ANTI-CANCER EFFECTS OF TAMARIND SEED AND PULP EXTRACTS FROM *TAMARINDUS INDICA L.*

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SUMMARY

Although diagnostic methods and medications have been significantly improved throughout the years, cancer still stands as one of the most concerning health-related problems worldwide. Compared to conventional anticancer therapies which hold many adverse effects, plant derivatives are preferred as they can minimize these disadvantages. Extracts of tamarind have been previously proved to have an antitumor effect, however, the mechanism underlying this phenomenon has not clearly understood. Hence, this study aimed to evaluate the cytotoxic effects of the ethanolic and methanolic extracts of tamarind seed and pulp from *Tamarindus indica* L. on two cancer cell lines A549 and HepG2 and a cell line RAW 264.7, as well as to discover whether apoptosis contributed to the death of cancer cells. The results revealed that tamarind seed and pulp extracts effectively inhibited the proliferation of cancer cells. Among 4 types of tamarind extracts, methanolic seed extract (MetOH_S) exerted the greatest inhibition on the cell viability. MeOH_S reduced the viability of A549 cells to 86% at 4 μg/mL ($p<0.01$). Interestingly, the multinucleated morphology was dominant compared to the nuclear morphology of apoptosis in the A549 cells treated with 16 μg/mL and 256 μg/mL MetOH_S. Thus, MetOH_S was shown to have the strongest antineoplastic outcome, suggesting another mechanism: mitotic catastrophe leading to autophagy. Further studies are needed to purify compounds from methanolic extracts and clarify their anticancer effects.

Keywords: Apoptosis, cell cytotoxicity, *Tamarindus indica*, tamarind extract.

INTRODUCTION

In 2019, WHO (World Health Organization) estimated that cancer ranked in the top two leading causes of death for people under 70 years old in 55 of 183 countries, just after stroke and coronary heart disease. Cancer refers to a large group of diseases that can affect any part of the body. One of the key characteristics for defining cancer is the overgrowth of abnormal cells that can proliferate beyond their usual boundaries. The danger of these cells comes from their ability to take over the adjacent parts and spread out to the whole body at a later stage, in a process called metastasis (World Health Organization, 2021).

One important hallmark of cancer is its resistance to cell death (Hanahan and Weinberg, 2011). Hence, inducing programmed cell death (PCD) is a potential target for cancer therapy. Based on the changes in morphology, triggering signals, and which downstream caspase that it activates, PCD can be divided in three main subcategories: apoptosis, autophagy, and programmed necrosis. In apoptosis, cells undergo morphological alterations including shrinkage, chromatin condensation and blebbing of plasma membrane. Eventually, this process leads to the formation of apoptotic bodies, which will be removed without causing inflammatory response. Meanwhile, autophagy is a conserved intracellular recycling system of various cytoplasmic components and a cellular self-degradation process that maintains metabolism and homeostasis. The last PCD is programmed necrosis, which occurs when there are errors in the apoptotic machinery, or when cells suffer from severe stress and cannot follow apoptotic process. In contrast to regular necrosis that involves swelling of organelles, cells in programmed necrosis die in an ordered and orchestrated manner (Mishra *et al.,* 2018).

Despite advances in medical technology, the treatment of many types of cancer still depends heavily on traditional methods, such as surgery, chemotherapy, radiotherapy, or a combination of these. Furthermore, in the later stages of cancer, chemotherapy is the most frequently used treatment (American Cancer Society, 2019). Although it results in cancer treatment, most chemotherapeutic agents have many adverse effects on patients, including anemia (Groopman and Itri, 1999), nausea, vomiting, diarrhea, constipation (Gibson, Keefe, 2006), organ damage (Thatishetty *et al.,* 2013), and hair loss (Yun, Kim, 2007). Moreover, the cancer cells seem to develop resistance against the old drugs that have been used for a long time, which is also the main cause of failure in the treatment of cancer with chemotherapeutic drugs (Liu, 2009). Hence, the demand for other substitutes with fewer side effects has become more urgent than ever. The natural compounds from plants appear to be promising candidates for improvement.

Tamarindus indica L., also known as tamarind, is a tropical plant found in many regions of the world. Its application in medicine is various. Any part of the tree can be used to treat diseases and conditions: tamarind fruit can be used as a laxative; bark, and root can be applied to relieve abdominal pain, pose anti-bacteria characteristics, aid in wound healing; seed extract has positive effects in the treatment of peptic ulcer, cancer and on nerve repair and cardiovascular system, as well as anti-oxidant and anti-diabetic properties; and leaves have been shown to protect the liver (Kuru, 2014). In the current study, anti-cancer effects of ethanolic and methanolic extracts of tamarind seeds and pulp on several cancer cell lines, including A549 (lung carcinoma) and HepG2 (hepatocellular carcinoma) were investigated. At the same time, the cytotoxic effect of these extracts on macrophage cells was studied on the RAW 264.7 cell line. Furthermore, the possibility to induce apoptosis, as well as gene expression changes relating to apoptosis of these extracts, were also examined.

MATERIALS AND METHODS

Materials

A549, HepG2, and RAW 264.7 were purchased from ATCC (American Type Culture Collection, Manassas, VA, USA). DMEM was purchased from Cytiva ((South Logan, Utah, USA). Penicillin/streptomycin, trypsin–EDTA, fetal bovine serum (FBS), thiazolyl Blue Tetrazolium Bromide 98% (MTT powder) were purchased from Sigma- Aldrich (St. Louis, MO, USA). DMSO (Dimethyl Sulfoxide) 99.9%, Hoechst 33342 solution, DNA Gel Loading Dye (6X) were purchased from Thermo Fisher Scientific™ (Waltham, Mass, USA). Easy-RED™ Total RNA Extraction Kit, Maxime™ RT PreMix (Random Primer), RedSafe™ Nucleic Acid Staining Solution were purchased from iNtRON Biotechnology (Seongnam, Kyonggi-do, South Korea).

Preparation and extraction of tamarind pulp and seeds

Tamarinds were dried in 4 hours at 70°C and then cooled down to room temperature. The seeds and pulp of tamarind were manually separated from the peel. Pulp was continued to be dried in 3 hours at 60°C. Seeds were removed from the brown outer layer by hands. The pulp and seeds were then blended into fine powder and sieved through a 0.18 mm sieve. Tamarind pulp or seed powder was then dissolved in methanol or ethanol in falcon tubes. The mixtures were settled overnight at room temperature. Subsequently, the precipitated fraction at the bottom of the tube was removed. The final tamarind pulp and seed extracts (TSP and TSE) in methanol or ethanol were obtained by concentrating the leftover solution using a rotary evaporator.

Cell culture

Cells were transferred into petri dishes and cultured with fresh DMEM/F-12 medium containing 10% of fetal bovine serum (FBS) and 1% of penicillin-streptomycin. The cultured dishes were placed in an incubator at 37°C and 5% CO_2. The culture medium was replaced with fresh medium every three days. When cells reached almost confluence density, cells were counted and then seeded at a density of $2x10^4$ cells/well in a 96-well plate.

MTT assay

Methanol and ethanol extracts of tamarind seeds and pulp were tested for their cytotoxic effect via MTT assay. After seeding the cells into a 96-well plate at a density of 2 × 104 cells/well, the cells were incubated in an incubator for 24 h. Next, cells were treated with the prepared extracts at different concentrations of 1, 4, 16, 64, 256 and 1024 µg/mL (repeated 3 times for each concentration), followed by another 1 or 3 days of incubation at 37℃ in a humidified CO_2 incubator. After that, the old culture medium in each well was removed, and MTT working solution (5 mg/mL) was added. The cells were further incubated for 4 hours before the old medium was replaced with DMSO to dissolve formazan crystals. The plate was then placed on a microplate reader at 570 nm to record the absorbance of the samples. Cell viability was calculated using the following equation:

Cell viability = $\frac{OD\ treated\ sample}{OD\ control\ (untreated)}$ x 100%

DNA (Hoechst) staining assay

Hoechst staining was used to determine the effect of the tamarind pulp and seed extracts on apoptotic cell death. Before staining, cells were washed with PBS two times and then fixed for 30 minutes. Hoechst dye stock solution was diluted at a ratio of 1:2000 in PBS to prepare Hoechst staining solution. After fixation, the cells were incubated with Hoechst staining solution for 15 minutes. Finally, the staining solution was removed and the cells were washed with PBS before being examined under a fluorescent microscope.

Statistical Analysis

The data are shown as the mean ± standard deviation (SD) for the MTT assay. Ordinary one-way analysis of variance (ANOVA) test was performed in GraphPad Prism 8 software to analyze the differences between the control and the treated samples. p-values < 0.05 were considered statistically significant.

RESULTS

Cytotoxic effect of ethanolic and methanolic extracts of tamarind pulp and seeds on cancer cell lines

The cytotoxic effect of ethanolic and methanolic extracts of tamarind pulp and seeds on A549 and HepG2 cell lines were examined by MTT assay. As indicated in Figure 1, on the A549 cell line, after 1 day of treatment, tamarind seed extracts (TSE) showed no significant difference between the control and treated group at concentrations lower than 64 µg/mL. However, at higher concentrations of 256 µg/mL and 1024 µg/mL, both EtOH_S and MeOH_S remarkably decreased cell viability to approximately 70% and 30%, respectively. Nevertheless, tamarind pulp extracts (TPE) started showing an inhibition effect on A549 at a lower concentration of 4 µg/mL for ethanolic extract and 16 µg/mL for methanolic extract.

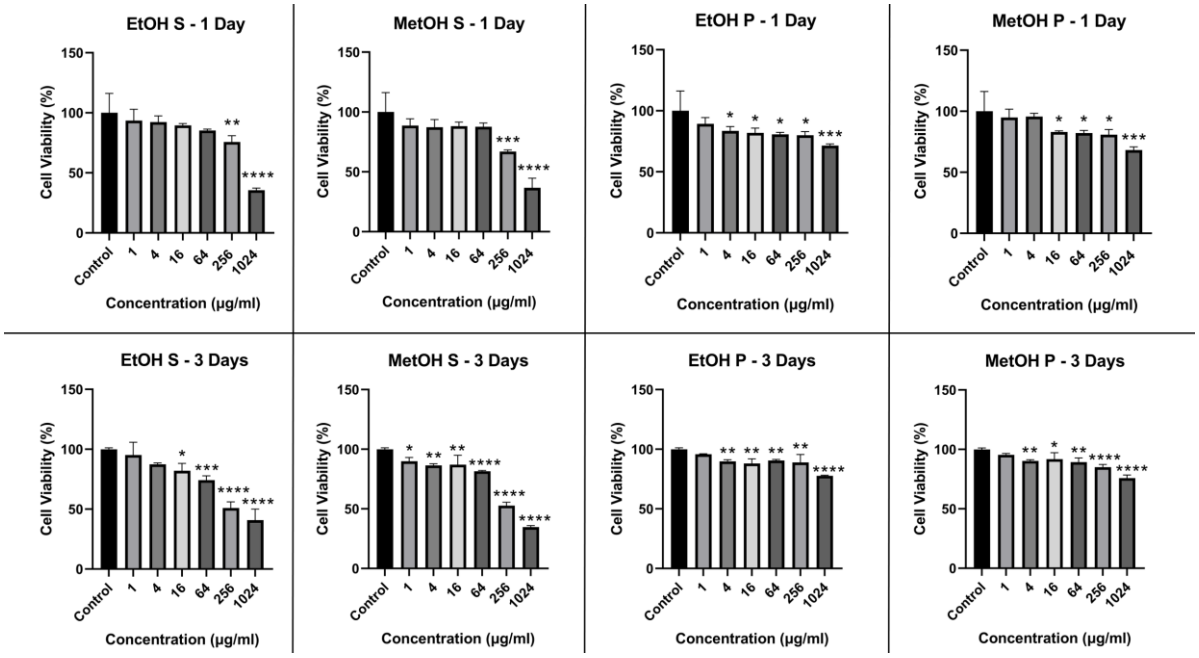

Figure 1. Cytotoxic effect of tamarind extracts on cell viability of A549 cell line after 1 day and 3 days of treatment

*Cells were seeded onto a 96-well plate at density of $2x10^4$ cells/well and treated with different concentrations of tamarind extracts ranging from 1 to 1024 µg/mL. Untreated cells served as control. Each bar was presented in form of means ± SD. EtOH_S: ethanol extract of tamarind seed; MetOH_S: methanol extract of tamarind seed; EtOH_P: ethanol extract of tamarind pulp; MetOH_P: methanol extract of tamarind pulp. Cell viability was determined by MTT assay. *: p<0.05 vs. control; **: p<0.01 vs. control; ***: p<0.001 vs. control; ****: p<0.0001 vs. control.*

After three days of incubation, the toxicity of TSE was slightly enhanced. At a lower concentration of 16 µg/mL, EtOH_S significantly inhibited A549 cell viability by 82%, whereas MetOH_S reduced the viability of A549 cells to 86% at 4 µg/mL. In contrast, the toxic effect of TPE remained stable over 3 days. The 50% inhibition concentration (IC_{50}) of TSE by ethanol and methanol in A549 lung cancer cells were 791.2 µg/mL and 599.5 µg/mL, respectively (Table 1). It was clear that tamarind extracts lowered the proliferation of A549 in a dose-dependent manner.

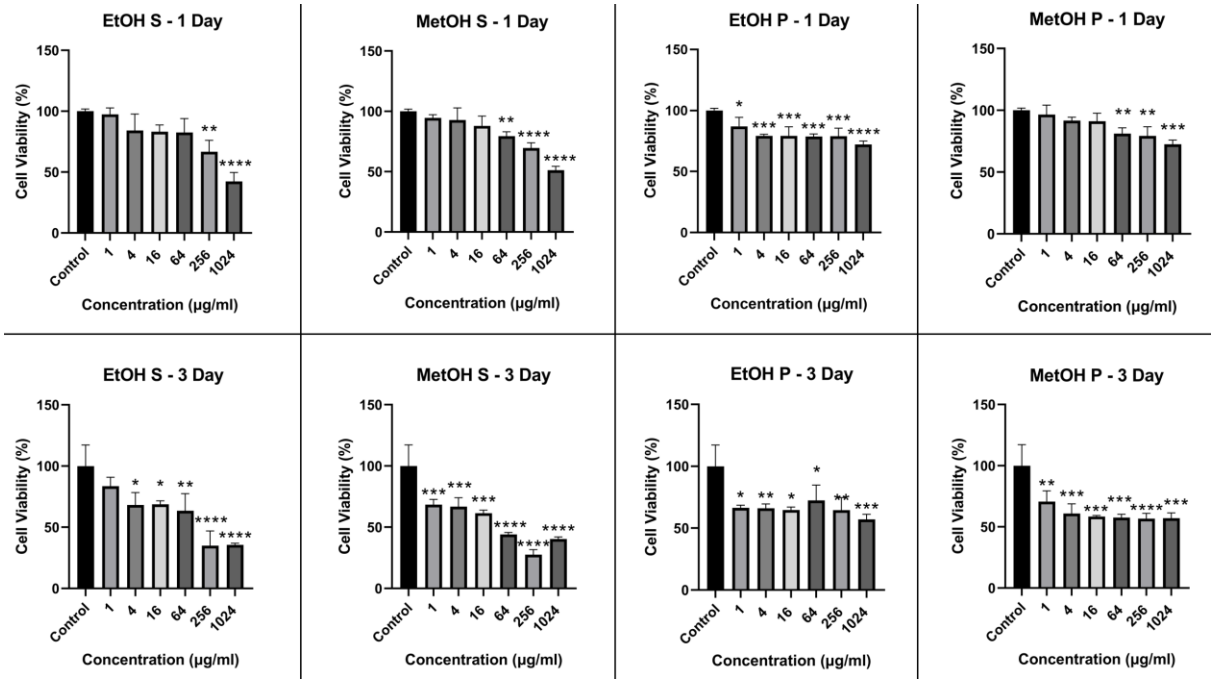

Figure 2. Cytotoxic effect of tamarind extracts on cell viability of HepG2 cell line after 1 day and 3 days of treatment

*Cells were seeded onto a 96-well plate at a density of 2x10^4 cells/well and treated with different concentrations of tamarind extracts ranging from 1 to 1024 µg/mL. Untreated cells served as control. Each bar was presented in form of means ± SD. EtOH_S: ethanol extract of tamarind seed; MetOH_S: methanol extract of tamarind seed; EtOH P: ethanol extract of tamarind pulp; MetOH_P: methanol extract of tamarind pulp. Cell viability was determined by MTT assay. *: p<0.05 vs. control; **: p<0.01 vs. control; ***: p<0.001 vs. control; ****: p<0.0001 vs. control.*

The cytotoxic effects of the ethanolic and methanolic extracts of tamarind pulp and seeds on HepG2 cells are shown in Figure 2, with similar patterns as the A549 cancer cell line. After 24 h of treatment, a smaller dose of MetOH_S is required to markedly inhibit HepG2 cells' viability compared to EtOH_S, at a concentration of 64 µg/mL and 256 µg/mL, respectively. For TPE, different concentrations from 1 µg/mL to 1024 µg/mL of EtOH_P significantly inhibited proliferation of HepG2 cells, whereas a minimum concentration of 64 µg/mL MetOH_P was needed to significantly suppress cell viability of HepG2.

After 3 days of treatment, the cytotoxic effect of tamarind seed extracts on HepG2 was notably improved, especially at high concentrations of 256 µg/mL and 1024 µg/mL. In particular, treating with EtOH S and MetOH_S at a concentration of 256 µg/mL, cell survival rate dropped to 34.95% ± 11.98% and 27.61% ± 4.07%, respectively. The TPE also witnessed the same trend. The IC_{50} of EtOH S and MetOH_S in HepG2 liver cancer cells were 164.5 µg/mL and 107.4 µg/mL respectively, while IC_{50} of EtOH P was 1007.2 µg/mL (Table 1).

Table 1. IC_{50} of tamarind extracts on 2 cancer cell lines A549, HepG2 after 3 days of treatment.

Cell line / Samples	IC_{50}	
	A549 (µg/mL)	HepG2 (µg/mL)
Ethanolic seed extract (EtOH_S)	791.2	164.5
Methanolic seed extract (MetOH_S)	599.5	107.4
Ethanolic pulp extract (EtOH_P)	N/A	1007.2
Methanolic pulp extract (MetOH_P)	N/A	N/A

The IC_{50} was graphed and calculated by Excel software. N/A: not available since treatment with samples in the chosen range concentrations were not able to decrease cell viability to less than 50%.

Cytotoxic effect of ethanolic and methanolic extracts of tamarind pulp and seeds on macrophage cell line

Both tamarind extracts showed no inhibitory effect on the viability of RAW 264.7 cells. Only at a very high concentration of 1024 µg/mL of EtOH_S and EtOH_P, the proliferation of RAW 264.7 declined. In contrast, at a lower concentration of 256 µg/mL, MetOH_S started exhibiting a repressive effect on the survival rate of the RAW 264.7 cell line. Meanwhile, MetOH_P was not toxic to the cells in the range of concentrations tested.

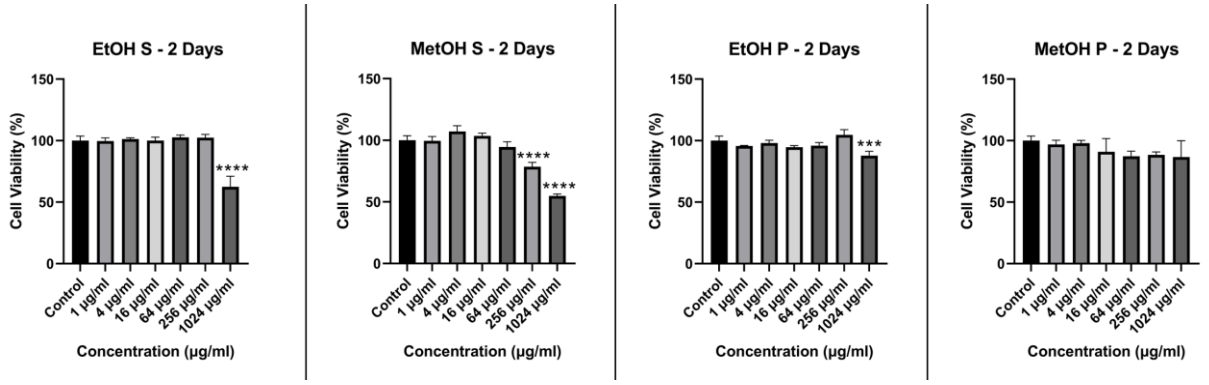

Figure 3. Cytotoxic effect of tamarind extracts on cell viability of RAW 264.7 cell line after 2 days of treatment

*Cells were seeded onto a 96-well plate at density of $2x10^4$ cells/well and treated with different concentrations of tamarind extracts ranging from 1 to 1024 µg/mL. Untreated cells served as control. Each bar was presented in form of means ± SD. EtOH_S: ethanol extract of tamarind seed; MetOH_S: methanol extract of tamarind seed; EtOH_P: ethanol extract of tamarind pulp; MetOH_P: methanol extract of tamarind pulp. Cell viability was determined by MTT assay. *: p<0.05 vs. control; **: p<0.01 vs. control; ***: p<0.001 vs. control; ****: p<0.0001 vs. control.*

Methanolic tamarind seed extract (MetOH_S) induces nuclear damage in A549 cells

The results of the MTT assay revealed that MetOH_S was more effective in inhibiting the proliferation of cancer cells and less toxic to macrophages at low concentrations. Thus, MetOH_S at three concentrations: 1 µg/mL, 16 µg/mL, and 256 µg/mL was chosen to use in subsequent experiments. A549 cells were incubated with MetOH_S for 24 hours. After that, changes in the nuclei morphology of the cells were studied by staining with Hoechst reagent and examined under the fluorescent microscope.

To elucidate how cell viability decreased when being treated with MetOH_S, apoptosis was considered as a possible mechanism. Thus, identifying shrunken and fragmented nuclei was necessary for this step. As seen in Figure 4, there were no differences in the morphology of the nucleus between the control group and cells that were treated with 1 µg/mL of MetOH_S. As expected, at a concentration of 256 µg/mL, the nucleus was found to be fragmented into small apoptotic bodies (indicated in red arrow). Interestingly, the multinucleated cells (indicated in white arrows) prevailed at concentrations of 16 µg/mL and 256 µg/mL, not the nuclear morphology of apoptosis.

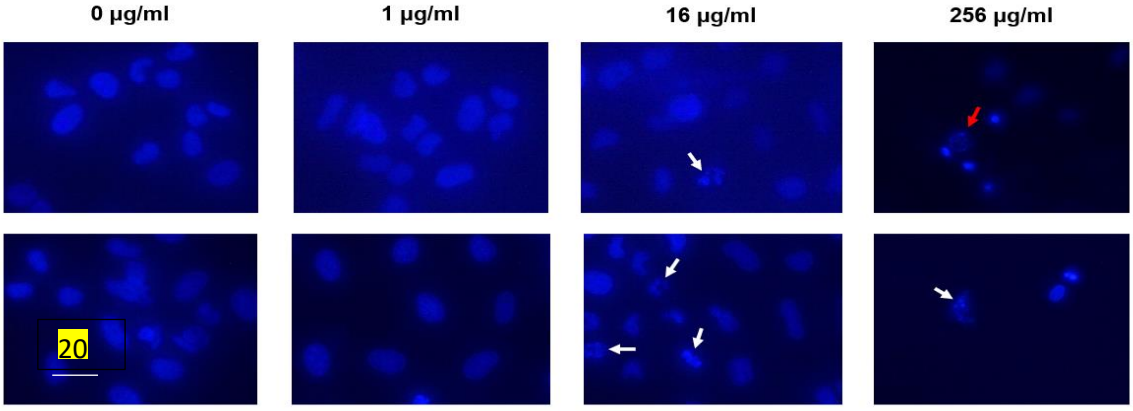

Figure 4. Effect of tamarind methanolic seed extracts (MetOH_S) on nuclear morphology of A549 cell line

Cells were treated with different concentrations of MetOH_S followed by 48 hour-incubation. Untreated cells (0 µg/mL) served as control. Cells were stained with Hoechst reagent and visualized under the fluorescent microscope. Red arrow indicated dwindled, fragmented nucleus; white arrows indicated the multinucleated. Scale bar: 20 µm.

DISCUSSION

In modern times, cancer remains one of the toughest obstacles that prevent the world population from increasing life expectancy. Besides traditional treatment of cancer such as surgery or radiation therapy, plant derivatives emerge as promising sources of drugs that can selectively target cancerous but not the macrophage cells. Thus, the side-effect of the old treatment can be minimized. From the MTT results of this study, tamarind seed and pulp

extracts were proven to have anti-cancer effect on 2 cancer cell lines: A549 and HepG2 as they could lower their cell viability to under 50% (Fig.1 and Fig.2). This is in accordance with published articles in which tamarind seed extracts were shown to inhibit the growth of Rhabdomyosarcoma cancer and Human Lymphoma cell line (Hussein *et al.,* 2017), while tamarind pulp extracts could effectively kill MCF-7 breast cancer cells (Durga *et al.,* 2020). Since the effect of MetOH_S on A549 was most significant after 24 hours of incubation, these conditions were chosen to further study the detailed mechanism.

Cancer is characterized by the unlimited proliferation of cells, which enables them to quickly invade the surrounding tissues and migrate to other parts of the body. The motivation behind this is the failure in regulating normal controls of the cells such as cell cycle arrest or programmed cell death. Thus, targeting these points has become a promising anti-cancer therapy recently (Sun and Peng, 2009). In this work, we closely examined if MetOH_S can eliminate cancer cells and whether it is related to the most popular programmed cell death pathway: apoptosis. Even though the result of nuclei staining with Hoechst reagent did show the morphology of apoptosis such as nuclear shrinkage and fragmentation, the number of the cells displaying multinucleated cells were predominant. This suggested cell underwent not only apoptosis but also mitotic catastrophe or autophagy (Figure 4).

Up to the present, many derivatives of tamarind plants have been demonstrated for cancer treatment. They are known to have different types of chemicals that can hinder cancer cell activities by inhibiting the proliferation of cancer cells or inducing apoptotic cell death (Greenwell and Rahman, 2015). Previous studies revealed that methanolic extract of tamarind seeds posed a strong anti-cancer effect on Rhabdomyosarcoma cancer and the Human Lymphoma cell line (Hussein *et al.,* 2017). In another experiment, polysaccharides extracted from tamarind seeds by petroleum ether were proved to have antitumor activity on human cancer cell lines A549, KB, MCF-7 (*in-vitro*), and murine cancer cell lines DLA and EAC (both *in-vitro* and *in-vivo*) (Aravind *et al.,* 2012). Not only seeds but also pulp of tamarind was shown to have a cytotoxic effect on cancer cells, and more specifically, on the MCF-7 cell line (Durga *et al.,* 2020). In the current study, we showed that tamarind pulp and seed extracts effectively inhibited the proliferation of A549 and HepG2 cancer cell lines while not being toxic for macrophage cells RAW 264.7. Among 4 types of extracts, MetOH_S exerted the greatest inhibition on the viability of cancer cells. All these results suggest that MetOH_S is a potential anti-cancer agent; however, further studies are needed for validation.

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TÁC DỤNG CHỐNG UNG THƯ CỦA CHIẾT XUẤT HẠT VÀ CÙI ME (*Tamarindus indica* L.)

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TÓM TẮT

Mặc dù các phương pháp chẩn đoán và thuốc men đã được cải thiện đáng kể trong suốt những năm qua, ung thư vẫn là một trong những vấn đề liên quan đến sức khỏe đáng lo ngại nhất trên thế giới. So với các liệu pháp chống ung thư thông thường có nhiều tác dụng phụ, các dẫn xuất thực vật được ưa chuộng hơn vì chúng có thể giảm thiểu những nhược điểm này. Chiết xuất me trước đây đã được chứng minh là có tác dụng chống ung thư, tuy nhiên, cơ chế gây ra hiện tượng này vẫn chưa được hiểu rõ ràng. Do đó, nghiên cứu này nhằm đánh giá tác dụng gây độc tế bào của dịch chiết etanolic và metanol của hạt và cùi me trên hai dòng tế bào ung thư A549 và HepG2 và một dòng tế bào RAW 264.7, cũng như khám phá xem liệu apoptosis có góp phần vào quá trình tiêu diệt ung thư hay không. Kết quả cho thấy chiết xuất từ hạt và cùi me có hiệu quả ức chế sự phát triển của tế bào ung thư nhưng không ảnh hưởng đến tế bào RAW 264.7. Trong số 4 loại chiết xuất me, chiết xuất hạt metanic (MetOH_S) có tác dụng ức chế lớn nhất đối với khả năng sống sót của tế bào ung thư. MeOH_S làm giảm khả năng tồn tại của tế bào A549 xuống 86% ở mức 4 µg/mL ($p<0,01$). Điều thú vị là, hình thái đa nhân được tìm thấy chủ yếu so với hình thái nhân của quá trình chết tế bào trong các tế bào A549 được xử lý với 16 µg/mL và 256 µg/mL MetOH_S. Do đó, MetOH_S đã được chứng minh là có kết quả chống ung thư mạnh nhất, gợi ý một cơ chế khác: phân bào dẫn đến bệnh tự thực. Tuy nhiên, cần nghiên cứu sâu hơn để tinh chế hợp chất từ chiết xuất metanol và làm rõ sâu sắc tác dụng chống ung thư của nó.

Từ khóa: Dịch chiết me, độc tính tế bào, sự chết tế bào theo chu trình, *Tamarindus indica*.

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