



Cytotoxic Effects of Polysaccharides from Medicinal Plants: *Syzygium aromaticum* (L.) Merr. & L.M.Perry, *Annona muricata* L., *Myrmecodia platytyrea* Becc., and *Averrhoa carambola* L. on MCF-7 Breast Cancer Cells

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ABSTRACT

Context: Polysaccharides are the most common natural renewable macromolecular polymers in medicinal plants. The polysaccharides of medicinal plants have been shown to have antioxidant, antitumor and antiviral effects, modulate immunity, lower blood lipids and have anticancer activity. **Methods:** In this study, the cytotoxicity of polysaccharides from *Syzygium aromaticum* (L.) Merr. & L.M.Perry, *Annona muricata* L., *Myrmecodia platytyrea* Becc., and *Averrhoa carambola* L. against human breast cancer cells MCF-7 was tested. The MTT assay was used to evaluate cell viability using different methods with different concentrations (0–300 µg/ml) of each polysaccharide to study the inhibitory effect. **Results:** A dose-dependent decrease in cell viability was observed, but none of the tested polysaccharides reached a 50% inhibitory concentration (IC₅₀) in the test area. Polysaccharide of *Myrmecodia platytyrea* Becc. proved to be the most cytotoxic among all extracts. In contrast, *Averrhoa carambola* L. and *Annona muricata* L. caused hardly any reduction in the viability of the cancer cells. **Conclusion:** Overall, all tested plant-derived polysaccharides exhibited only weak direct cytotoxicity against MCF-7 breast cancer cells within the tested concentration range, as none achieved an IC₅₀ below 300 µg/mL. This has not yet been fully investigated and requires further research to investigate higher doses, longer treatment duration or a possible synergistic effect with other cancer treatments.

Keywords: Anticancer, breast cancer, cytotoxicity, MCF-7, medicinal plants, polysaccharides

INTRODUCTION

Breast cancer is among the most common and deadly cancers in the world, with high morbidity and mortality in women (Sung *et al.*, 2021; Wilkinson and Gathani, 2022). Despite the innovation of traditional treatments such as chemotherapy, radiation and

targeted therapy, the search for new, less toxic and more effective anti-cancer drugs continues to be an area of research (DeSantis *et al.*, 2019). In the last several years, naturally occurring molecules derived from medicinal plants have attracted much interest for their anticancer activity, low side effects and ability to target multiple cellular signaling pathways involved in cancer development (Newman and Cragg, 2020). Polysaccharides are the most abundant components in plants (Minjares-Fuentes *et al.*, 2018). Polysaccharides have emerged as promising candidates for the treatment of cancer due to their broad spectrum of biological activities, including antioxidant, anti-inflammatory and immunomodulatory effects (Salehi and Rashidinejad, 2025). The substances were discovered to possess anti-cancer effects via mechanisms that include DNA damage response, cancer cell proliferation, apoptosis, host immunity, gut microbiota and therapeutic sensitivity (Wang *et al.*, 2022a). Besides that, it was found that the vast majority of plant polysaccharides are relatively non-toxic and do not cause significant side effects (Yin *et al.*, 2019). MCF-7 breast cancer cell line is a widely used model of estrogen receptor-positive breast cancer that has been widely used to determine the cytotoxicity of numerous natural compounds (Holliday and Speirs, 2011). Polysaccharides have been found to modulate some of the key signaling pathways of cancer cell survival, including control of oxidative stress, mitochondrial dysfunction, and immune activation (Gan *et al.*, 2020). Nevertheless, their effectiveness at inducing cytotoxicity and as monotherapy or adjunct therapies is an area of ongoing research.

This study aims to examine the cytotoxicity of polysaccharides from *P. macrocarpa*, *M. platytyrea*, *A. carambola*, *A. muricata*, and *S. aromaticum* on MCF-7 breast cancer cells. It provides a comparative evaluation of polysaccharide-rich fractions from selected medicinal plants against MCF-7 breast cancer cells, focusing specifically on polysaccharides rather than commonly studied phenolic constituents. By dose-dependent analysis of the effect of these polysaccharides on cell viability, we aim to provide an insight into their anticancer activity and its inhibition concentrations.

METHODS

Polysaccharide extraction

A polysaccharide-rich fraction of the medicinal plants was isolated according to standardized procedures with minimal modifications for maximum yield and economic considerations (Zhang *et al.*, 2014; Wang *et al.*, 2025). Fresh plant materials of *P. macrocarpa* (fruit), *S. aromaticum* (buds), *A. muricata* (leaves), *M. platytyrea* (tuber), and *A. carambola* (fruit) were washed, dried at 55°C for 48 h and ground into fine powder. The powder plant material was subjected to hot water extraction by boiling in distilled water (1:10 w/v) at 100°C for 2 hours, and the mixture was filtered to remove plant residues. The filtrate was concentrated under reduced pressure with a rotary evaporator and subjected to ethanol precipitation. For polysaccharide precipitation, four volumes of absolute ethanol were added to the extract and kept at 4°C for 24 hours. The precipitated polysaccharides were harvested through centrifugation at 4000 rpm for 15 minutes, washed with 80% ethanol, and vacuum dried. The polysaccharide-rich fraction was lyophilized and stored at -20°C for future use.

Polysaccharide content

Total polysaccharide content was quantified by subjecting polysaccharide-rich samples to acid hydrolysis according to a modified Saeman *et al.* (1954) method. Briefly, samples were incubated in 72% (w/w) sulfuric acid for 60 minutes at room temperature. The hydrolysate was diluted with ultrapure distilled water to 2 M H₂SO₄ final concentration. The solution was then diluted and autoclaved at 120°C for 120 minutes for complete degradation of polysaccharides. The hydrolysate was neutralized with appropriate base after the solution had cooled to room temperature, and excess water was removed on a rotary evaporator under vacuum.

Total carbohydrate content was measured by the phenol–sulfuric acid colorimetric assay, originally described by Dubois *et al.* (1956), with glucose as standard. A stock solution of 50 mg D-glucose in distilled water was prepared. A 1% (v/v) aliquot of the stock was diluted further to prepare a working solution. 0.2, 0.4, 0.6, 0.8, and 1.0 mL standard solutions. Then, 2% phenol (w/v) and concentrated sulfuric acid were added to each aliquot, incubated at room temperature for 30 minutes, and absorbance was read at 483 nm using a UV–Visible spectrophotometer. The readings were used for preparation of standard curve.

A 50 mg of sample was dissolved in distilled water to obtain the stock solution. A 1% aliquot of the solution was diluted further to make the working solution. An aliquot of 1 mL was combined with 2% phenol and concentrated sulfuric acid, and incubated at room temperature for 30 minutes. The absorbance was read at 483 nm, and the total polysaccharide concentration was determined from the standard curve. Screening of anticancer properties of polysaccharides using *in vitro* cell culture. These extracted polysaccharides were subsequently dissolved in sterile phosphate-buffered saline (PBS) and filtered through a 0.22 µm membrane before use in cytotoxicity assays.

Cytotoxicity

The (MCF-7) Breast cancer cell line was provided by Nuclear Malaysia, Bangi. The cells were grown in Roswell Park Memorial Institute (RPMI 1640) media enriched with 4 mM sodium pyruvate, 4 mM L-glutamine and 5 % heat-treated bovine serum albumin (BSA). The MCF-7 cells were cultured in a 75 ml cell-culture flask and finally incubated at 37 °C under 5 % CO₂ humidified conditions. MCF-7 cells were pre-incubated with 1 × 10⁴ cells per well in 96-well plates to determine the cytotoxic activity of the extracts and their putative IC₅₀. The cells were incubated with different concentrations of the rich fractions provided (0.3–5 mg/ml) and then incubated overnight under a humidified atmosphere of 37°C and 5% CO₂. Cisplatin was used as positive control. After 24 hours, the medium was aspirated and the cells were washed three times with PBS. Then 100 µL of medium was added to the wells. Then, 10 µl of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reagent was added per well, reaching a final concentration of 0.5 mg/ml. The plate was then incubated for 4 hours at 37°C and 5% humidified CO₂. Then, 100 µl DMSO was added per well. The plate was shaken for 30 minutes. Cell viability and cytotoxic concentration were measured as a function of the amount of formazan dye, which was determined by measuring the absorbance at 570 nm.

Statistical analysis

RESULTS

Polysaccharide content

Among the samples, *A. carambola* had the highest total content of polysaccharides ($11.21 \pm 0.88\%$) (Table 1) suggesting it as a valuable source of bioactive polysaccharides. On the other hand, *M. platytyrea* and *P. macrocarpa* showed the lowest yields, with values below 3%. The relatively high RSD values observed for *P. macrocarpa* and *M. platytyrea* might be related to natural variability in the composition matrix, plant maturity, or environmental factors influencing phytochemical profiles (Tiwari and Cummins, 2013). Polysaccharides have been known to possess pharmacological activities, including antioxidant, anti-inflammatory, immunomodulatory, and anticancer activities (Zhao *et al.*, 2019). In this context, the polysaccharide content in *A. carambola* is in agreement with other studies that have indicated high pectic polysaccharide and hemicellulose content in the fruit, which are accountable for the fruit's antioxidant activity and glycemic control capacity (Mao *et al.*, 2021). Similarly, the polysaccharide content in *A. muricata* ($6.23 \pm 1.59\%$) concurs with Suárez *et al.* (2020), who identified polysaccharide-rich extracts with immunomodulatory activity from leaves and fruit pulp.

On the other hand, *S. aromaticum* possessed moderate polysaccharide content ($3.32 \pm 2.99\%$). While essential oils (eugenol) are the major phytochemicals responsible for their pharmacological activity, a recent report by Nisar *et al.* (2021) also demonstrated that aqueous polysaccharide extracts of clove buds exhibit significant antioxidant activity, supporting the importance of their moderate polysaccharide content.

Phaleria macrocarpa and *M. platytyrea* had relatively low polysaccharide yields. This is consistent with a study by Ahmad *et al.* (2023), where it was established that flavonoids, lignans, and tannins, rather than polysaccharides, are the significant bioactive constituents of *P. macrocarpa*. Similarly, the medicinal properties of *M. platytyrea* are largely attributed to its phenolic and flavonoid constituents, according to Dirgantara *et al.* (2022).

Table 1: Results of Analysis of Total Percentage of Polysaccharide Content by UV-VIS Spectrophotometer

Species	Plant part	Percentage of Total Polysaccharide content \pm RSD
<i>P. macrocarpa</i>	Fruit	2.97 ± 3.33
<i>M. platytyrea</i>	Tuber	2.80 ± 3.53
<i>A. carambola</i>	Fruit	11.21 ± 0.88
<i>A. muricata</i>	Leaves	6.23 ± 1.59
<i>S. aromaticum</i>	Buds	3.32 ± 2.99

Cytotoxicity

In Figure 1, the *P. macrocarpa* polysaccharide treatment showed a moderate decline in cell viability with increasing concentration. Cell viability is greater than 80% at lower concentrations ($<50 \mu\text{g/ml}$), indicating little cytotoxic effect compared to cisplatin. With increasing concentration above $100 \mu\text{g/ml}$, there is a gradual decline in viability, although the decline is moderate, and cell viability is still greater than 70% at the highest concentration tested ($350 \mu\text{g/ml}$). The IC_{50} is the point at which 50% of the cells have lost viability. From the graph, it can be seen that cell viability is very high

even at 350 µg/ml, which means that the IC₅₀ value would be beyond the range that has been tested. Since the highest concentration tested remains with viability above 70%, the calculated IC₅₀ would be much higher than 350 µg/ml.

In Figure 2, can be seen trend points to a dose-dependent decrease in cell viability, where at lower concentrations (0–50 µg/ml), cell viability is very high (~80–100%), with little variance. With increased concentration beyond 100 µg/ml, there is a gradual decrease in cell viability, with the highest concentration tested (~300 µg/ml) reducing viability to about 60%.

In Figure 3, the pattern is a moderate, dose-dependent reduction in the viability of cells with rising concentration. At lower concentrations (0–50 µg/ml), cell viability is high, ranging between 80% and 100%. As the concentration rises above 100 µg/ml, viability is lost gradually, though the reduction is not sharp, with the highest concentration used (~300 µg/ml) also showing viability above 70%.

In Figure 4, the polysaccharide treatment showed a mild dose-related decrease in viability with increasing concentration. At lower concentrations (0–50%), viability was relatively high (~80–100%) without significant fluctuations. With higher concentrations exceeding 100%, the decrease in viability was small, even with the highest concentration tested (~300%), recording a viability of ~80%.

In Figure 5, the sample treatments showed a dose-dependent decreasing trend in cell viability with, at lower concentrations (0–50 µg/ml), relatively high viability (~80–100%) with little fluctuation. When the concentration was continued above 100 µg/ml, there was a general decrease with the highest concentration tested (~300 µg/ml) reducing viability to approximately 70%.

DISCUSSION

The cytotoxic activities of polysaccharides of *P. macrocarpa*, *M. platytyrea*, *A. carambola*, *A. muricata*, and *S. aromaticum* exhibit mild to low cytotoxic activities towards the MCF-7 breast cancer cells compared to cisplatin. Despite a dose-related reduction in cell viability being noticed, combined cytotoxicity were modest using the tested doses, as represented by significantly high percentages of cell viability under the highest doses. These results suggest that the polysaccharides themselves may not be active anticancer agents at these concentrations but are of potential value as adjuvants or in combination with established chemotherapeutics.

The low cytotoxicity displayed by *P. macrocarpa* polysaccharides is in line with previous work on plant-derived polysaccharides exhibiting anticancer properties through the induction of pathways such as oxidative stress and mitochondrial damage (Xu *et al.*, 2025). However, the relatively high IC₅₀ values indicate that increased concentrations or alternate routes of delivery may be necessary to achieve optimal bioactivity, as has been observed in previous work where high dosages were required to produce significant cytotoxicity (Berrouet *et al.*, 2020).

Similarly, *A. carambola* and *M. platytyrea* polysaccharides showed progressive, dose-dependent cell viability inhibition, but the impact was still moderate, with greater than 60% viability sustained at maximum concentrations. This corresponds with recent evidence showing that plant polysaccharides can modulate cancer cell growth through immunomodulatory mechanisms, cell cycle arrest, and indirect pathways (Guo *et al.*, 2022). Nevertheless, moderate efficacy in this case underlines the requirement for combinatorial approaches to enhance therapeutic action.

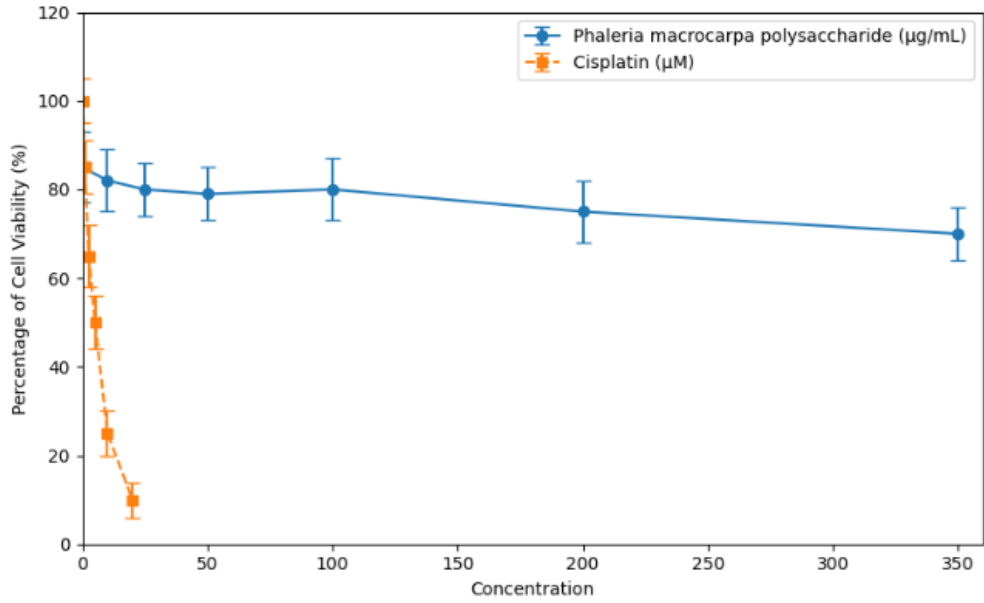


Figure 1: Effects of *P. macrocarpa* polysaccharide and cisplatin on MCF-7 breast

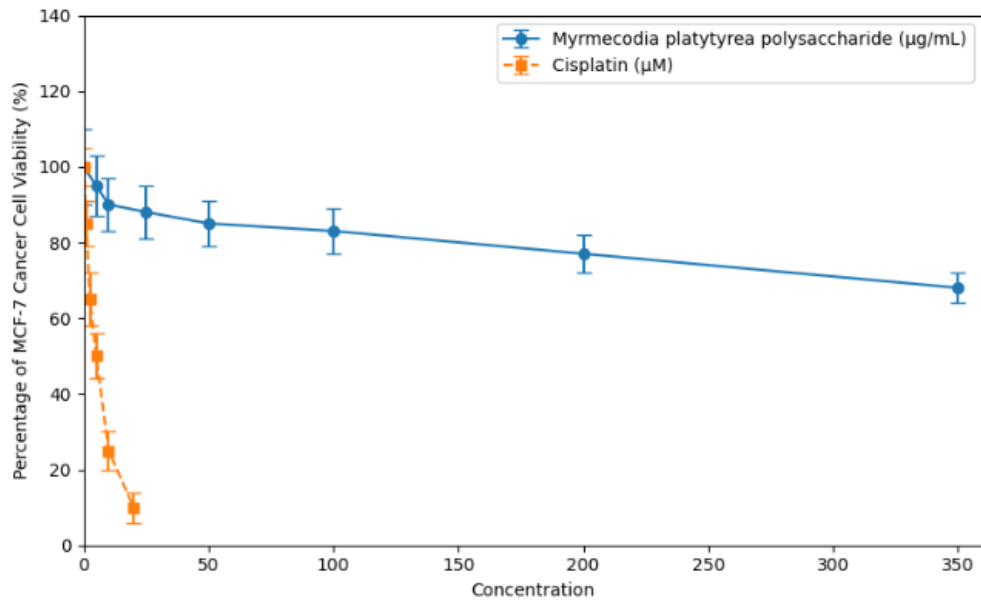


Figure 2: Effects of *M. platytyrea* polysaccharide and cisplatin on MCF-7 breast cancer cell viability.

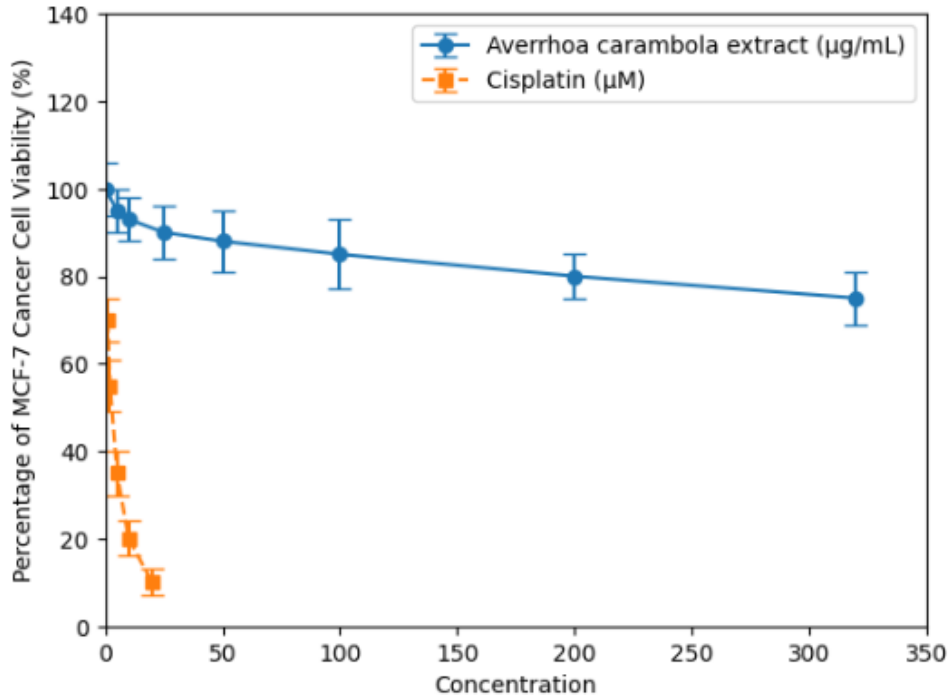


Figure 3: Effect of *A. carambola* extract and cisplatin on MCF-7 breast cancer cell viability.

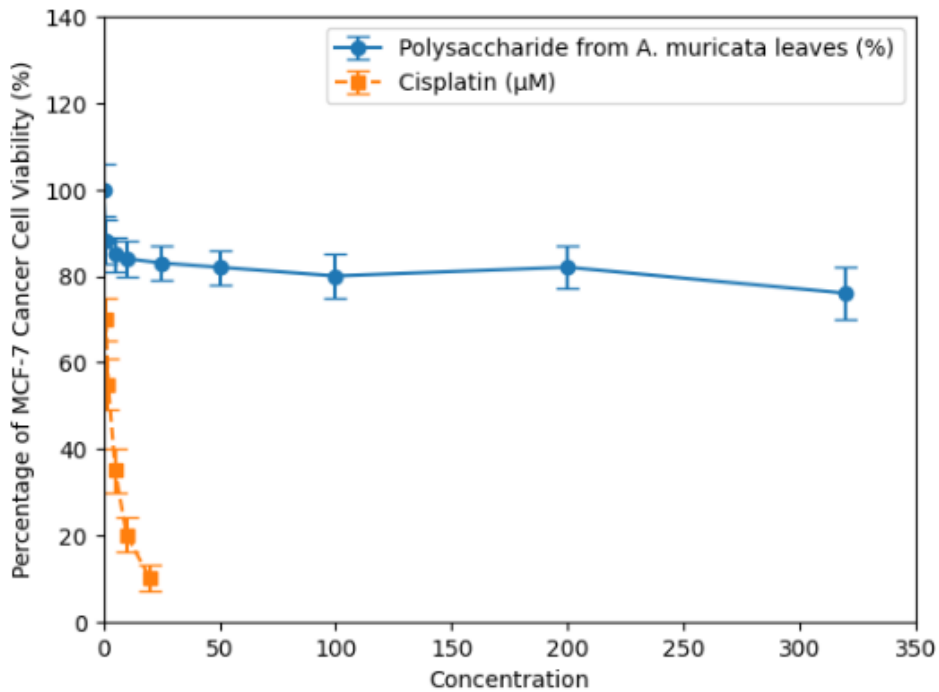


Figure 4: Effects of polysaccharide fraction from *A. muricata* leaves and cisplatin on MCF-7 breast cancer cell viability.

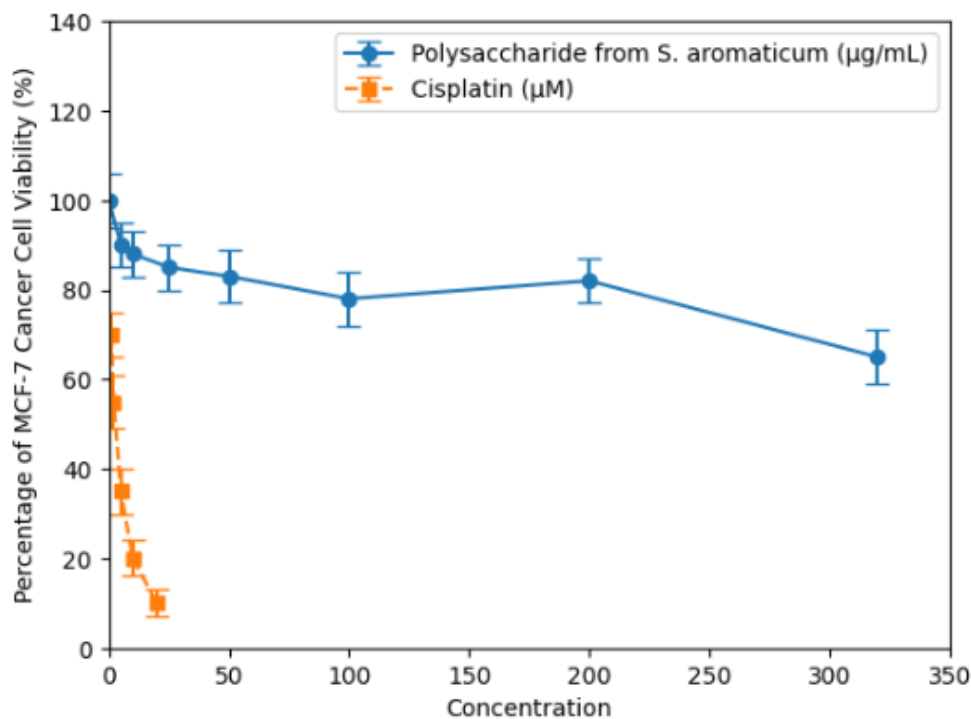


Figure 5: Effects of polysaccharide fraction from *S. aromaticum* and cisplatin on MCF-7 breast cancer cell viability.

Polysaccharides of *S. aromaticum* and *A. muricata* leaves exhibited the least cytotoxic responses at all tested concentrations. These results confirm earlier findings demonstrating the low in vitro cytotoxicity of these plant polysaccharides, perhaps due to their role in modulating oxidative balance and immune response but not inducing apoptosis (Gan *et al.*, 2020).

The determination of total polysaccharide content revealed high interspecies variability, with *A. carambola* with the highest content ($11.21 \pm 0.88\%$) and *M. platytyrea* and *P. macrocarpa* with the lowest ($2.80 \pm 3.53\%$ and $2.97 \pm 3.33\%$, respectively). Nonetheless, cytotoxic activity did not directly correspond to total polysaccharide yield. *M. platytyrea*, despite its reduced polysaccharide content, exhibited the most significant viability reduction of MCF-7. This verifies the hypothesis that plant polysaccharide biological activity is more dependent on structural complexity and functional moieties than on concentration (Wan *et al.*, 2022).

On the other hand, sulfated residue-containing polysaccharides, β -glucans, and sophisticated branching patterns promote stronger bioactivity with increased cellular uptake as well as with intracellular signaling pathways (Alfinaikh *et al.*, 2025). The comparatively better activity recorded in *M. platytyrea* polysaccharides may suggest the presence of such structure active domains although structural study could not be extended in this current study. This finding is in agreement with previous research showing that branched or low-molecular-weight polysaccharides are more anticancer than their linear or high-molecular-weight analogs (Alfinaikh *et al.*, 2025; Wang *et al.*, 2022b).

Mechanistically, various research studies have elucidated that plant polysaccharides exhibit anticancer activity via multiple mechanisms, including induction of apoptosis by triggering caspases, disruption of mitochondrial membranes, inhibition of cell proliferation by causing cell cycle arrest, and inhibition of oncogenic signaling pathways like PI3K/Akt and MAPK (Gan *et al.*, 2020). They may also exhibit indirect activities via enhancing the host's innate and adaptive immunity. In our study, none of the tested polysaccharide fractions had IC₅₀ values below 300 µg/mL. This finding is consistent with those from *S. aromaticum* and *A. muricata* extracts, which have been shown to possess minimal direct cytotoxicity but potent immunomodulatory and synergistic effects when used in combination with chemotherapy (Dibazar *et al.*, 2015; Yajid *et al.*, 2018).

In comparison with cisplatin, all tested plant-derived polysaccharides exhibited markedly lower cytotoxic effects against MCF-7 breast cancer cells. Cisplatin induced a pronounced, dose-dependent reduction in cell viability, achieving substantial cytotoxicity at relatively low micromolar concentrations, consistent with its established role as a DNA-damaging chemotherapeutic agent (Altunkaya *et al.*, 2025). In contrast, none of the polysaccharide fractions reduced cell viability below 50% within the tested concentration range, indicating the absence of strong direct cytotoxic activity. This clear contrast highlights the fundamentally different biological profiles of plant polysaccharides and conventional chemotherapy agents, where cisplatin acts through direct induction of apoptosis and DNA crosslinking (Dasari *et al.*, 2014), whereas polysaccharides are more commonly associated with indirect anticancer mechanisms.

Notably, among the tested samples, *M. platytyrea* polysaccharide demonstrated the greatest reduction in MCF-7 cell viability when compared with other plant polysaccharides, although its effect remained substantially weaker than that of cisplatin. This suggests that while *M. platytyrea* polysaccharide possesses a relatively higher biological activity, it does not function as a standalone cytotoxic agent comparable to conventional chemotherapy. Instead, its moderate, dose-dependent effect may reflect mechanisms such as modulation of cellular stress responses, immune-related pathways, or enhancement of therapeutic sensitivity, which have been widely reported for plant polysaccharides (Xu *et al.*, 2025).

The low cytotoxicity observed for all polysaccharide fractions relative to cisplatin also supports their favorable safety profile. Unlike cisplatin, which is associated with severe systemic toxicity and off-target effects in clinical use, plant polysaccharides are generally recognized for their biocompatibility and minimal adverse effects. Therefore, the present findings suggest that these polysaccharides may be better positioned as complementary or adjunct agents rather than primary cytotoxic drugs, potentially enhancing therapeutic outcomes when combined with conventional chemotherapeutics such as cisplatin.

These results emphasize the importance of structural analysis in further research. Advanced analytical techniques such as FTIR, GC-MS, NMR, and LC-MS/MS are required to identify active structural motifs and understand molecular mechanisms. More research on the synergistic value of these polysaccharides with conventional anticancer drugs is also warranted. The dose-dependent but weak activity of *M. platytyrea* suggests it as a good candidate for further pharmacological development, particularly in combinatory treatment regimens. Additional research, such as apoptosis assays, cell cycle determination, and gene expression analysis,

should be conducted to elucidate its complete anticancer activity, mechanism of action, and synergism with other therapies.

CONCLUSION

In conclusion, polysaccharides extracted from the selected medicinal plants exhibited weak cytotoxic effects against MCF-7 breast cancer cells, with *M. platytyrea* showing the most promising activity. These findings highlight the safety potential of locally derived plant polysaccharides and support their further development as complementary agents in integrated cancer therapy, in line with Malaysia's Traditional and Complementary Medicine (T&CM) framework and the growth of the national herbal bioeconomy.

DECLARATIONS OF INTEREST

None

DECLARATION OF HONOUR

We declare in our honor that our results are not fake and made up.

AI ASSISTANCE DISCLOSURE

The authors used [ChatGPT/GPT-5] to improve the clarity and readability of the manuscript. The authors carefully reviewed and edited the content to ensure accuracy and take full responsibility for the final text.

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