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Original Research Article

The Antiproliferative Activity of *Syzygium malaccense* Fruit

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ABSTRACT

Despite recent global efforts to combat cancer through prompt diagnosis and prevention, it remains a predominant cause of death around the world. Epidemiological research has shown that frequent intake of fruits and vegetables is linked to lower risk of acquiring chronic diseases like cancer. *Syzygium malaccense*, an underutilized fruit, is known for its high phytochemical content and potential health benefits. This study examined the antiproliferative activity of different solvent extracts of *S. malaccense* fruits (flesh and peel) on human colorectal (HCT-15), cervical (HeLa), and prostate (PC-3) cancer cells in comparison to normal human prostate (PNT-2) cells. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay was employed to evaluate the antiproliferative activity of the extracts. The findings indicated that the extracts demonstrated different levels of antiproliferative activity against the cancer cells. The aqueous flesh (AF) and peel (AP) displayed significant activity against PC-3 and HCT-15 (IC_{50} = 522.12±28.65µg/mL and 837.59±48.65 µg/mL, respectively). None of the extracts had an IC_{50} within the range of the tested concentration on HeLa cells. When compared to the positive control, curcumin, the extracts are regarded as having weak cytotoxic effect. Moreover, the aqueous peel and flesh extracts were not cytotoxic to the normal cell line, indicating the safety of the fruits on daily consumption. The findings showed that the aqueous extract of *S. malaccense* fruit, contains compounds with antiproliferative activity. Despite the neglected status of *S. malaccense* fruit, this study supports the need to improve its utilization and identify the bioactive compounds responsible for its antiproliferative activity.

Keywords: *Myrtaceae, Syzygium malaccense*, Antiproliferation, Bioactive compounds.

Introduction

Food habits and environmental changes are having an increasing impact on human health, causing an increase in new diseases and disorders.[1] Cancer is one of the diseases resulting from bad diets, inactivity, obesity, microbial infections, environmental factors, alcohol and cigarette use.[2]Despite attempts to prevent and detect the disease early, cancer is still a major cause of death in the world, with 10 million deaths and 19.3 million new cases reported in 2020. Prostate and colon cancer are the second and third most common cancers in men,[3] with cervical and colon cancer being the second and fourth most common cancers in women. For both sexes, colon cancer ranks as the second-most common cause of death.[4]In Africa, prostate and colon cancer rank first and third among cancers in men, with estimated cases of 93,173 and 34,060 (age-standardized incidence rates (ASRs) of 29.7 and 9.4 per 100,000) and a death rate of 47,249 and 21,762 (ASRs of 16.3 and 5.6 per 100,000). Meanwhile, cervical and colon cancer are the second and third most common in African women, with estimated cases of 117,316 and 32,138 (ASRs of 25.6 and 7.6 per 100,000) and a death rate of 76,745 and 21,762 (ASRs of 17.7 and 5.6 per 100,000).[4]

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Traditional techniques such as radiotherapy, immunotherapy, surgery, hormonal therapy, and chemotherapy commonly used to treat cancer are expensive and adversely affect healthy cells. Thus, there is a need to investigate safe cancer treatment options. Chemoprevention is an active research area and a major therapy used in cancer treatment that utilizes natural or synthetic compounds to delay cancer progression in normal and preneoplastic conditions.[5] Based on the concept that prevention is better than cure, chemoprevention and treatment using natural phytochemicals have proven to be viable strategies, and they will remain a promising and active field of study. Epidemiological research has repeatedly demonstrated that regular intake of fruits and vegetables lowers the chance of acquiring cancer and other chronic diseases.[6] The complex combination of additive and synergistic effects of bioactive compounds in whole food instead of a single compound contributes to the health benefits of fruits and vegetables. [7]

Myrtaceae is one of the plant families distinguished for its anticancer activity, mainly in the *Eucalyptus*, *Melaleuca*, *Eugenia*, *Myrcia*, *Psidium*, and *Syzygium* genera.[8-10]*Syzygium malaccense* is an underutilized plant, belonging to one of the over 1200 species of the *Syzygium* genus, with numerous properties such as antioxidant, anti-inflammatory, cytotoxic power, hypoglycemic, and cholesterol-lowering effects.[11] The main product of this plant is the fruit, which has several benefits for human health.[12] Previous scientific investigations have revealed that *S. malaccense* fruit has high nutrients, phytochemicals, and antioxidant activity concentrated in the fruit peel, which differ according to the cultivar, growing conditions, and topographical location.[11,13] In Malaysia and Brazil, *S. malaccense* fruit was reported to possess antiproliferative activity in breast and liver cancer cell lines.[14,15] However, there is a shortage of information in the global literature about the antiproliferative activity of the African *Syzygiummalaccense* and the effect of different solvents on its antiproliferative activity.

Therefore, the current study explores the antiproliferative effects of aqueous and ethanol extracts of *S. malaccense* fruit parts (peel and flesh) on colon (HCT-15), cervical (HeLa), and prostate (PC-3) cancer

cells relative to normal prostate cells (PNT-2) as a measure of anticancer activity. The purpose of this research is not only to evaluate the antiproliferative effect of *S. malaccense* fruit but also to promote its usage, irrespective of its present underutilized status.

Materials and Methods

Plant materials and extract preparation

The identification of *S. malaccense* fruit and SM preparation were done as reported previously.[16] Briefly, the fruits were divided into peel, flesh, and seeds (which were discarded). The peel and flesh were separately dried and pulverized using a grinding machine to obtain 250 g of the dried fruit parts. They were macerated separately and homogenized using 2.5 liters of water and 70% ethanol. The aqueous extracts (AP and AF) were lyophilized using a freeze dryer, and the hydroethanolic extracts (EP and EF) were dried under reduced pressure at 30°C. All extracts were kept at -20 °C until use.

Cytotoxicity assay

HCT-15, HeLa, PC-3, and PNT-2 cells were cultured in RPMI-1640 medium and supplemented with 10% fetal bovine serum containing 1% penicillin-streptomycin. Cultured cells were maintained in a humidified 5% CO_2 incubator at 37 °C with periodic changes in medium and passaging until they were ready for use. The aqueous and ethanol extracts of *S. malaccense* peel and flesh (AP, AF, EP, and EF)were examined for anticancer efficacy based on their ability to reduce cancer cell growth by the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay.[17] HCT-15, HeLa, PC-3, and PNT-2 viable cells were seeded at a density of $1x10^4$ (100 μL/well) in a 96-well plate and incubated in a humidified 5% CO_2 atmosphere and 95% air at 37°C for 24 hours to form a cell monolayer. Five different concentrations of the extracts and the positive control, curcumin, were prepared from their stock solutions using 10% dimethyl sulfoxide (DMSO) as the solvent. After 24 hours, the cells were treated with different concentrations of extracts (0–1000 µg/mL) and curcumin (2-38 µg/mL). The blank was the medium without cells and extracts, the negative control was the medium with cells but without extracts, and the positive control was the medium with cells and curcumin. After 72 hours of incubation, 20 µL of MTT solution (2.5 mg/mL) was added to each well, and the incubation period was extended for 4 hours. This was done for all the plates. Acidified isopropanol (150 µL) was added to stop the reaction. Afterward, the cells were incubated at room temperature for an entire night in the dark. The absorbance was measured at 570 nm using a fluorescence microplate reader (Tecan Infinite M200, Austria). Based on the absorbance values, the percentage cell viability for the different extract concentrations and the positive control was calculated using the following formula:

$$Percentage\ cell\ viability = \frac{(Absorbance\ of treated\ cell - Absorbance\ of\ blank)}{(\text{Absorbance of control} - \text{Absorbance of blank})} \times 100$$

The linear regression equation, Y = mX + C, was used to calculate the IC_{50} values for each extract and the positive control for the four cell lines.[18]

The PNT-2 normal cell line was used to calculate the selectivity indices (SI) of the extracts using the following equation:[19]

$$SI = \frac{IC50(\text{treated normal cells})}{IC50\ (\text{treated cancer cells})}$$

Statistical analysis

The results were summarized as the mean ± standard deviation (SD). The data were compared with the control using Dunnett's multiple comparisons to determine the statistically significant differences. A p-value ≤0.05 was considered significant. Analysis was done using GraphPad Prism (version 5.0).

Results and Discussion

There are several scientific findings on the importance of vegetables and fruits consumption in cancer prevention and reduction due to the presence of super-nutrients, such as micronutrients, phytochemicals, and antioxidants.[7] Previous studies have investigated the antiproliferative properties of *S. malaccense* fruit,[9,14-15,20] which were restricted to one or two cancer cell lines and either the peel or whole fruit. To our knowledge, this is the first comparative investigation of the antiproliferative effect of different solvent extracts of *S. malaccense* peel and flesh against various cancer cells. The in vitro antiproliferative activity of the solvent extracts of *S. malaccense* peel and flesh was evaluated on three cancer cell lines and one normal cell line. The findings demonstrated a decrease in cell viability with an increase in extract concentration in this order: AP > EP > AF > EF (HCT-15), EF > EP > AF > AP (HeLa), AF > AP > EP > EF (PC-3). In the HCT-15 cell line, the peel of the extracts showed significant antiproliferative activities as the number of viable cells reduced from 100% (negative control) to 44.47% and 70.27% in AP and EP at the maximum concentration of 1000 µg/mL (Figure 1). On the contrary, there was a reduction in the percentage of HeLa cells from 100% (the negative control) to 83.56% and 59.50% in AF and EF at the maximum dose of 1000 µg/mL (Figure 2). All extracts demonstrated dose-dependent antiproliferative activity on the PC-3 cell line, AF showed significant activity ($p<0.0001$) as the viable cell count decreased from 100% (negative control) to 35.993% at 1000 µg/mL. (Figure 3). In PNT-2 cells, the number of viable cells reduced significantly at the highest concentration of 1000 µg/mL in all the extracts except AP (Figure 4). Moreover, the untreated cell lines did not exhibit cytotoxicity, and there was a significant decrease in viable cells after treatment with the positive control in all the cell lines.

The study revealed that *S. malaccense* peel and flesh inhibited cancer cell proliferation dose-dependently by exerting different antiproliferative effects on the various cancer cell lines. The variance among the cell lines could be that cancer cells have distinct genetic makeup, sensitivity, and morphology doubling time, resulting in different responses to the same bioactive compound.[21,22] Since cancer is a group of diseases that involve multiple genes and biological mechanisms, one size does not fit all. Antiproliferation or apoptosis may be responsible for the decreased cell viability in treated cells compared to untreated cells.

The IC_{50} values, which indicate the extract concentration that inhibits cell population growth by 50%, are given in Table 1. Of the four extracts tested, only AP and AF had significant IC_{50} on PC-3 and HCT-15 cancer cells (522.12 ± 28.65, 837.59 ± 48.65 µg/mL). Interestingly, none of the extracts had an IC_{50} within the dose of the tested concentration on HeLa cells. However, the IC_{50} of curcumin was much lower in all the cell lines. Nevertheless, given the American National Cancer Institute's criteria for the cytotoxic activity of crude extracts (IC50: < 30 µg/mL),[23] none of the extracts were cytotoxic on the cells.The result agrees with similar studies that demonstrated the varying antiproliferative effects of *S. malaccense* fruit extracts on various cancer cell lines. Rabeta *et al.* reported an IC_{50} value of 632.3 µg/mL for *S. malaccense* fruit methanolic extract on MCF-7 cell,[14] Vuolo *et al.* reported an IC_{50} value of 40.92 mg/mL for ethanolic peel extract on HepG2 cell,[15] Luciana *et al.* reported no IC_{50} for aqueous extract of the fruit on CP-H460 cell at a concentration of 2 mg/ml,[9] and Frauches *et al.* reported reduced cell viability of 16.08% and 38% of aqueous extract and dried peel of *S. malaccense* on HT-29 cell at 1 mg/mL.[19]

Selectivity indices (SI) were calculated by comparing the IC_{50} value of the cancer cells to those of normal human cells. SI measures the ability of the extract to distinguish between malignant and nonmalignant cells in exerting their antiproliferative effects. According to Segun et al.,[24] SI value > 1 indicates that an extract has a therapeutic effect and is less toxic to normal cells than cancer cells. Table 2 shows the SI values of *S. malaccense* fruit extracts. AF inhibited PC-3 cells with an SI value of 1.92, and AP inhibited HCT-15 cells with an SI value of 1.19, suggesting that these extracts had selective toxicity to the cancer cells.

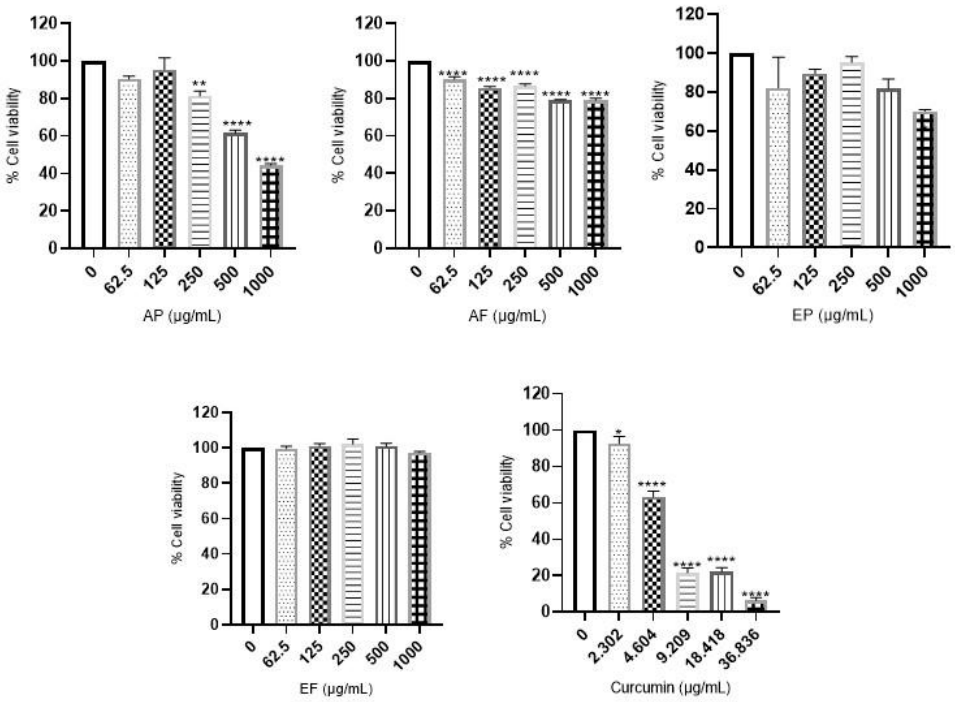

Figure 1: Antiproliferative effects of *S. malaccense* extracts on HCT-15 cells. Curcumin was used as the positive control. Values are means ± standard deviation of three different experiments
*P < 0.05, **P < 0.005 and ****P < 0.0001, compared with the negative control (DMSO)

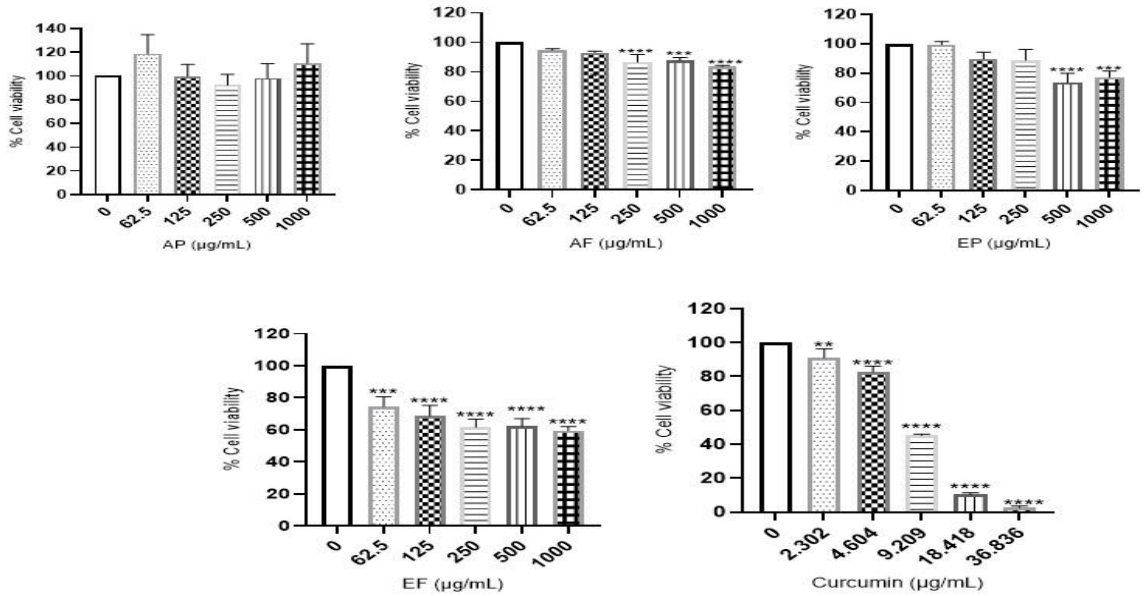

Figure 2: Antiproliferative effects of *S. malaccense* extracts on HeLa cells. Curcumin was used as the positive control. Values are means ± standard deviation of three different experiments
**P < 0.005, ***P < 0.0005 and ****P < 0.0001, compared with the negative control (DMSO)

On the other hand, EP and EF inhibited the growth of cancer cells with SI values less than 1. This study showed that the aqueous extracts (AP and AF), which are the readily edible state of the fruit, exerted a discriminatory pattern of activities between cancer and non-cancer cells. This indicates the safetyof the fruit for daily consumption as it has several functional effects against metabolic, inflammatory, and degenerative diseases.[25] Meanwhile, the ethanol extracts (EP and EF) were more toxic to normal cells than cancer cells. The different antiproliferative activities of the extracts on the cells might be related to their sensitivity to diverse mechanisms of action of the phytochemicals present, such as apoptosis induction or cell growth inhibition.[26]The amount of bioactive compounds in the extract varies greatly since different solvents have been used to extract and isolate different bioactive compounds, and the group of compounds extracted or separated is largely solvent-dependent.[27,28]

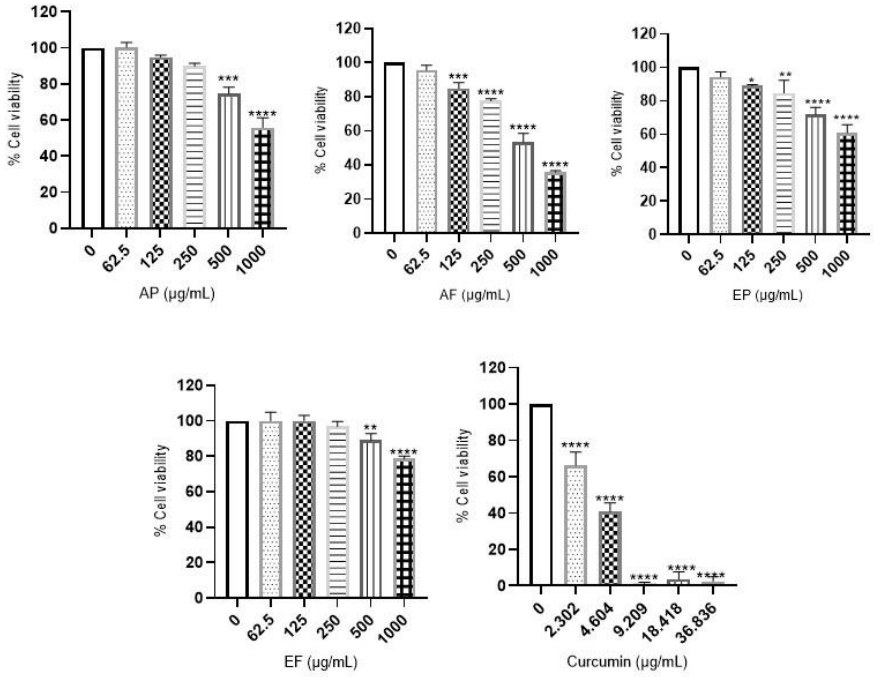

Figure 3: Antiproliferative effects of *S. malaccense* extracts on PC-3 cells. Curcumin was used as the positive control. Values are means ± standard deviation of three different experiments
*P < 0.05, **P < 0.005, ***P < 0.0005 and ****P < 0.0001, compared with the negative control (DMSO)

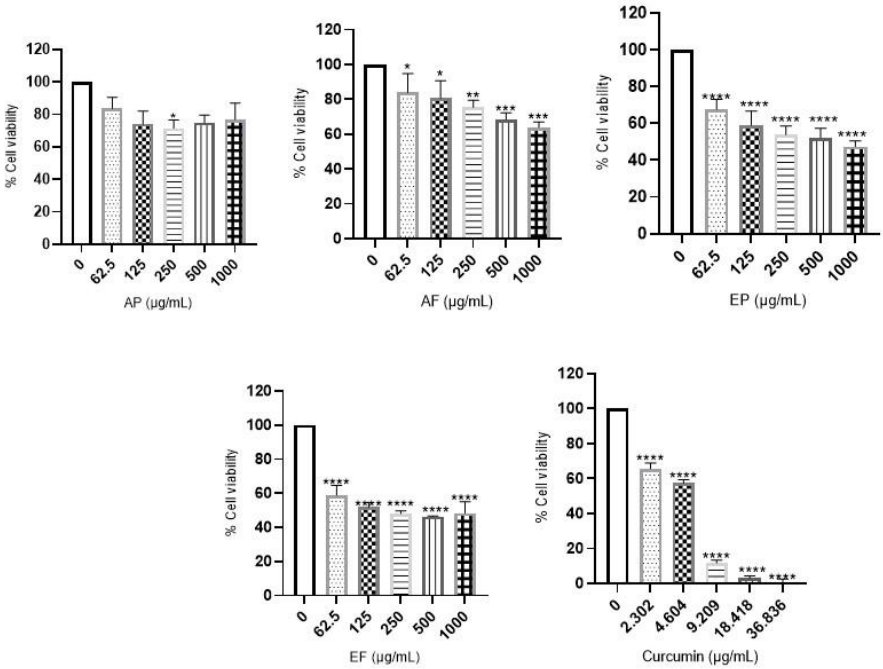

Figure 4: Antiproliferative effects of *S. malaccense* extracts on PNT-2 cells. Curcumin was used as the positive control. Values are means ± standard deviation of three different experiments.
*P < 0.05, **P < 0.005, ***P < 0.0005 and ****P < 0.0001, compared with the negative control (DMSO)

According to Frauches *et al*. (2016),[29]the therapeutic effect exerted by *Myrtaceae* family fruits may be due to the presence of several bioactive compounds, including flavonoids, sterols, phytic acid, tocopherols, ascorbic acid, the phenol class of phenolic acids, and their derivatives. Similarly, a previous study by Omojufehinsi *et al*.,[16] has shown that *S. malaccense* is rich in primary and secondary metabolites that can satisfy dietary and antioxidant requirements. This study contributes to the increasing scientific information indicating the presence of nutrients and bioactive compounds in *S.malaccense* fruit, which can modulate functional effects in disease prevention and health promotion when consumed.[25]

Table 1: Antiproliferative IC_{50} (μg/mL ± SD) values of different extracts of *S. malaccense*

Treatment	HCT-15	HeLa	PC3	PNT-2
AP	837.59 ± 48.65	>1000	>1000	>1000
AF	>1000	>1000	522.12 ± 28.65	>1000
EP	>1000	>1000	>1000	680.59 ± 390.66
EF	>1000	>1000	>1000	176.53 ± 64.01
Curcumin	6.08 ± 0.33	8.62 ± 0.14	3.74 ± 0.56	5.36 ± 0.19

Table 2: The selectivity indices of *S. malaccense* extracts and curcumin

Treatment	HCT-15	HeLa	PC3
AP	>1.19	1	1
AF	1	1	>1.92
EP	0.68	0.68	0.68
EF	0.18	0.18	0.18
Curcumin	0.88	0.62	1.43

Conclusion

This study discovered that *S. malaccense* extracts displayed varying antiproliferative activities on different cancer cell lines due to the presence of various phytochemicals and their modes of action. This result showed that the aqueous extracts might be a possible nutraceutical with anticancer properties, thus providing a scientific rationale that consuming *S. malaccense* fruit can reduce cancer risk significantly. This study suggests that more investigation is needed to isolate specific compounds from the crude extract and examine how they can affect cancer signaling pathways.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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