmacological effects of other mushrooms on non-urological diseases/disorders were also described herein.

MATERIALS & METHODS

Cell Culture

Human prostate cancer PC-3 cells, bladder cancer T24, renal cell carcinoma ACHN cells and other cancer cells used in our study were all obtained from the American Type Culture Collection (ATCC, Manassas, VA). All cells were maintained in RPMI 1640 medium, supplemented with 10% fetal calf serum (FBS), penicillin (100 U/ml) and streptomycin (100 μg/ml). For experiments, cells were seeded in 6-well plates or T-75 flasks and cultured/treated with agents or drugs for indicated times. Cell viability was then determined by MTT assay as described below.

MTT Assay (Cell Viability Test)

After cells were treated with or without agents/drugs in the 6-well plate, 1 ml of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide) reagent was added to each well. The plate was incubated at 37 °C for 3 h and dimethyl sulfoxide was added to the plate, followed by the absorbance readings of samples in a microplate reader. Cell viability was then expressed by the % of sample readings relative to the control reading (100%).

In Situ Hybridization (ISH)

In situ hybridization (ISH) was performed using the non-isotopic ApopTag kit, following the manufacturer's protocol (Oncor, Gaithersburg, MD). Briefly, cells were first fixed in 4% neutral buffered Formalin on the slides, and endogenous peroxidase was quenched in 2% hydrogen peroxide. Digoxigenin-nucleotides were first added to the 3'-ends of DNA using terminal deoxynucleotidyl transferase, and digoxigenin antibody was then allowed to bind to them. After such antibody binding was detected by diaminobenzidine, the slides were counterstained with methyl green and the positive brown stains (indicating apoptosis) were seen on cells under a microscope.

Lipid Peroxidation (LPO) Assay

Severity of oxidative stress (OXS) was assessed by LPO assay, measuring the amount of malondialdehyde (MDA) formed in the plasma membrane due to oxidative stress.[11] The detailed procedures are described in the vendor's protocol (ABCAM, Waltham, MA). Briefly, cells exposed to agents or drugs for indicated times were lysed to obtain cell extracts. The reaction was then initiated by mixing cell extracts with thiobarbituric acid solution and incubated in a boiling water bath (~100 °C) for 1 h. Samples were read at A_{532} on a microplate reader, and the amount of MDA formed was calculated from the MDA standards and expressed by μM. In general, *the more MDA formed, the greater OXS*.

Statistical Analysis

All data are presented as the mean ± SD (standard deviation), and statistical differences between groups are assessed with either one-way analysis of variance (ANOVA) or the unpaired Student's t test. Values of $p < 0.05$ are considered to indicate statistical significance.

RESULTS

Anticancer Effect of Maitake Extract (PDF) on Prostate Cancer Cells

We first performed a dose-dependent study of PDF on human prostate cancer PC-3 cells. Cells were treated with varying concentrations (0-700 μg/ml) of PDF for 72 h and cell viability was determined by cell viability test (MTT assay). The results showed that PDF led to a significant reduction in PC-3 cell viability by ~23% and ~60% with 500 and 700 μg/ml of PDF, respectively (Figure 2A). Thus, ≥500 μg/ml of PDF demonstrated the potent anticancer effect (23% - 60%) on PC-3 cells, leading to a significant cell viability reduction.

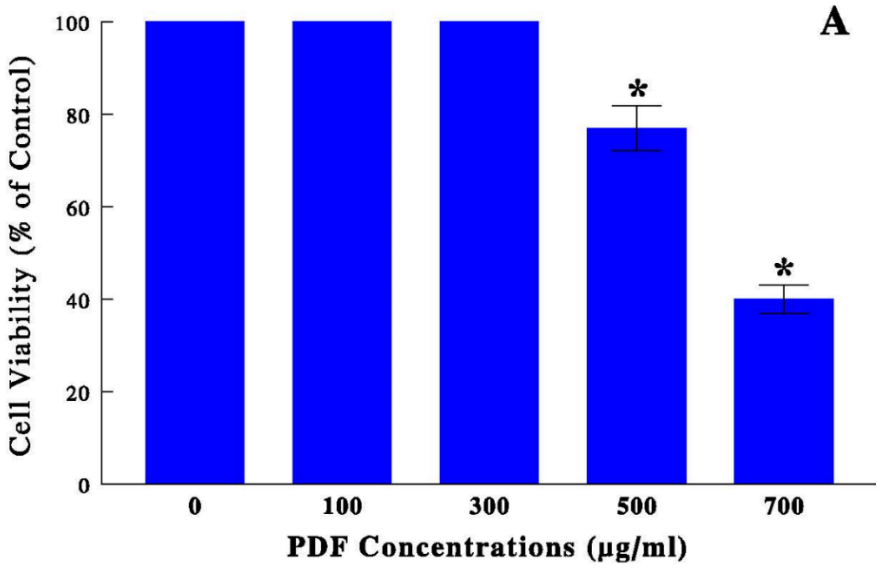

Figure 2. (A) Anticancer effect of PDF (maitake extract). Prostate cancer PC-3 cells were treated with varying concentrations of PDF (0-700 μg/ml) for 72 h and cell viability was determined by MTT assay. Cell viability was expressed by the percent (%) of viable cells relative to controls (100%). The data are mean ± SD (standard deviation) from three separate experiments (*$p < 0.05$ compared with control).

Synergistic Potentiation of PDF with Vitamin C (VC)

As it has been reported that bioactivity of *β-glucan*, active compound of PDF, could be enhanced when combined with vitamin C (VC),[12] this possibility was then tested. When PC-3 cells were treated with the combination of *ineffective* concentrations of PDF (100 μg/ml) and VC (50 μM) for 72 h, cell viability drastically reduced to <10% or

lost by >90% (Figure 2B). This demonstrates a *synergistic potentiation* of PDF with VC.

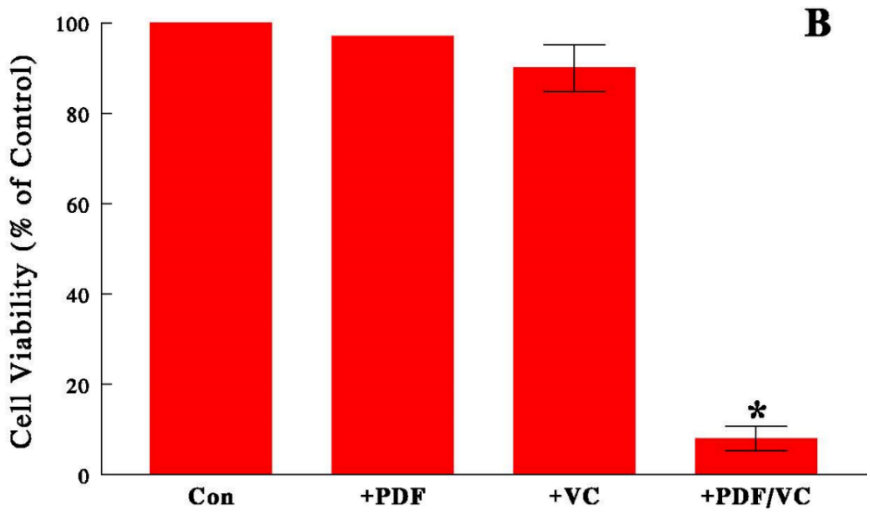

Figure 2. (B) After cells were treated with PDF (100 μg/ml), VC (50 μM), or the PDF and VC combination for 72 h, cell viability was then determined. The data are mean ± SD from three independent experiments (*p <0.05 compared with control).

Induction of Apoptosis with PDF/VC Combination

To learn what would eventually happen to those cells treated with the PDF/VC combination or whether they may undergo "apoptosis", PC-3 cells treated with the combination of PDF (100 μg/ml) and VC (50 μM) for 72 h were subjected to *in situ* hybridization (ISH) assay. The results revealed that PDF/VC-treated cells were positively stained (brown) (Figure 3B), while control cells remained unstained (negative) (Figure 3A). Since such positive staining indicates induction of apoptosis, the PDF/VC combination would ultimately induce apoptosis in PC-3 cells. Thus, this induction of apoptosis may account for a significant cell viability reduction and also implying a potential clinical utility that will be discussed later.

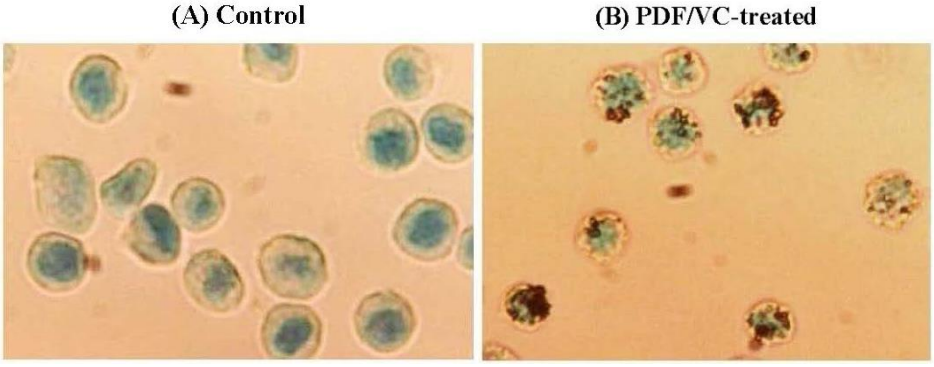

Figure 3. Induction of apoptosis. After PC-3 cells were treated with the combination of PDF (100 μg/ml) and VC (50 μM) for 72 h, they were subjected to *in situ* hybridization (ISH) assay as described in Materials and Methods. Dark brown staining seen in PDF/VC-treated cells **(B)** indicates induction of apoptosis, while no such staining was seen in control cells **(A)**.

Possible Anticancer Mechanism of PDF/ VC Combination

Now, the question is – How does the PDF/VC combination work? As it has been

shown that VC had a dual role, acting as antioxidant or prooxidant,[13] it was possible that VC could act as a prooxidant with PDF, exerting oxidative stress (OXS) on PC-3 cells. This possibility was tested by determining severity of OXS using lipid peroxidation (LPO) assay. Since OXS usually takes place at the early stage, PC-3 cells were exposed to PDF (100 μg/ml), VC (50 μM), or PDF/VC combination for merely 3 or 6 h and severity of OXS was immediately measured. Compared to control cells, severity of OXS, determined by the amount of malondialdehyde (MDA) formed, was ~3.2-fold higher/stronger in cells treated with PDF/VC combination for 6 h (Figure 4). It is thus plausible that this exertion of OXS would primarily damage or kill PC-3 cells, resulting in a significant reduction in cell viability.

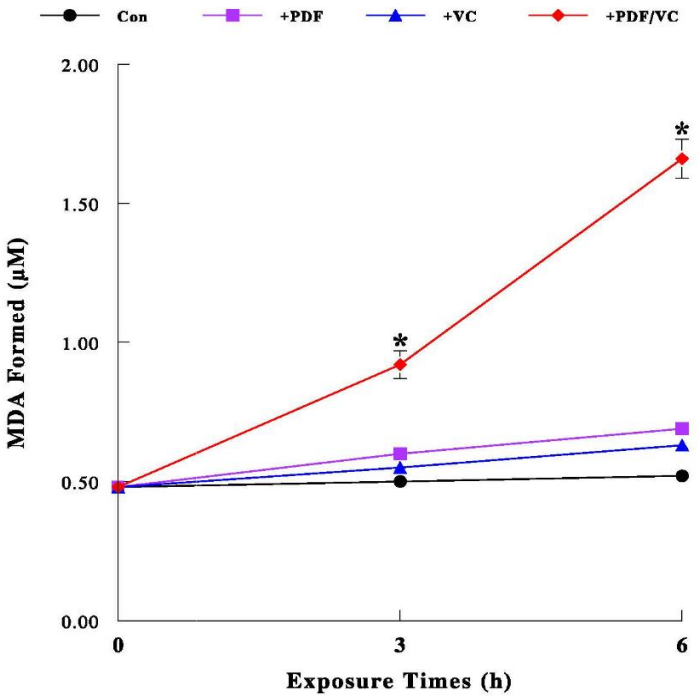

Figure 4. Exertion of oxidative stress (OXS). Cells were exposed to PDF (100 μg/ml), VC (50 μM), or PDF/VC combination for 3 or 6 h, and severity of OXS was then assessed by lipid peroxidation (LPO) assay. All data are mean ± SD from three separate experiments (*p <0.05 compared with control).

Anticancer Effect of PDF or PDF/VC Combination on Other Cancer Cells

We extended our study of PDF to bladder and renal cell carcinoma. Human bladder cancer T24 and renal carcinoma ACHN cells were treated with PDF (100 μg/ml) alone or the combination of PDF (100 μg/ml) and VC (50 μM) for 72 h, and cell viability was determined by MTT assay. PDF alone and the PDF/VC combination led to a significant cell viability reduction in both T24 and ACHN cells (Figure 5A and B), similar to prostate cancer cells. Additionally, the same study was also performed in non-urological cancer cells, lung cancer A549 and colorectal cancer Caco-2 cells. The results again showed the same significant cell viability reduction in A594 and Caco-2 with PDF alone or the PDF/VC combination (Figure 5C and D). Additionally, the PDF/VC combination induced the higher/greater cell viability reduction than PDF alone in all four cancer cells. Therefore, anticancer effect of PDF by itself or PDF/VC combination is unlikely limited to urological cancers but is rather *universal* to other non-urological cancers as well. Further studies indeed showed that cancer cells, including breast,

stomach, liver, brain, leukemia etc., all resulted in a significant cell viability reduction with PDF alone or PDF/VC combination.[3]

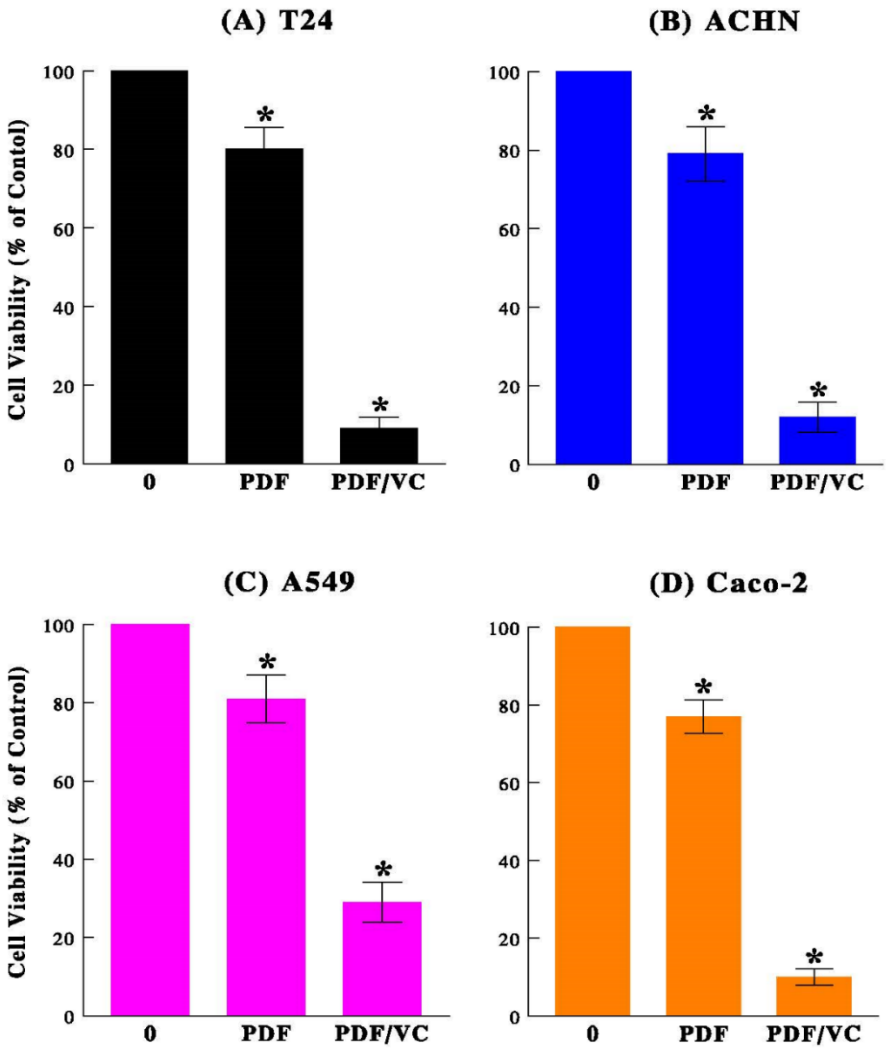

Figure 5. Anticancer effect of PDF or PDF/VC combination on other cancer cells. Four types of cancer cells, bladder cancer T24 **(A)**, renal cell carcinoma ACHN **(B)**, lung cancer A549 **(C)**, and colorectal cancer Caco-2 **(D)** cells, were treated with PDF (100 μg/ml) alone or combination of PDF (100 μg/ml) and VC (50 μM) for 72 h, and cell viability was determined. All data are mean ± SD from three independent experiments (*p <0.05 compared with control).

Chemosensitizing Effect of PDF

There was a possibility of PDF that might have a chemosensitizing effect, capable of improving anticancer activity of chemotherapeutic drugs being clinically used. Those included paclitaxel, 5-fluorouracul, cisplatin (CPL), mitomycin C, gemcitabine, carmustine (BCNU) etc. When these drugs were individually combined with PDF, certain combinations, not all combinations, demonstrated *improved* anticancer activity. For instance, BCNU (50 μM) itself led to a ~50% cell viability reduction in prostate cancer PC-3 cells but nearly 90% reduction was observed when combined with PDF (100 μg/ml) (Figure 6A). Similarly, little change in bladder cancer T24 cell viability with CPL (10 nM) alone resulted in a ~60% cell viability reduction when combined with PDF (Figure 6B). Thus, these results suggest that certain chemotherapeutic drugs could be sensitized with PDF, enhancing anticancer activity (against prostate and bladder cancer cells).

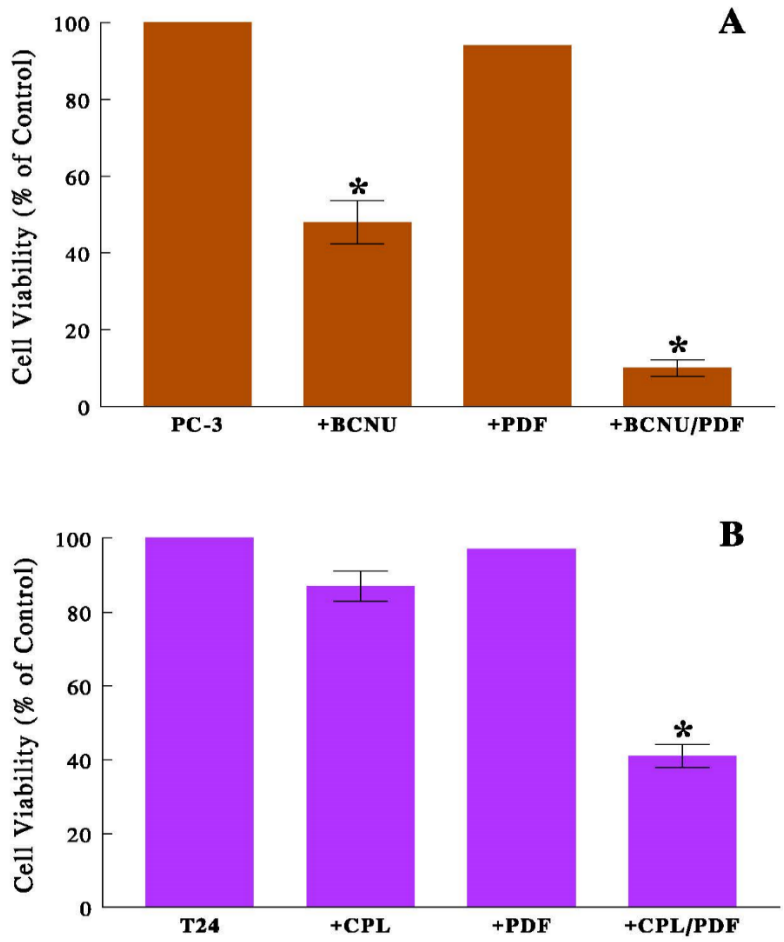

Figure 6. Chemosensitizing effect of PDF. PC-3 cells were treated with BCNU (50 μM) alone or its combination with PDF (100 μg/ml) for 72 h and cell viability was determined **(A)**. Separately, T24 cells were treated with CPL (10 nM) or its combination with PDF (100 μg/ml) for 72 h and cell viability was determined **(B)**. All data are mean ± SD from three separate experiments (*p <0.05 compared with control).

Other Pharmacological Effects of Mushroom Extracts

Besides anticancer effect of PDF, other medicinal/pharmacological effects have been also reported in various mushrooms.[14] Interestingly, PDF may also have antiviral activity against flu viruses, as its antiviral activity on HIV has been confirmed by NCI.[10] Although no organized clinical studies have yet been conducted, the volunteer-based study showed the alleviation of flu symptom, the prevention of turning it into a full-blown flu, a quick recovery (from flu) etc. when patients took PDF. This is believed to be more likely attributed to immunostimulatory activity of PDF.[4] Another bioactive extract isolated from the same maitake is called *SX-Fraction (SXF)*, which showed to have anti-diabetic and hypoglycemic effects. Especially, hypoglycemic effect to lower the serum glucose level was seen in volunteers with type 2 diabetes when they took SXF for 2-4 weeks.[15] This was more likely due to sensitization of insulin receptor (IR) and insulin receptor substrate 1 (IRS-1) with SXF,[15] reactivating the insulin signal transduction pathway to facilitate an uptake of serum glucose by muscle and adipose cells.

In addition, other mushrooms have been shown to possibly prevent Alzheimer's disease and osteoporosis,[16,17] slow down the progression of chronic kidney disease (CKD),[18] weight loss, skin juvenilization[19] etc. Taken together, mushrooms appear to

have the known and unidentified potentials, which may provide us with great health benefits.

DISCUSSION

A variety of medicinal mushrooms have been extensively studied and a number of their pharmacological properties were unveiled. Among them, certain mushrooms with anticancer effect were further investigated for potential therapeutic or clinical utility. For instance, PDF (maitake extract) could be the good candidate for an *unconventional* approach to urological and non-urological cancers. A particular interest is the combination of PDF and VC, which led to nearly complete cell death (<10% cell survival) in urological cancers, especially bladder cancer cells (Figure 5A), implying possible *intravesical* therapy of PDF/VC combination in patients with bladder cancer. Currently, intravesical instillation of *bacillus Calmette-Guerin* (BCG), an attenuated strain of *Mycobacterium bovis*, is the most effective immunotherapy for early bladder cancer.[20] However, it has the limited clinical use, due to potential side effects, and a better regimen with fewer side effects needs to be established.

There are a couple of reasons why the PDF/VC combination may work in intravesical therapy. First of all, PDF and VC are not drugs and safely taken *orally* by humans, and some animal studies using their intraperitoneal injection showed little side effects. Secondly, the *in vitro* study performed in the culture plate/flask is considered to be similar to intravesical therapy taking place within the bladder – both are carried out in a similar fashion or in a *closed system*. In such a closed system, PDF and VC would make a *direct contact* with cancer cells (*in vitro*) or tumors (in the bladder), ultimately leading to apoptosis in bladder cancer cells *in vitro* as shown earlier (Figure 3). Unlike systemic administration of drugs/agents dispersed throughout the body, a direct effect of PDF/VC will be also seen in bladder tumors with intravesical instillation. We thus think that intravesical "PDF/VC" therapy may work well. However, the IRB-approved study and clinical trial must be yet completed prior to its use.

Speaking of apoptosis, *why* is apoptotic cancer cell death clinically relevant or significant? Cell death can be generally categorized in the two distinct pathways: passive *necrosis* or active *apoptosis*.[21] Passive necrosis typically caused by chemotherapy might be considered *random cell murder*. It is a disorganized, chaotic process of death where cancer cells as well as healthy normal cells will be randomly attacked (by drugs) and release toxic cytoplasmic materials through abrupt cell rupture. Those toxic materials will then adversely affect healthy neighboring or adjacent cells, causing the secondary inflammation. This is a major problem with necrotic cell death and is responsible for the unwanted side effects (due to chemotherapy). By contrast, apoptosis, which can be defined as "cell suicide", is a highly organized biochemical process.[21] In this form of meticulously orchestrated death, only specific cells are programmed to die or commit "suicide" *without* cell rupture or release of cytotoxic materials, thereby leaving all neighboring cells intact. This is the primary advantage of apoptosis, and the reason why, if regimens specifically triggering the targeted apoptosis of cancer cells become available, they may represent a great advance over chemotherapeutic regimens in terms of reducing side effects. It is thus important to search and identify other natural agents with apoptosis-inducing potential.

Interestingly, induction of apoptosis in our study appears to be triggered by OXS through the PDF/VC combination (Figure 4), but OXS has been also reported to often induce apoptosis in cancer cells.[22,23] If it were the case, cancer cells would be killed by OXS but what would happen to normal (non-cancerous) cells because OXS is infamously known to randomly attack normal and cancer cells alike. There is yet another interesting fact that cancer cells are shown to be *more*

susceptible/vulnerable to OXS than normal cells.[24] In other words, even weak OXS (exerted by PDF/VC combination) could severely damage or kill cancer cells but may not be strong/severe enough to harm normal cells. As a result, only cancer cells could be exclusively killed by (weak) OXS but normal cells remain intact. The exact reason has not been fully elucidated, but a number of studies/reports indicated that cancer cells had weak or little *antioxidant enzymes* (catalase, superoxide dismutase etc.).[25,26] It is then plausible that the lack of such an antioxidative defense may account for a vulnerability of cancer cells to OXS, whereas normal cells have the strong defense against OXS. This is one possible explanation and more studies are yet required for further elucidation. Meanwhile, an approach of utilizing OXS against cancer cells has been commonly accepted as one of anticancer strategies and a number of such research are currently underway.

Lastly, another clinical application of PDF could be used as an adjuvant agent for chemotherapy. PDF demonstrated to enhance anticancer activity of certain chemotherapeutic drugs (Figure 5), suggesting a chemosensitizing effect. Although PDF may *selectively* sensitize drugs, it could be yet useful as an adjuvant agent in a current chemotherapy protocol. Instead of multidrug combinations that will inevitably worsen side effects, this "drug and PDF" combination may improve the drug efficacy with little side effects. Furthermore, anticancer effect of PDF alone or PDF/VC combination appears to be *universal*, not cancer-specific. Thus, natural products, such as PDF, with anticancer and chemosensitizing effects are indeed valuable to us, and the right combinations of *drug* and *non-drug* (e.g. PDF) should be also actively and extensively explored.

CONCLUSION

This study demonstrates anticancer effect of a maitake mushroom extract (PDF) on urological cancer cells. PDF was also found to be synergistically potentiated with VC, greatly reducing cell viability. Such a combination of PDF and VC appeared to induce OXS, which might trigger and ultimately induce apoptosis in cancer cells. Moreover, since PDF was capable of enhancing anticancer activity of certain drugs, exhibiting a chemosensitizing effect, it could be possibly used as an adjuvant agent for chemotherapy. These findings thus validate the significance of maitake and other mushrooms in urological diseases/disorders. However, this yet represents only one of numerous pharmacological properties of various mushrooms, which would undoubtedly benefit our health. More studies on mushrooms and other natural products are warranted.

Declaration by Authors

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