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Potential Anticancer Effect of Bioactive Extract of Monk Fruit (*Siraitia grosvenori*) on Human Prostate and Bladder Cancer Cells

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Abstract

Prostate and bladder cancers are the two prevalent urological cancers, and several therapeutic options are currently available but the outcomes have not been satisfactory. To find the better therapeutic option, we investigated if the bioactive extracts of monk fruit, *mogrosides*, with potential anticancer activity might have anticancer effect against prostate and bladder cancer cells. Four of commercial products made of mogrosides known as Lakanto® (LKT) products, LK1, LK2, LLE, and MOG, were then tested. A dose-dependent study at given concentrations of four products showed that LK1 and LK2 had little effects, while LLE and MOG showed a significant cell viability reduction in both PC-3 and T24 cells. To explore the anticancer mechanism of such products, cell cycle analysis was first performed. Such analysis revealed that LLE and MOG, not LK1 and LK2, led to a G_1 cell cycle arrest. Potential induction of endoplasmic reticulum (ER) stress was next examined because it is known to be linked to a cell cycle arrest. The three key regulators involved in ER stress were all up-regulated with LLE or MOG, indicating induction of ER stress. As ER stress is also known to induce apoptosis, this possibility was tested. The two apoptotic regulators were modulated in a specific manner with LLE or MOG, indicating induction of apoptosis. Lastly, to validate anticancer effect of LLE or MOG, anticancer effect of four chemotherapeutic drugs was also assessed in comparison with that of LLE/MOG. None of drugs had any effects but two products showed significant anticancer effect. In conclusion, two monk fruit products, LLE and MOG, demonstrated anticancer activity against PC-3 and T24 cells, significantly reducing cell viability and ultimately inducing apoptosis. Therefore, these two LKT products with few side effects may have clinical implications in the treatment of urological cancers.

Keywords

Monk Fruit, Mogroside, Anticancer, Prostate Cancer, Bladder Cancer, Lakanto

1. Introduction

Prostate cancer is the most common malignancy in elderly men with the estimated 270,000 new cases in 2022 and the second-leading cause of male cancer death with the estimated 34,500 deaths in the United States [1]. The initial response to primary hormonal therapy usually shows a good prognosis with remission lasting 1 - 2 years [2]. However, cancer cells become somehow resistant to this therapy in a few years, progressing to a state of castration resistant prostate cancer (CRPC) with metastatic potential [2] [3]. Once it becomes metastatic CRPC, unfortunately there are little effective treatment available and patient has a poor prognosis with a limited survival rate (~14 months) [4]. Nevertheless, it is true that several new therapies [5], such as *immunotherapy* using vaccines, checkpoint inhibitors etc., *targeted therapy* with PARP [poly (ADP-ribose) polymerase] inhibitors, monoclonal antibodies etc., *combination therapy* with hormone therapy and immunotherapy etc., are clinically evaluated. Unfortunately, as it will need more times and trials to obtain the reliable data, the outcomes have not been fully assessed yet.

Bladder cancer is the second leading urologic malignancy next to prostate cancer with estimated 82,000 new cases and 17,000 deaths this year [1]. The majority (90%) of bladder cancers are urothelial cell carcinoma with 80% presenting as superficial cancer, 15% as invasive cancer, and 5% as metastatic disease [6]. Although endoscopic transurethral resection is a primary therapy, 60% - 70% of patients will yet recur and about 25% progress to invasive disease within 5 years [7]. Moreover, intravesical administration of *Bacillus Calmette-Guerin* (BCG), an attenuated strain of *Mycobacterium bovis*, is currently the most effective immunotherapy for superficial bladder cancer and carcinoma *in situ* (CIS) [8]. However, the therapeutic benefits of BCG are sometimes outweighed by its severe side effects, limiting its use in clinical practice [8] [9].

Therefore, these two common urological cancers urgently command the more effective and safer therapeutic options without further delay.

Besides various conventional therapies, we have been working on *natural products* with anticancer activity as an alternative approach. Those include phenolic acid, flavonoids, anthocyanins etc., which mostly come from fruits, flowers, seeds, vegetables, mushrooms etc. [10] [11] [12] [13]. We believe that they may offer anticancer activity with the alternative, improved, and safer regimens against various cancers. We then came across the bioactive extracts of monk fruit (*Siraitia grosvenori*) [14] whose name is believed to come from an anecdote that Chinese Buddhist monks have used this fruit as a sweetener for

teas or cooking. It has been also used as a folk medicine for cough, sore throat, bronchitis etc. [15]. Active compounds of monk fruit are "mogrosides", terpenoid glycosides (**Figure 1**) [14] [16], which have been shown to have medicinal/pharmacological properties, including anticancer, anticarcinogenic, antioxidant, anti-diabetic, anti-inflammatory activities etc. [17]-[22]. In addition, mogrosides have been widely used for commercial dietary products as the US Food and Drug Administration (FDA) had approved them for Generally Recognized As Safe (GRAS) for its intended use as a food sweetener [23]. Particularly, one of several derivatives, *mogroside V* (*MOG*), is the most abundant and commercially used in food products [16] known as Lakanto® (LKT). However, these MOG-based LKT products have not yet been fully studied in terms of anticancer activity.

Accordingly, it was of our interest to investigate if four different LKT products would have anticancer activity against bladder and prostate cancer cells *in vitro*. More details are described and the interesting findings are also discussed herein.

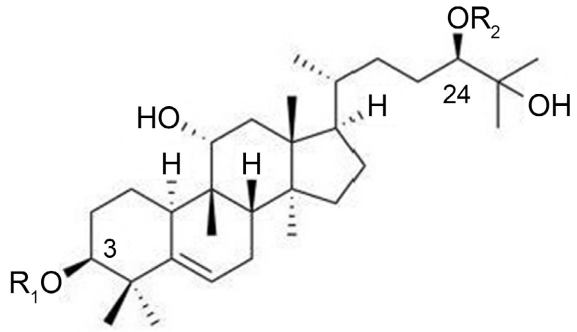
2. Materials and Methods

2.1. Cell Culture

Human prostate cancer PC-3 and bladder cancer T24 cells were obtained from the American Type Culture Collection (ATCC; Manassas, VA). They were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum, penicillin (100 U/ml), and streptomycin (100 μg/ml). Possible anticancer effect of four LKT products, *LK1*, *LK2*, *LLE*, and *MOG*, were examined on these cancer cells. Briefly, all LKT products are the proprietary products with different physical forms, containing the varying amounts of MOG—LK1 is a coarse powder with relatively low MOG content; LK2 is a fine powder with 50% MOG; LLE is a liquid form with MOG; and MOG is a highly purified MOG powder. All products were generous gifts from a manufacturer (Saraya Co., Ltd., Osaka, Japan). Experimentally, their anticancer effect was determined by cell viability (MTT) assay described below.

2.2. MTT (Cell Viability) Assay

Anticancer activity is defined by cell viability showing the % of viable cell number in treated-cells relative to that in control cells (100%). PC-3 and T24 cells were separately seeded in the 6-well plate (2 ml/well) at the initial cell density of 2×10^5 cells/ml and cultured with varying concentrations of four LKT products for 72 h. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide) reagent (1 mg/ml) was added to each well in the plate, which was then incubated for 3 h in an incubator at 37˚C. Dimethyl sulfoxide (DMSO) was added to the plate and absorbance of samples was read in a microplate reader. Cell viability was then expressed by the % of sample readings of optical density (OD) relative to the control reading (100%)—"the greater cell viability *reduction*, the *greater* anticancer activity".



Mogroside IIe: R_0=β-D-glu, R_2=β-D-glu
Mogroside III: R_0= β-D-glu, R_2=β-D-glu-(1→6) β-D-glu
Mogroside IIIe: R_0=β-D-glu, R_2= =β-D-glu-(1→2) β-D-glu
Mogroside IV: R_0=β-D-glu-(1→6) β-D-glu, R_2=β-D-glu-(1→2) β-D-glu
Mogroside V: R_0=β-D-glu-(1→6) β-D-glu, R_2=β-D-glu-(1→6) β-D-glu
(1→2) β-D-glu

Figure 1. Structures of mogroside derivatives.

2.3. Cell Cycle Analysis

PC-3 and T24 cells treated with given products for 72 h were harvested and subjected to cell cycle analysis. Cells (~1 × 10^6 cells) were first resuspended in propidium iodide solution, followed by a 1-h incubation at room temperature. Approximately 10,000 nuclei from each sample were then analyzed on a FACScan flow cytometer (Becton-Dickinson, Franklin Lakes, NJ), equipped with a double discrimination module. CellFit software was used to quantify cell cycle compartments to estimate the % of cells distributed in the different cell cycle phases (G_1, S, and G_2/M).

2.4. Western Blot Analysis

Whether any of four products would induce endoplasmic reticulum (ER) stress linked to apoptosis (programmed cell death) was examined. Briefly, an equal amount of proteins (10 μg) from control and product-treated cell lysates was resolved by 10% SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) and transferred to a nitrocellulose membrane (blot). The blot was first incubated for 90 min with the primary antibodies (Santa Cruz Biotechnology, Santa Cruz, CA) against glucose-regulated protein 78 (GRP78), activating transcription factor 4 (ATF4), and C/EBP homologous protein (CHOP) for ER stress and also bcl-2 and Bax for apoptosis, followed by incubation with the appropriate secondary antibody conjugates (Santa Cruz Biotechnology) for 30 min. After discarding antibodies, the specific immunoreactive proteins (GRP78, ATF4, CHOP, bcl-2, and Bax) were then detected by chemiluminescence (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, MD) on an X-ray film (autoradiography).

2.5. Statistical Analysis

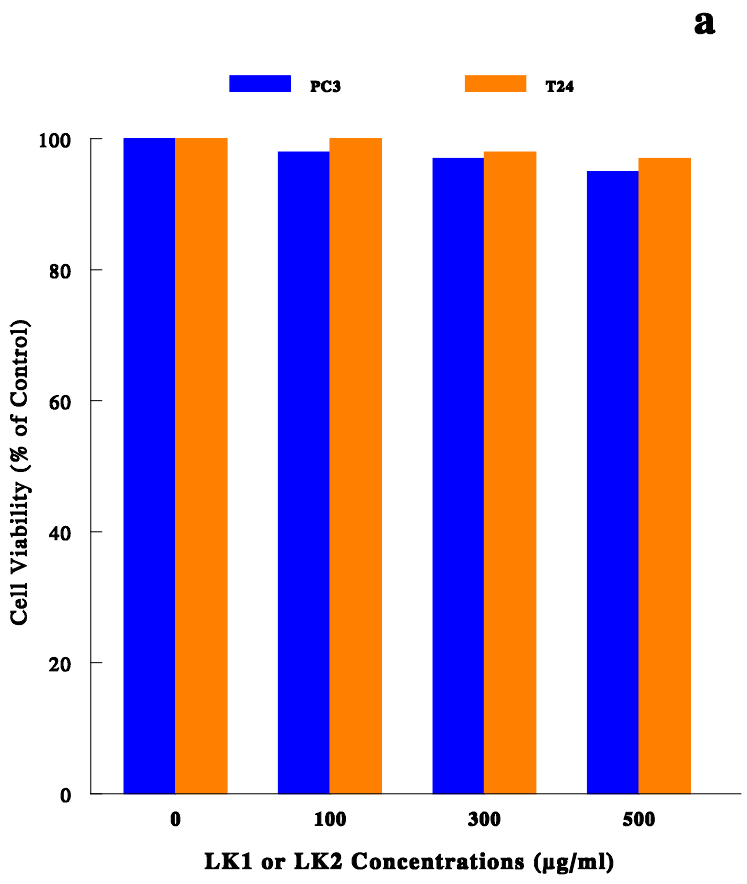
All data are presented as the mean ± SD (standard deviation), and statistical dif-

ferences 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.

3. Results

3.1. Effects of Four LKT Products on Cell Viability of PC-3 and T24 Cells

Prostate cancer PC-3 and bladder cancer T24 cells were treated with the varying concentrations of four different LKT products described earlier, LK1, LK2, LLE, and MOG. Cell viability was determined at 72 h by MTT assay and the results showed that both LK1 and LK2, up to 500 μg/ml, had little to no effects on cell viability (**Figure 2(a)**). In contrast, LLE ≥ 2 μg/ml led to a 30% - 41% cell viability reduction or anticancer effects on PC-3 and T24 cells (**Figure 2(b)**). The fourth product was tested at the relatively high concentrations (0 - 2000 μg/ml) because *purified* MOG has been reported to require the high concentrations (>1000 μg/ml) to be effective [18]. Although little effects were seen up to 1000 μg/ml of MOG, a significant reduction became apparent at 1500 μg/ml and down to 20% - 26% ($P < 0.05$) with 2000 μg/ml in both cancer cells (**Figure 2(c)**). Thus, LLE and MOG have anticancer effect on PC-3 and T24 cells, whereas LK1 and LK2 have little effects and were omitted from the rest of our study.



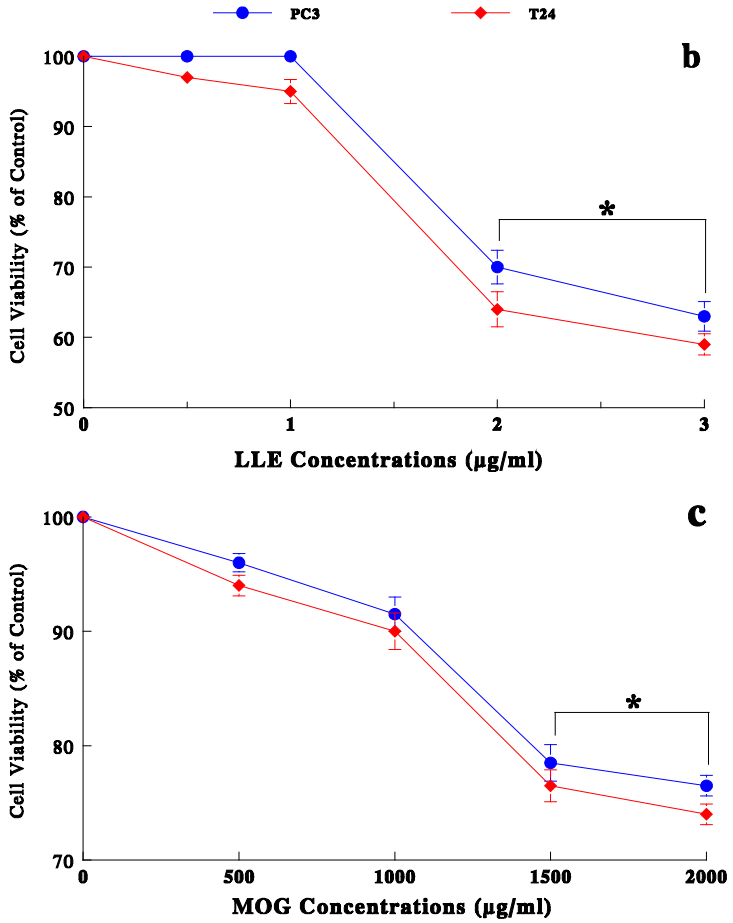


Figure 2. Effects of four LKT products (LK1, LK2, LLE, and MOG) on cell viability. PC-3 and T24 cells were treated with LK1 or LK2 (0 - 500 μg/ml), LLE (0 - 3 μg/ml), or MOG (0 - 2000 μg/ml) for 72 h. All data of MTT assay were calculated by the mean ± SD (standard deviation) from three independent experiments. Cell viability of LK1 or LK2-treated (a), LLE-treated (b), or MOG-treated (c) cells were then expressed by the % of viable cell numbers relative to that in control cells (100%) (*P < 0.05 compared with respective controls).

3.2. Effects of LLE and MOG on Cell Cycle

To have a better understanding of the anticancer mechanism(s) of LLE and MOG, we looked into their possible effects on cell cycle that would regulate cell division and cell growth [24]. PC-3 and T24 cells were treated with LLE (3 μg/ml) or MOG (2000 μg/ml) for 72 h and subjected to cell cycle analysis. Compared to respective control cells, the G_1-phase cell population *increased* while the S-phase population *decreased* significantly in both cancer cells treated with LLE or MOG (**Figure 3**). For instance, the G_1 population *increased* from 47.7% in PC-3 (control) cells to 67.2% in those treated with LLE, while the S population *decreased* from 38.4% (control) to 23.1% (LLE-treated) (**Figure 3**). The similar trend was also observed in T24 cells as shown. This accumulation of cells in the G_1 phase is known as a G_1 cell cycle arrest [25], subsequently leading to the growth cessation and cell viability reduction. Thus, LLE and MOG may primari-

ly target a G_1 phase of cell cycle, inducing a G_1 cell cycle arrest.

3.3. Induction of Endoplasmic Reticulum (ER) Stress with LLE and MOG

It has been documented that a cell cycle arrest resulted from endoplasmic reticulum (ER) stress [26], so that whether LLE and MOG may induce ER stress was examined. PC-3 and T24 cells treated with LLE (3 μg/ml) or MOG (2000 μg/ml) for 72 h were analyzed for three key regulators involved in ER stress, GRP78, ATF4, and CHOP [27], using Western blots. Such analysis revealed that the expressions of all three proteins were significantly elevated with LLE and MOG (compared to those in control), although those with LLE were more enhanced than those with MOG. Virtually, the same protein patterns/results were seen in both cancer cells (**Figure 4**). Since the increased expression or up-regulation of these three regulators is indicative of ER stress [28], LLE and MOG appear to induce such ER stress, presumably leading to a G_1 cell cycle arrest.

3.4. Induction of Apoptosis with LLE and MOG

As it has been shown that ER stress would often induce apoptosis (programmed cell death) [29], this possibility was then tested. Cells treated with LLE (3 μg/ml) or MOG (2000 μg/ml) for 72 h were subjected to Western blot analysis for the two specific apoptotic regulators, bcl-2 and Bax. Compared to respective control cells, the bcl-2 expression was *down*-regulated (decreased) while the Bax was *up*-regulated (increased) with LLE or MOG treatment in both PC-3 and T24 cells (**Figure 5**). Since bcl-2 is an anti-apoptotic regulator and Bax is a pro-apoptotic regulator [30], the protein profile with *decreased bcl-2* and *increased Bax* (with LLE or MOG) indicates induction of apoptosis. Thus, LLE or MOG appears to ultimately induce apoptosis in these cancer cells.

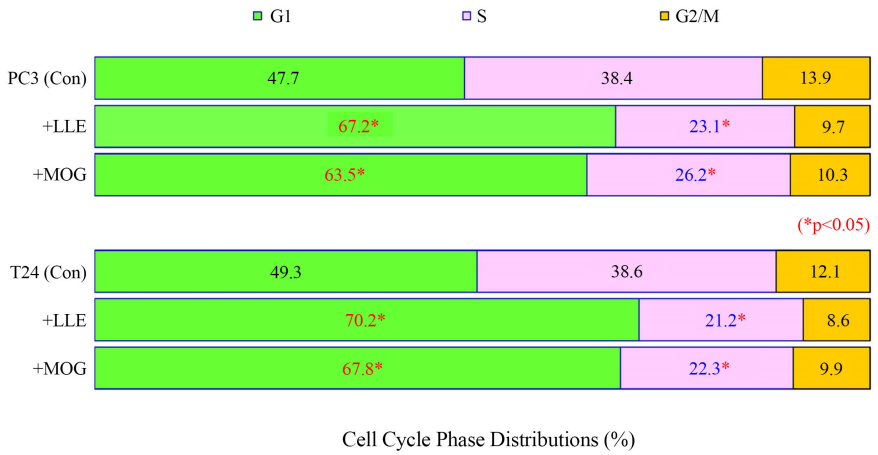


Figure 3. Cell cycle analysis. PC-3 and T24 cells were treated with LLE (3 μg/ml) or MOG (2000 μg/ml) for 72 h and subjected to cell cycle analysis. The cell distribution (%) of each cell cycle phase (G_1, S, and G_2/M) in PC-3 and T24 cells is illustrated. Only the mean values (without SD) are shown, although % of G_1 and S phases in cells treated with LLE or MOG are statistically (*P < 0.05) different from % in respective controls.

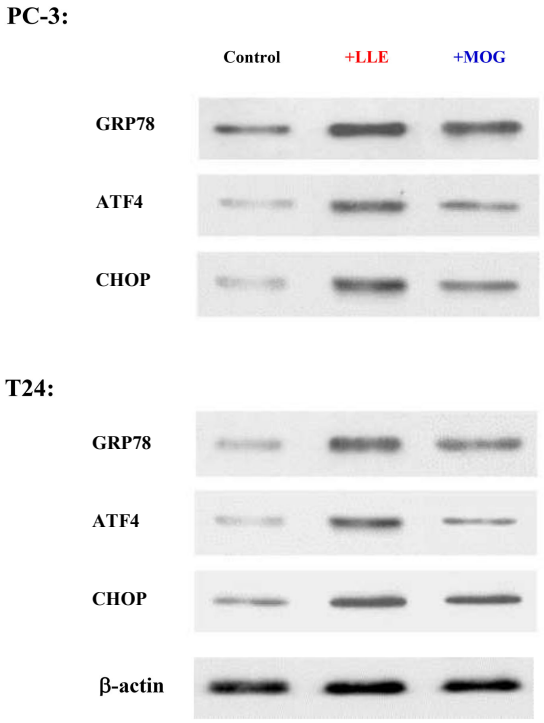


Figure 4. Induction of endoplasmic reticulum (ER) stress with LLE or MOG. Cells treated with LLE or MOG for 72 h were analyzed for three factors related to ER stress, GRP78, ATF4, and CHOP, using Western blots. The protein expressions of these factors in LLE- or MOG-treated cells, compared to those in control cells, are shown in autoradiographs. Beta-actin is also included as an internal loading control.

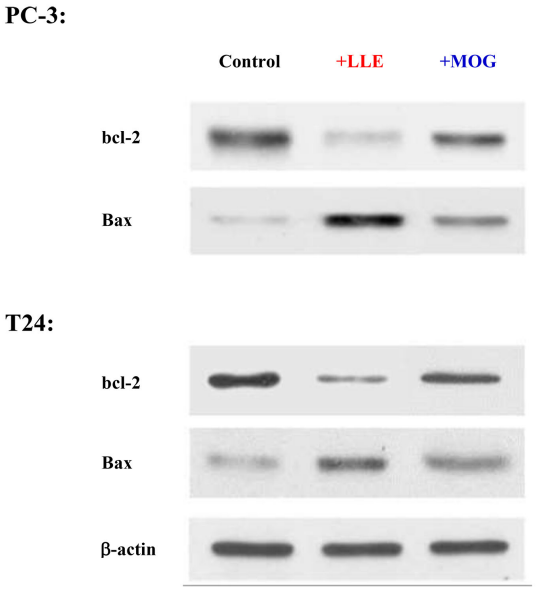


Figure 5. Induction of apoptosis with LLE or MOG. Cells treated with LLE or MOG for 72 h were subjected to Western blot analysis for two apoptotic regulators, bcl-2 and Bax. Autoradiographs of the protein expressions of bcl-2 and Bax in control, LLE-treated, or MOG-treated cells are shown with β-actin as a loading control.

3.5. Anticancer Effect of LLE/MOG Validated by Compared with Chemotherapeutic Drugs

Additionally, anticancer effect of LLE or MOG was validated by comparing with that of typical chemotherapeutic drugs clinically used (with the physiologically-achievable concentrations). PC-3 and T24 cells were separately treated with four drugs, 5-fluorouracil (5FU, 1 μg/ml), cisplatin (CPL, 100 nM), doxorubicin (DOX, 10 ng/ml) or cyclophosphamide (CyP, 100 μg/ml), or two products, LLE (3 μg/ml) or MOG (2000 μg/ml), and cell viability was determined at 72 h. The results showed that none of chemotherapeutic drugs at given concentrations had any significant effects on cell viability, whereas both LLE and MOG led to a significant cell viability reduction (24% - 41%, $P < 0.05$) in PC-3 and T24 cells (Figure 6). Therefore, the two LKT products, LLE and MOG, appear to have better/higher anticancer activities on PC-3 and T24 cells than those four chemotherapeutic drugs.

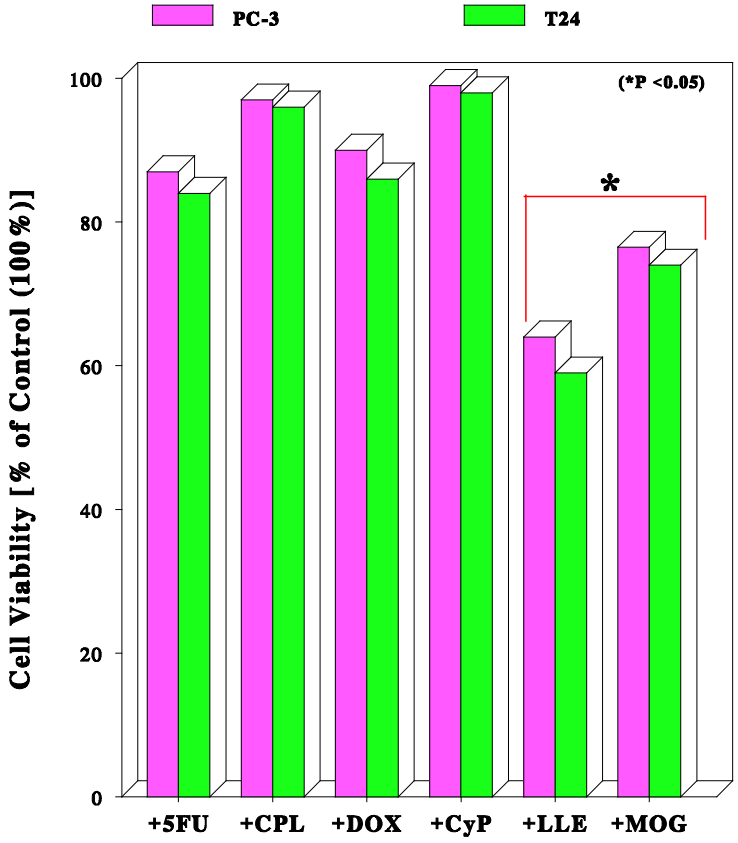


Figure 6. Validation of anticancer effect of LLE or MOG in comparison with chemotherapeutic drugs. Cells were treated individually with four different chemotherapeutic drugs, 5 FU (1 μg/ml), CPL (100 nM), DOX (10 ng/ml), or CyP (100 μg/ml), or also treated with LLE (3 μg/ml) or MOG (2000 μg/ml). Cell viability of all treated cells was determined at 72 h and expressed by the % of viable cell numbers relative to that in control cells (100%). The data were calculated by the mean ± SD from three separate experiments (*$P < 0.05$ compared with respective controls).

4. Discussion

To find the safer and improved therapy for prostate and bladder cancers, we studied an interesting natural product with *anticancer* activity, which might work on these cancers. It is called *mogroside V* (*MOG*) [16], one of mogroside derivatives isolated from monk fruit, which has been reported to have anticancer activity [17]. MOG has been primarily used in the commercial food products as the Lakanto® (LKT) products because it gives such high sweetness, *i.e.*, 200 - 350 times sweeter than sucrose [17]. With our best knowledge, anticancer effect of those LKT products has not been fully studied yet. Since they are easily available and could be used/consumed daily, they would be rather beneficial to people if they indeed have such biological activity. We thus investigated their possible anticancer activity against prostate cancer PC-3 and bladder cancer T24 cells.

Four representatives of LKT products, LK1, LK2, LLE, and MOG, were chosen in this study, and we found that two products, LLE and MOG, were capable of significantly ($P < 0.05$) reducing cell viability in PC-3 and T24 cells, suggesting anticancer activity (**Figure 2(b)** and **Figure 2(c)**). However, two other products, LK1 and LK2, had little to no such activity (**Figure 2(a)**).

We then explored the anticancer mechanism of LLE and MOG, focusing on cell cycle first. Such study showed that treatment of LLE or MOG led to a G_1 cell cycle arrest [25] where cells accumulated in the G_1 phase, due to cells being prevented from entering to the next S phase (**Figure 3**). As a result, cell cycle will not be completed (required for cell division and growth), eventually leading to the growth cessation and cell viability reduction. Hence, a cell cycle arrest induced with LLE and MOG may account for anticancer mechanism.

We also found that both PC-3 and T24 cells treated with LLE or MOG resulted in the *up-regulated* expression of ER chaperons, GRP78, ATF4, and CHOP (**Figure 4**), indicating induction of endoplasmic reticulum (ER) stress [28]. This was expected because under ER stress, protein synthesis is decreased/halted to restore ER homeostasis and subsequently induces a G_1 cell cycle arrest [26]. Induction of ER stress with LLE or MOG may primarily account for the resulting cell cycle arrest we have observed. Additionally, if ER stress is too severe to restore ER homeostasis, it then follows the cell death (apoptosis) pathway by further activating ATF4 and CHOP [28]. In fact, we also confirmed that PC-3 and T24 cells treated with LLE or MOG followed the apoptotic pathway, evidenced by the down-regulated bcl-2 with the up-regulated Bax proteins (**Figure 5**). It is thus plausible that LLE and MOG could act as apoptotic inducers by inducing severe (irreversible) ER stress, followed by a G_1 cell cycle arrest, and ultimately leading to apoptosis in these cancer cells.

Moreover, anticancer activity of LLE and MOG was validated using four common chemotherapeutic drugs (5FU, CPL, DOX, and CyP) clinically used today as references. Such study showed that all drugs had little anticancer activities, while LLE and MOG demonstrated anticancer effect with a significant cell viability reduction (**Figure 6**). However, this finding should be carefully inter-

preted. Although all drug concentrations used were physiologically achievable (with little effects), whether concentrations of LLE and MOG could be physiologically achievable yet requires additional study using animals. Despite these drugs being ineffective in this *in vitro* study, they are indeed clinically used, so that LLE and MOG may have a good potential to demonstrate actual efficacy on animals and humans as they have shown it here *in vitro*.

Speaking of the effective concentrations as well as physiologically-achievable concentrations of LLE and MOG, they are quite different as only 3 μg/ml of LLE and 2000 μg/ml of (purified) MOG are required to be most effective. Actually, there is also a physical difference between them. LLE is originally in a *liquid* form and much *less* purified, while MOG is a *highly* purified powder form. LLE with less purity would indicate that it contains some other components (of monk fruit), which may cooperatively work with MOG to enhance anticancer activity. It could be then speculated that anticancer activity of MOG may require *something* for further or full activation. Initially, LKT products were commercially sold as sweetener and their *sweetness* primarily comes from MOG, so that the higher the MOG is purified, the higher the sweetness is given way. In other words, *purity* of MOG could be essential to sweetness (of LKT products), but anticancer activity or biological activity of MOG may not substantially depend on its purity. Instead, MOG may rather require something like a *co-factor* working cooperatively to fully activate its anticancer activity. If this hypothesis were valid, that may explain why *less purified* LLE (with a co-factor) could have better or higher anticancer activity than that of highly purified MOG. It will be then worthwhile unveiling such an unidentified factor/component, which might be coexisting with MOG in this particular preparation of LLE. In the meantime, finding physiologically-achievable concentrations of LLE and MOG has to rely on the animal study.

After all, this is the *in vitro* study and further studies on LLE and MOG are required for addressing their actual efficacy, dosages, and safety in animals (*in vivo*). Hence, our next study will focus on antitumor activity of these products on tumor-bearing mice.

5. Conclusion

In this study, two of four Lakanto® products, LLE and MOG, demonstrated anticancer activity. They are capable of reducing cell viability in PC-3 and T24 cells and ultimately inducing apoptosis. Therefore, these products containing MOG of monk fruit may have clinical implications as a viable option for patients with urological cancers. Further studies are warranted.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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