A high mannose concentration is well tolerated by colorectal adenocarcinoma and melanoma cells but toxic to normal human gingival fibroblast: an in vitro investigation

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Abstract

Background: The primary cause of cancer is gene mutation which allows the growth of abnormal and damaged cells. Nutrition is one of the key factors that either increases or decreases the risk of cancer. Mannose has been found in many fruits such as oranges, apples and berries. Mannose has been linked to increase the risk factors or potential therapeutic for cancers. However, insufficient information is available on the effects of high mannose concentration on the normal and cancer cell lines. This study aimed to evaluate the viability patterns of human cancer and normal cell lines treated with mannose. Human gingival fibroblast (HGF), skin malignant melanoma (A375) and colorectal adenocarcinoma (HT29) cell lines were cultured and treated with additional mannose in three respective concentrations: 1 mg/ml, 5 mg/ml and 10 mg/ml. Then, cell viability was measured using an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide)-assay.

Results: The HGF cells' percentage pattern of viability showed a rapid decline of nearly 95% on the third day of treatment. A375 cells were able to survive in high mannose condition as the cell viability percentage was at the highest value on Day 5. Meanwhile, HT29 cells showed declining cell viability pattern when treated with mannose. The data exhibited significance; the p value was less than 0.001.

Conclusions: High mannose concentration can be toxic to HGF. In addition, A375 is adaptive to mannose at all concentrations in which it shares the same pattern with the untreated group. However, the cell viability pattern for HT29 cell is declining.

Keywords: In vitro technique, Fibroblasts, Adenocarcinoma, Malignant melanoma, Mannose, Cancer

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Background

Cancer is a multifactorial disease that could be the result from various factors including diet, lifestyle, environment, chemical and so forth [1]. However, the prime aetiology of cancer is gene mutation as it would lead to the production of abnormal or damaged cells. Physiologically, p53 is the tumour suppressor protein which plays an important role in arresting or eliminating abnormal and damaged cells [2]. Basically, the cell death would be due to autophagy, apoptosis or necrosis. Autophagy is a mechanism in which the cytoplasmic components are engulfed in double-membraned vesicles before the lysosome degrades the vesicles [3]. Apoptosis is defined as the process of cell shrinkage, DNA fragmentation and phagocytosis by macrophages or neighbouring cells [4]. Meanwhile, necrosis is a mode of cell death that results from the loss of integrity of the plasma membrane and the breakdown of organelles with the release of proteolytic enzymes which subsequently initiate the destruction of the surrounding cells and promote the inflammation [5]. In terms of cell death mechanism, apoptosis is better than necrosis as it avoids the trauma towards the neighbouring cells while necrosis increases the inflammation. Chronic inflammation is one of the risk factors that could lead to the formation of cancer [6]. Among cancer survivors, food that could contribute to inflammation need to be controlled.

Since a cancer survivor has the tendency to undergo the recurrence of cancer, it is very essential to manage the survivors of cancer in terms of dietary intake. Dietary factors have been recognized to have significant effects on increasing and decreasing the cancer risk [7]. The needs and metabolic physiology of cancer survivors might differ from normal people. A regimen of food could possibly be designed to avoid the recurrence of cancer among cancer survivors. For instance, one meta-analysis study had summarized the adherence to a high-quality diet and healthy dietary pattern is inversely associated with the mortality of cancer survivors [8]. In order to develop this regimen, it is necessary to conduct scientific researches to understand the needs of either cancer patients or the survivors. For instance, it is compulsory to understand the behaviour and pattern of the cell lines when they are treated with monosaccharides.

The focus of this study was to observe the cell viability pattern of the normal and cancer cell lines when treated with mannose. Mannose is a sugar monomer of the aldohexose series of carbohydrates [9]. Commonly, mannose could be abundantly found in varieties of fruits such as apples, oranges and berries [10]. Mannose has been reported to play a vital role for the treatment of congenital disorder of glycosylation (CDG) as the mannose improved the protein glycosylation [11]. In addition, oral administration of mannose suppressed the immunopathology in models of autoimmune diabetes and airway inflammation [12]. However, high dosage of mannose could cause injury towards the kidneys [13]. Furthermore, the scientific evidence on the cell viability pattern of the normal and cancer cell lines that were treated with mannose is insufficient. The findings of this study will probably become a starting point to discover more about cancer and sugar which would eventually help the physician by suggesting the cancer patients to avoid or reduce the intake of sugar derivatives that may increase the risk factor of getting cancer. It is a fact that our body needs sugar, but it is better to have options to choose sugar that is less favourable by cancer cells. In addition, the therapy for cancer could also be designed in the future by incorporating the most favourable monosaccharide with nanoparticles. Herein, this study aimed to investigate the pattern of cell viability of normal and cancer cell lines when they are treated with mannose for therapeutic value.

Methods

Selection and preparation of normal and cancer cell lines

The cell lines that were used in this study were normal human gingival fibroblast (HGF-1, ATCC CRL-2014, USA), human colorectal adenocarcinoma (HT-29, ATCC HTB-38, USA) and human malignant melanoma (A375, ATCC CRL-1619, USA). The cells were purchased from American Type Culture Collection (ATCC) in which the cells had undergone authentication and mycoplasma tests.

Media preparation, optimization of concentration and treatment period

In this study, complete media was used for the cellular growth. The complete media was formulated with Dulbecco's modified Eagle's medium (DMEM) (Nacalai Tesque, Japan) added with 10% of foetal bovine serum (FBS) (Himedia Laboratories Pvt Ltd, India) and 1% of antibiotic (streptomycin and penicillin) (Himedia Laboratories Pvt Ltd., India). This complete media was used as the control. Meanwhile, the treatment groups were prepared by dissolving mannose in the complete media. The optimization of concentration and treatment period for in vitro stability studies was adapted and modified from Shahbuddin [14]. Mannose was diluted properly at three different concentrations which were 1 mg/ml, 5 mg/ml and 10 mg/ml. Then, the mixture of mannose and complete media were sterilized by using the filter at 0.22 μm., Meanwhile, there were four different incubation periods (1, 3, 5 and 10 days) that were applied as a treatment parameter to investigate the effect of mannose on the cell viability of the tested cell lines.

Culturing the cells for testing

The cells (HGF, A375 and HT29) were thawed and revived in 25-ml culture flasks containing complete media and incubated in CO_2 incubator at 37°C with 5% CO_2. The complete media were changed after 3 days of incubation to ensure that the nutrients were sufficient for cell growth and development. Once the cells had achieved 80% of confluency, the cells were dissociated for the cell viability test. The cell seeding was conducted prior to the cell viability test. The cell was counted by using haemocytometer with the ratio for the cells and trypan blue of one to one. Approximately, 1000 cells were aliquoted into 12-well plate as an initial seeding. Then, the cells (HGF, A375 and HT29) were treated with 1 mg/ml, 5 mg/ml and 10 mg/ml of mannose. Meanwhile, the control group was treated with the complete media which did not contain mannose. After that, the treated cells were incubated at four incubation periods (1, 3, 5 and 10 days). The fresh media of the control and treatment groups were changed every three days of incubation to ensure the nutrient was sufficient. The cell lines underwent the cell viability test once the incubation period was completed.

Viability test by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay

MTT assay was conducted as a colourimetric technique to assess the cell metabolic activity. The viable cell number is reflected from the mitochondrial activity through the oxidoreduction reaction [15]. The treated cell lines in the well plate were washed with phosphate buffer saline (PBS) before the MTT reagent (Nacalai Tesque, Japan) was added. Twenty microlitres of MTT reagent with a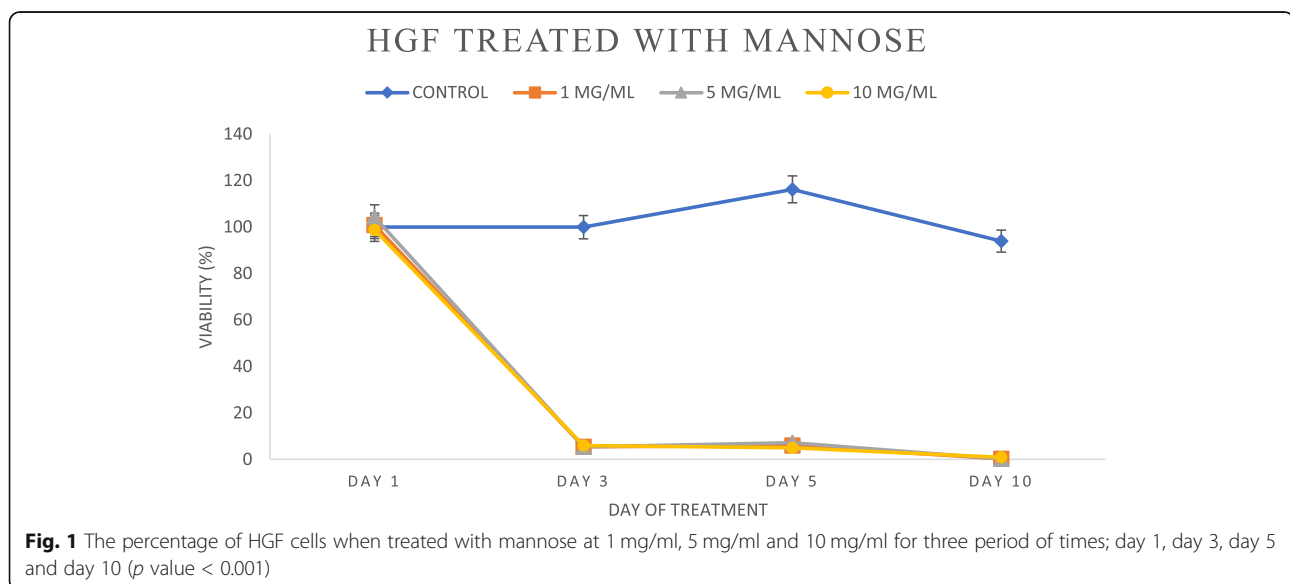 concentration of 0.5 mg/ml was dispensed into each well and incubated for at least 2 h. Subsequently, after 2 h of incubation, the MTT reagent was aspirated and 200 μl of dimethyl sulfoxide (DMSO) was added to solubilize the formazan crystals. The absorbance was measured with microplate spectrophotometer (Tecan Trading AG, Switzerland) under a wavelength of 450 nm. All the cell viability processes were treated as a light-sensitive process and wrapped with aluminium foil.
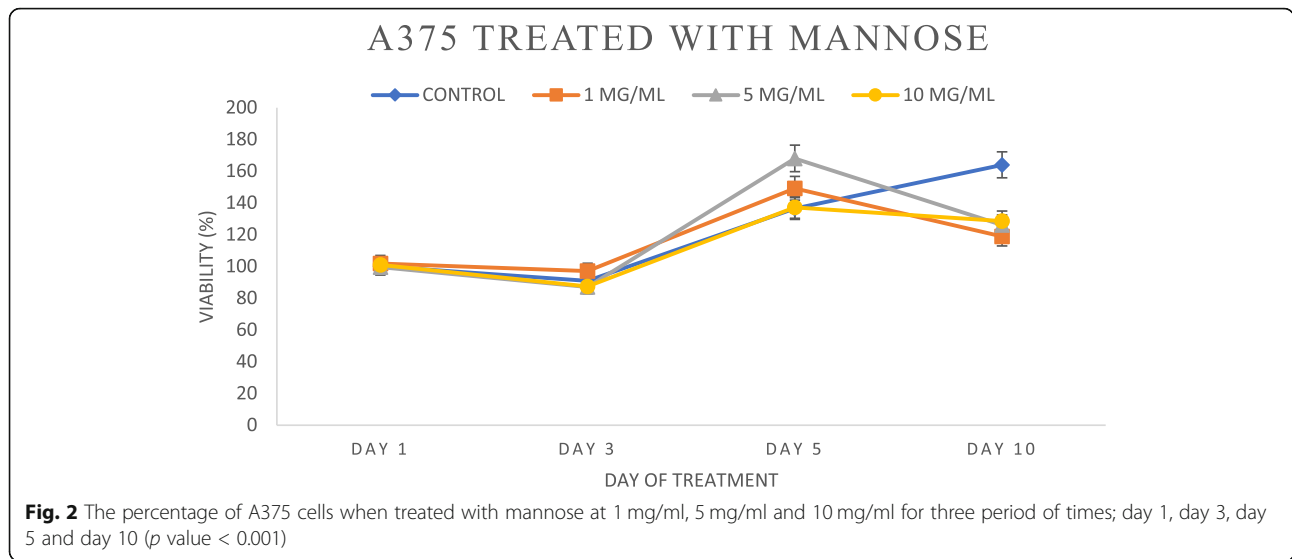
Data analysis

The Statistical Package for the Social Sciences (SPSS) software version 22 was used to analyse the data obtained from this study. The data were collected by triplicating for each of the treatments at two independent experiments. The treated groups with mannose were compared with the control group. The values were expressed as the standard error of the mean ± standard deviation. The one-way ANOVA statistical test was conducted in this study. p value ≤ 0.05 was considered significant.

Results

This study was conducted to evaluate the role of mannose on the viability pattern, the cell lines (human gingival fibroblast (HGF), skin malignant melanoma (A375) and colorectal adenocarcinoma (HT29)) that were treated with mannose at three different concentrations (1 mg/ml, 5 mg/ml and 10 mg/ml). The groups that were treated with mannose were compared with the control group (complete media). The graph portrays the cell viability pattern of HGF cells that were treated with mannose at three different concentrations (Fig. 1). Overall, the groups that were treated with mannose had caused the cell viability pattern of the HGF cells to decline after

Fig. 1 The percentage of HGF cells when treated with mannose at 1 mg/ml, 5 mg/ml and 10 mg/ml for three period of times; day 1, day 3, day 5 and day 10 (p value < 0.001)

Fig. 2 The percentage of A375 cells when treated with mannose at 1 mg/ml, 5 mg/ml and 10 mg/ml for three period of times; day 1, day 3, day 5 and day 10 (p value < 0.001)

day 1 at all concentrations (1 mg/ml, 5 mg/ml and 10 mg/ml). At day 3, the treatment groups (1 mg/ml and 5 mg/ml) declined dramatically from day 1. However, the cell viability of these groups slightly increased at day 5 and continued to decline until day 10. Meanwhile, the HGF cells that were treated with 10 mg/ml mannose experienced rapid decline after day 1 until day 10.

The plotted graph depicts the cell viability pattern of A375 cells which were treated with mannose with the respective concentrations (Fig. 2). Based on the plotted graph, the cell viability pattern of A375 cells shows the potential to survive when treated with mannose. The pattern of the cell viability of all groups that were treated with mannose showed reduction after day 1. From day 3, the cell viability was increasing until day 5 and then decreased on day 10. For the control group, after day 1,

the cell viability of A375 cells showed slightly declining pattern which then continued to increase from day 3 until day 10.

The graph illustrates the cell viability of the HT29 cells that were treated with mannose at three different concentrations (Fig. 3). In terms of cell viability pattern, all groups that were treated with mannose distributed similar pattern which is a dramatic declining from day 1 until day 3. Then, the groups showed slight increment from day 3 to day 5. Finally, the cell viability of the treatment groups continued to decline until day 10. In contrast, the HT29 cells that were treated with complete media (control group) showed a different pattern of cell viability. The HT29 cells extremely increased from day 1 until day 5 of the incubation period. However, the cells started to decline from day 5 until day 10.
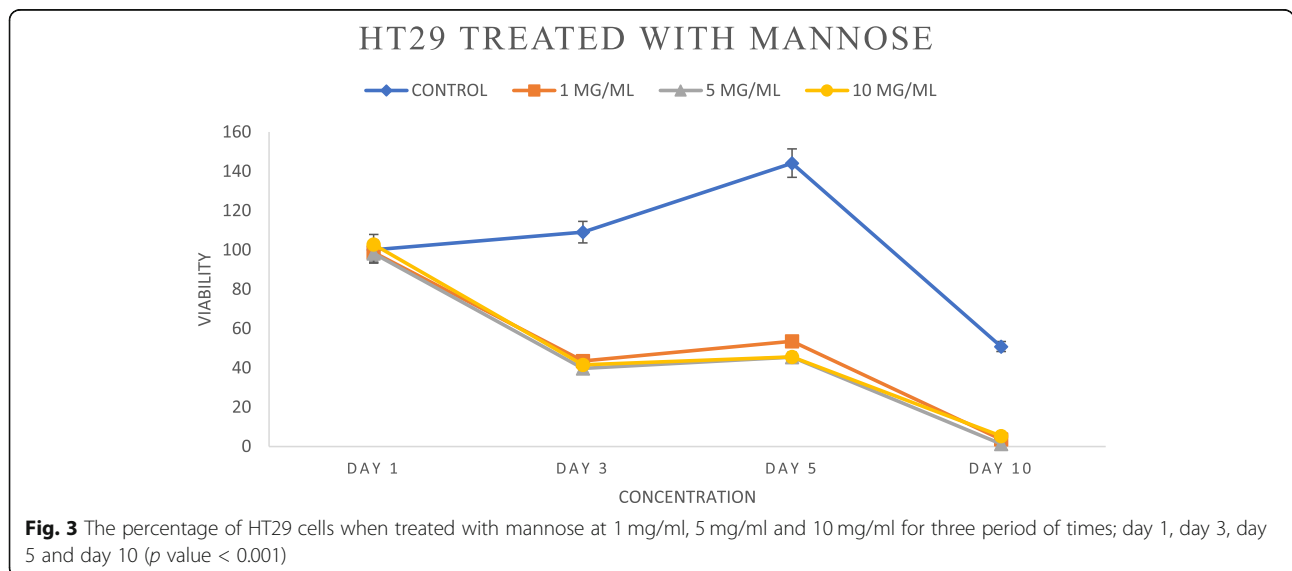

Fig. 3 The percentage of HT29 cells when treated with mannose at 1 mg/ml, 5 mg/ml and 10 mg/ml for three period of times; day 1, day 3, day 5 and day 10 (p value < 0.001)

Table 1 One-way ANOVA table

	Sum of squares	Df	Mean square	F	p value
HGF–mannose					
Between groups	0.005	15	< 0.001	8.308	< 0.001
Within groups	0.005	128	< 0.001		
Total	0.011	143			
A375–mannose					
Between groups	67.000	15	4.467	50.277	< 0.001
Within groups	41.223	464	0.089		
Total	108.223	479			
HT29–mannose					
Between groups	6.353	15	0.424	180.266	< 0.001
Within groups	1.062	452	0.002		
Total	7.415	467			

The results of ANOVA are significant with the values of all data were less than 0.05 which are considered as significant (Table 1).

Discussion

The genetic changes that allow the growth of abnormal cells would subsequently lead to cancer formation because of abundant of damaged cells in the body system. From the findings, the cell viability of the normal cell line that was treated with mannose at different concentrations continued to reduce from day 1 and onwards of the incubation. Meanwhile, the cancer cell lines (A375 and HT29) that were treated with the mannose in vitro showed the capability to adapt and survive. The genetic between the normal and cancer cell lines play an important role for the metabolism of mannose.

Mannose's toxicity is due to the shortage of mannose phosphate isomerase which results in the accumulation of mannose-6-phosphate [16]. The mannose-6-phosphate is the result of the phosphorylation of mannose by gluco-mannokinase [17]. In addition, mannose toxicity leads to the depletion of adenosine triphosphate (ATP), a source of energy [18]. Therefore, normal HGF cells could not undergo the replication as the source of the energy is depleted. In addition, by-products of the mannose metabolism process such as reactive oxygen species (ROS) could also potentially cause the cell death of normal HGF cells. It has been reported that free radicals such as ROS could induce oxidative stress, a condition that would subsequently lead to cell death [19].

Some studies have proven that mannose could help in treating cancer. For instance, one study reported that mannose causes growth retardation in some tumour types in vitro, and intensifies the cell death in response to major forms of chemotherapy [20]. In addition, mannose is beneficial in treating urinary tract infections [21]. The mannose binds to the *E. coli* which are then

discharged in the form of urine [22]. Chronic *E. coli* infection might play a role in the development of bladder cancer [23]. The infection causes the activation of nuclear factor kappa light chain enhancer of activated B cells (NF-kB) pathway resulting in the inhibition of apoptosis and increases the inflammation [24]. Therefore, the survivability of the cancer cells would be due to the activation of the NF-kB mechanism which blocks the apoptosis pathway.

On the other hand, it has been reported that among diabetic patients, mannose has the potential to enhance diabetic complications as mannose glycated protein five times better than glucose [10]. Glycation process would lead to the production of advance glycation end products (AGEs). AGEs are collective name given to proteins, lipids and nucleic acids that undergo irreversible modification by reducing sugars or sugar-derived products [25]. It has been reported that the AGEs and AGE receptors interaction would stimulate the growth of human pancreatic cancer via the autocrine induction-derived growth factor-B [26]. Another study also reported that AGEs triggered the growth and migration of culture human melanoma cells [27]. AGEs have been reported to have the capability to mimic hormones or regulate their receptors mechanism at DNA level [28]. Therefore, the accumulation of these AGEs would interfere with normal physiological condition.

One of the limitations in this study is that only three types of cell lines were used. It would be better if more types of cancer and normal cell lines undergo the cell viability testing in order to understand the effect of mannose on the cell lines. In addition, the metabolites that were associated to cause cell death among the cell lines were not tested. Therefore, in the future, a study to detect the metabolites that enable the cell death or the ability to survive would benefit in developing diagnostic and therapeutic procedures for cancer.

Conclusions

In conclusion, high mannose concentration caused the cell viability of normal human gingival fibroblast (HGF) to rapidly decline since day 1 of treatment. The skin malignant melanoma (A375) and colorectal adenocarcinoma (HT29) have the potential to adapt to the high mannose condition. Based on the cell viability pattern showed by the A375 cell line, the cells displayed a similar pattern with the control group. Meanwhile, the cell viability pattern of the HT29 cell line that was treated with mannose showed a declining pattern. This could indicate that mannose could possibly help in combating the colorectal adenocarcinoma cell line. Therefore, the findings of this study suggest that mannose has the potential to be one of the alternatives of source energy among colorectal adenocarcinoma cancer patients. Nevertheless, further research still needs to be conducted in order to evaluate the efficiency of mannose in treating colorectal adenocarcinoma.

Abbreviations
A375: Skin malignant melanoma; AGE: Advance glycation end product; ANOVA: Analysis of variance; ATCC: American Type Culture Collection; ATP: Adenosine triphosphate; CDG: Congenital disorder of glycosylation; CO_2: Carbon dioxide; DMEM: Dulbecco's modified Eagle's medium; DMSO: Dimethyl sulfoxide; DNA: Deoxyribonucleic acid; FBS: Foetal bovine serum; HGF: Human gingival fibroblast; HT29: Colorectal adenocarcinoma; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; NF-kB: Nuclear factor kappa light chain enhancer of activated B cells; PBS: Phosphate buffer saline; ROS: Reactive oxygen species; SPSS: Statistical Package for the Social Sciences

Authors' contributions
MAM had assembled the data and drafted the article for publication. MLMI had provided the materials and important contents for the article. MI had contributed in terms of emphasizing the methods that were used in this study. All authors designed the concept for the project and worked together to analyse and interpret the data and approved the final manuscript.

Availability of data and materials
All data generated or analysed during this study are included in this published article (at 'Results' section).

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare there is no competing interest.

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