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EVALUATION OF THE CYTOTOXICITY OF SOME BIOMATERIALS DERIVED FROM ALGAL POLYSACCHARIDES USING MATH MODELS

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Abstract

This study aimed to predict, through applying math models, the cytotoxic effects of marine algae-derived biomaterials. The tested bioproducts included both polysaccharide-rich and gold-functionalized extracts, and the cytotoxicity was evaluated in vitro on HepG2 and Caco-2 cell lines. The results obtained revealed that the bioproduct derived from Chlorella sp., enriched with gold, exhibited the highest cytotoxicity (100%), with an IC50=134.75 µL/mL. The bioproduct containing only polysaccharides showed significantly lower cytotoxicity. Predictions regarding the cytotoxicity of selected bioproducts on HepG2 cells highlighted the enhanced activity of gold-functionalized extracts compared to simple polysaccharides. Among all the tested samples, the polysaccharides derived from Undaria pinnatifida exhibited the strongest cytotoxic effect on the Caco-2 cell line, followed by the extract from Porphyra umbilicalis. In conclusion, the results obtained through mathematical prediction demonstrate the potential of marine-derived sources in developing new bioproducts with antitumor properties.

Key words*: prediction cytotoxicities, algal derived biomaterials.*

INTRODUCTION

Biomaterials obtained from algae marine biomass are currently used as raw materials for the development of controlled-release drugs (Cardoso et al., 2016; Cunha & Grenha, 2016; Rahmati et al., 2019; Ramadan et al., 2025), composite materials, thin films, biocompatible and biodegradable dressings (de Jesus Raposo, 2015; Maver et al., 2019; Ioan et al., 2020), or gels with dermato-cosmetic applications (Mourelle et al., 2017; Alves et al., 2020; López-Hortas et al., 2021; Morais et al., 2022; Lin et al., 2022; Dini, 2023). Algae-based biomaterials containing polysaccharides are the most commonly used, and are typically obtained through hot water extraction (Chemat et al., 2012; Patra et al., 2022; Lin et al., 2022; Ciric et al., 2022), supercritical fluid extractions (Uwineza & Waśkiewicz, 2020; Ballesteros-Vivas et al., 2021), or ultrasound- and microwave-assisted extractions under pressure (Mussato, 2015; Hamamouche et al., 2024). Aqueous extracts obtained from marine algae contain soluble polysaccharides, sugars, polyphenols, or minerals (Draget et al., 2005; Lee & Mooney, 2012; Andrade et al., 2008; Pereira & Cotas, 2023). These biomaterials, in the presence of trivalent gold ions, deposit metallic gold in the form of nano or microparticles with antitumour properties (Hamouda et al., 2021; Gürsoy et al., 2021; Toader et al., 2025). In the previous study by Toader et al. (Toader et al., 2025), it was demonstrated that biopreparations obtained in aqueous media from algae such as *Porphyra umbilicalis, Undaria pinnatifida*, *Cystoseira barbata,* and *Chlorella* sp. can reduce the viability of certain tumour cell lines below 70%, finding also confirmed by other studies (Lemieszek & Rzeski, 2020). The reported results (Toader et al., 2025) showed that both simple biomaterials containing polysaccharides derived from four species of algae and biomaterials obtained in the presence of trivalent gold ions exert a cytotoxic effect on

Caco-2 and HepG2 tumour cell lines. However, preliminary data failed to demonstrate the existence of a mathematical dose-effect relationship that would allow the calculation of a maximum cytotoxicity value or an LD50 value. For this reason, the present study aimed to conduct predictive studies to evaluate the cytotoxicity of polysaccharide-based bioproducts derived from four species of marine algae, to determine whether, in their presence, the viability of Caco-2 and HepG2 tumour cell lines decreases below the threshold at which they exhibit cytotoxicity (i.e. a cytotoxicity greater than 30%).

MATERIALS AND METHODS

The math predictions were made using the previous data obtained from cytotoxicity studies conducted on eight biomaterials containing polysaccharides derived from *Porphyra umbilicalis* (A1), *Undaria pinnatifida* (A2), *Cystoseira barbata* (A3), and *Chlorella* sp. (A4), as well as gold-enriched biopreparations derived from these sources (A1+Au, A2+Au, A3+Au, and A4+Au) (Toader et al., 2025). T

The methodologies used for obtaining these biomaterials in the lab and for *in vitro* proliferation studies are those described by Toader et al., 2025, Radu et al., 2010, and Zaharie et al., 2022, respectively.

The dried algae were extracted with hot water under reflux at t<100 °C. Following extraction, the mixture was allowed to cool, and the resulting suspension was centrifuged at 8000 rpm using a Hettich Universal 320 centrifuge. The supernatant was then concentrated at t<50 °C using a rotary evaporator. The crude biomaterial obtained was weighed and dissolved in a minimal volume of 20% aqueous dimethyl sulfoxide (DMSO). Gold-containing bioproducts were synthesized from each polysaccharide extract using a 1 mM aqueous tetrachloroauric (III) acid trihydrate solution. To assess the specific cytotoxicity induced by exposing Caco-2 or HepG2 cell lines to the studied biomaterials, math models generated by the Systat 4.0 software (Inpixon, Palo Alto, CA, USA) were used. The selected math models met the following imposed conditions: a) Pearson correlation coefficient greater than 0.8 ($R^2 > 0.8$); b) Confidence interval set at 95%; c) Fitting of experimental data with well-defined mathematical functions that allow the identification of a maximum cytotoxicity value within the studied concentration range (0-80 µL/mL); d) Maximum cytotoxicity: 100%; e) Exposure time of tumour cell lines to each of the studied biomaterials: t = 24 h. In the conducted studies, the biomaterial content in the culture medium was expressed as volumetric concentration to facilitate a better comparison of the obtained results.

RESULTS AND DISCUSSIONS

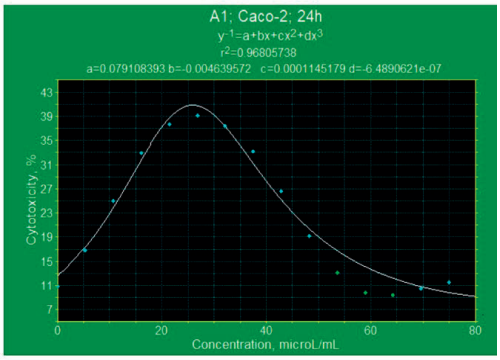
Cytotoxicity predictions for the Caco-2 cell line

Under certain conditions, algal polysaccharides may paradoxically stimulate tumour cell proliferation. This effect can arise through several mechanisms: 1). Specific monosaccharides or polysaccharides, such as fucose, glucose, fucoidan, alginate, or laminarin, may mimic or enhance the activity of growth factors. This can promote tumour cell growth via direct binding to growth factor receptors, stabilization of receptor–ligand interactions, modification of the extracellular matrix to facilitate signalling, or modulation of cellular responses that support tumour progression (Toader et al., 2025); 2). Crude algal polysaccharide extracts may also contain other water-soluble bioactive compounds such as proteins, peptides, or small molecules that interact with tumour cell receptors and influence signalling pathways, potentially enhancing cell proliferation (Toader et al., 2025).

In the case of the bioproducts (biomaterials) obtained from *Porphyra umbilicalis* (biomaterial A1), the results showed that the experimental data could be approximated with a good correlation coefficient using a third-degree inverse polynomial function.

In this case, the maximum cytotoxicity is 41% at a concentration of 26 µL/mL (Figure 1a). For the gold-containing biomaterial (A1+Au), the maximum cytotoxicity observed is 45% at c=7.5 µL/mL.

The math model generated for fitting the experimental data is complex (Figure 1b, Table 1).



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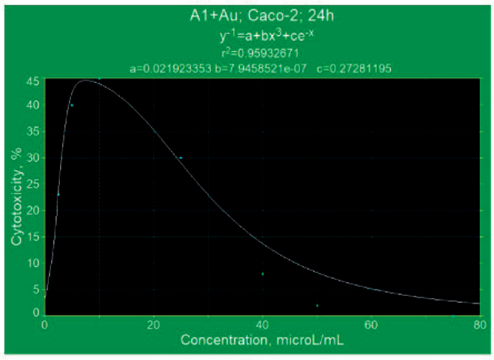

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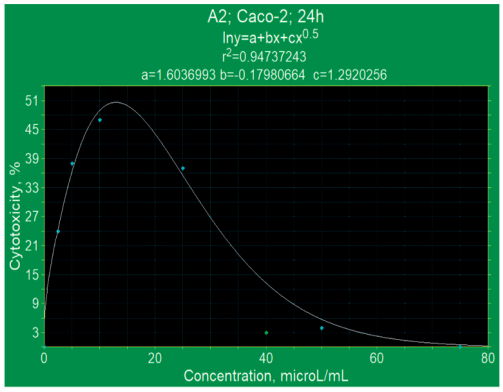
Figure 1. The effect of biomaterials obtained from *Porpyra umbilicalis* on the Caco-2 cell line: a) the effect of the bioproduct containing polysaccharides A1; b) the effect of the gold-polysaccharides bioproduct (A1+Au)

The data obtained for the two biomaterials derived from the brown alga *Undaria pinnatifida* (Figure 2a, b) show that in the case of the biomaterial enriched in polysaccharides, maximum cytotoxicity of 51% is obtained at a bioproduct concentration of 12.5 µL/mL in the culture medium (Figure 2a). For the bioproduct containing nano-dispersed gold particles, the maximum cytotoxicity obtained is 18% for a bioproduct concentration of 7.5 µL/mL in the culture medium (Figure 2b, Table 1). Regarding the cytotoxicity of biomaterials containing polysaccharides derived from the brown alga *Cystoseira barbata* (A3), the modelling program indicates a maximum cytotoxicity of 27.8%, which is reached at a biomaterial concentration of 5 µL/mL in the culture medium (Figure 3a, Table 1).In the case of the biomaterial containing microsynthesized gold particles (A3+Au), the maximum cytotoxicity obtained is 41%, corresponding to a bioproduct concentration in the culture medium of 17.5 µL/mL (Figure 3b, Table 1). The data provided by the modelling program for the bioproducts derived from the green microalga *Chlorella* sp. (Figure 4a, b) show that for the extract containing only polysaccharides, a maximum cytotoxicity of 100% is achieved at a bioproduct concentration in the culture media of 105 µL/mL (Figure 4a, Table 1). In this case, the DL50 value is 44 µL/mL. For the biomaterial containing gold (A4+Au), a maximum cytotoxicity (100%) can be reached at a biomaterial concentration in the system of 385 µL/mL. The DL50 value obtained in this case is IC50 = 134.75 µL/mL (Figure 4b, Table 1).



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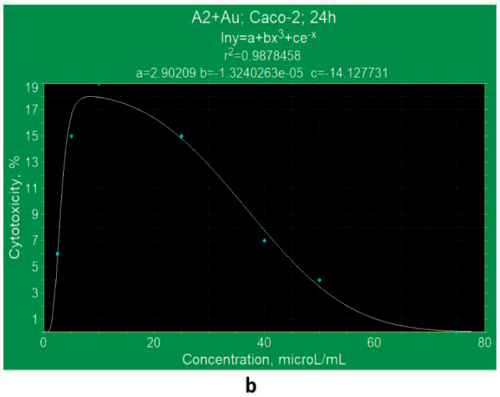

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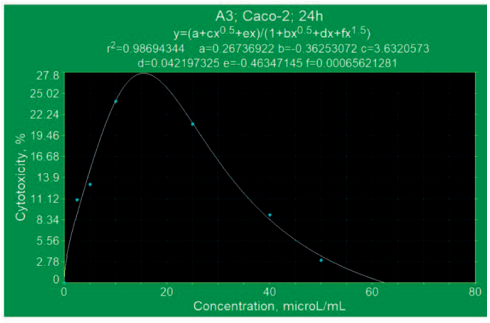
Figure 2. The effect of biomaterials obtained from Undaria pinnatifida, on the Caco-2 cell line: a) the effect of the bioproduct containing polysaccharides A2; b) the effect of the gold-polysaccharides bioproduct (A2+Au)

Table 1. Predictions regarding maximum cytotoxicity of studied bioproducts for the study tumour cell lines (Source: adaptation after Toader et al., 2025)

Biomaterial	Polysacharides content (mg/mL) ± St. Dev./Gold content (mM±St. Dev.)	Maximum cytotoxicity (%)	Corresponding concentration for maximum cytotoxicity (µL/mL)
Caco-2 cell line			
A1	27.27±0.01	41	26
A2	60±0.10	51	12.5
A3	176.40±0.05	27.8	15
A4	55.55±0.10	100	105
		50 (DL50)	44
A1+Au	0.812±0.008	45	7.5
A2+Au	0.809±0.001	18	7.5
A3+Au	0.876±0.01	41	17.5
A4+Au	0.832±0.041	100	385
		50 (DL50)	134.75
HepG2 cell line			
A3	176,40±0.05	48	80
A4	55,55±0.10	68	5.1
A3+Au	0.876±0.01	14.5	83
A4+Au	0.832±0.041	34	92.5



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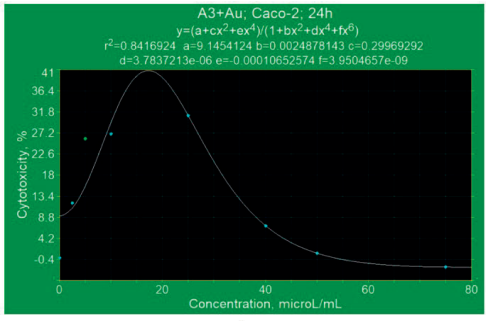

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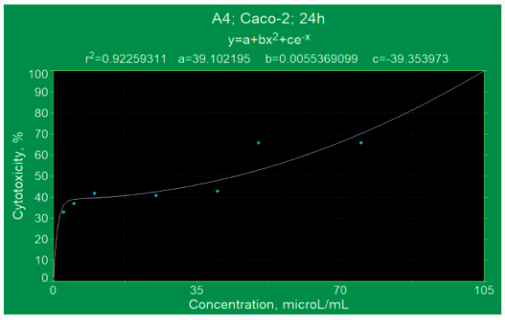
Figure 3. The effect of biomaterials obtained from *Cystoseira barbata* on the Caco-2 cell line: a) the effect of the bioproduct containing polysaccharides A3; b) the effect of the gold-polysaccharides bioproduct (A3+Au)



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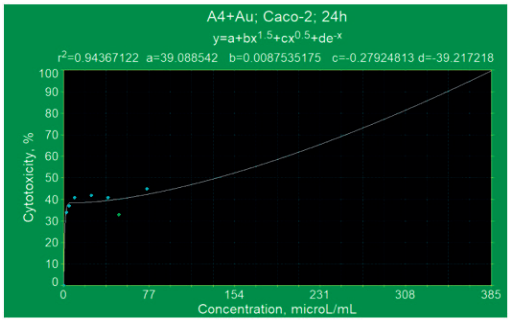

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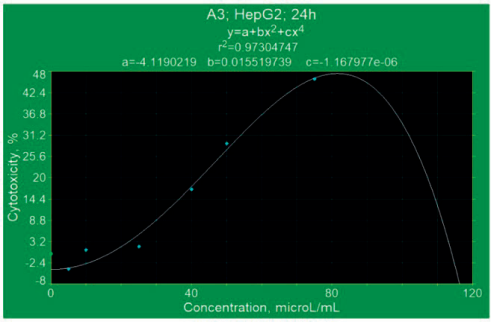
Figure 4 The influence of bioproducts obtained from *Chlorella* sp. on the Caco-2 cell line: a) the effect of the bioproduct containing polysaccharides (A4); b) the effect of the gold-polysaccharides bioproduct (A4+Au)

Cytotoxicity predictions for the HepG2 cell line

In this case, only the data obtained for the bioproducts derived from *Cystoseira barbata* (A3; A3+Au) and *Chlorella sp*. (A4; A4+Au) were subjected to math modelling. The results obtained showed that the biomaterial containing polysaccharides derived from *Cystoseira barbata* may exhibit maximum cytotoxicity of 48% for c=80 µL/mL (Figure 5a, Table 1). In the case of the corresponding bioproduct containing micro-synthesised gold (A3+Au), the maximum cytotoxicity obtained is 14.5% for a biomaterial concentration in the system of c=83 µL/mL (Figure 5b, Table 1).



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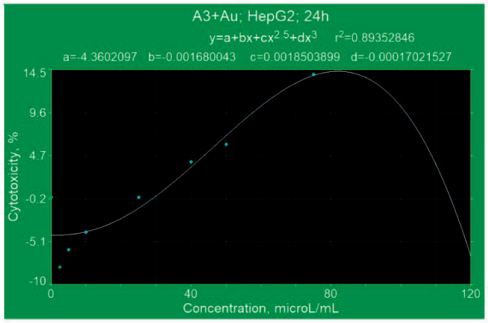

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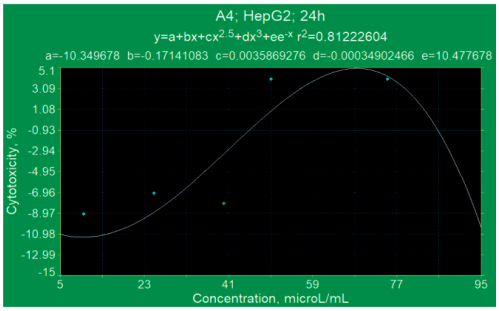
Figure 5. The influence of bioproducts obtained from *Cystoseira barbata* on the proliferation of the HepG2 cell line: a) the effect of the bioproduct containing polysaccharides (A3); b) the effect of the gold-polysaccharides bioproduct (A3+Au)

Regarding bioproducts derived from *Chlorella* sp. (Figure 6a, b), the mathematical model used indicated that for the biomaterial containing only algal polysaccharides (A4), the maximum cytotoxicity obtained is 5.1% at a bioproduct concentration in the system of 68 µL/mL (Figure 6a, Table 1). The corresponding bioproduct containing micro-synthesised gold (A4+Au) can induce a maximum cytotoxicity of 34% for a biomaterial concentration in the system of c=92.5 µL/mL (Figure 6b).



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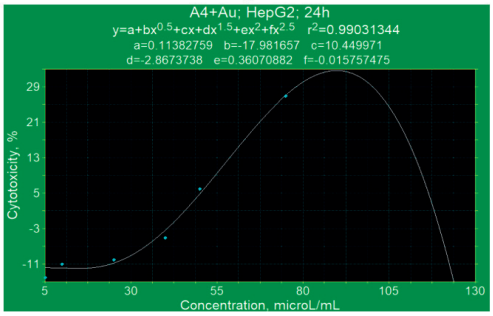

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Figure 6. The influence of bioproducts obtained from *Chlorella* sp. on the HepG2 cell line: a) the effect of the bioproduct containing polysaccharides (A4); b) the effect of the gold-polysaccharides bioproduct (A4+Au)

The results obtained in this study are in agreement with data reported by Toader and collaborators (Toader et al., 2025), but in this case, the imposed conditions allowed the obtaining of a single cytotoxicity value for each bioproduct studied, thus enabling the differentiation of the efficacy of the obtained biomaterials. Furthermore, the results obtained for the A4 biomaterial are consistent with those reported by Andrade and collaborators (Andrade et al., 2018) for studies conducted on HCT-78 tumour cell lines on biomaterials derived from different *Chlorella* sp. Similar conclusions to those obtained in this study were also reported by Lemiesezek and Rzeski (Lemiesezek and Rzeski, 2020) in studies conducted on standardised HT-29 colon cancer cell lines. Regarding the results obtained in vitro on HepG2 cell lines, the tests showed that, nevertheless, the bioproduct that contains polysaccharides derived from *Chlorella* sp. and

micro-synthesised gold particles (A4+Au), has a superior cytotoxic effect in comparison with the biomaterial containing only simple polysaccharides. These results were also confirmed by in vitro tests conducted and reported by other scientists (Toader et al., 2025; Nigram et al., 2022; Vizetto-Duarte et al., 2016).Vizetto-Duarte et al. (2016), in the studies conducted with crude extracts obtained from three *Cystoseira* species (*Cystoseira humilis*, *Cystoseira tamariscifolia,* and *Cystoseira usneoides*) HepG2 and HUVEC cells line, have reported that the biomaterial derived from *Cystoseira tamariscifolia* present the highest level of cytotoxicity for the HepG2 cell line (DL50 = 2.31 µg/mL). Moreover, the authors demonstrated that the bioproduct derived from *Cystoseira humilis* exhibits a selective cytotoxicity, with a selectivity index (S.I.) of 12.6 (S.I. calculated against HUVEC). Tumour cell proliferation, in this case, was inhibited two times (Vizetto-Duarte et al., 2016) due to the presence of a specific biomolecule's *Cystoseira humilis,* in the obtained bioproduct, named demethoxy cystoketal chromane (Figure 7), which exhibits pro-apoptotic properties. These results were also confirmed by in vitro tests conducted and reported by other scientists (Toader et al., 2025; Nigram et al., 2022; Vizetto-Duarte et al., 2016).Vizetto-Duarte et al. (Vizetto-Duarte et al., 2016), in the studies conducted with crude extracts obtained from three *Cystoseira* species (*Cystoseira humilis*, *Cystoseira tamariscifolia*, and *Cystoseira usneoides*) HepG2 and HUVEC cells line, have reported that the biomaterial derived from *Cystoseira tamariscifolia* present the highest level of cytotoxicity for the HepG2 cell line (DL50 = 2.31 µg/mL). Moreover, the authors demonstrated that the bioproduct derived from *Cystoseira humilis* exhibits a selective cytotoxicity, with a selectivity index (S.I.) of 12.6 (S.I. calculated against HUVEC). Tumour cell proliferation, in this case, was inhibited two times (Vizetto-Duarte et al., 2016) due to the presence of a specific biomolecule's *Cystoseira humilis,* in the obtained bioproduct, named demethoxy cystoketal chromane (Figure 7), which exhibits pro-apoptotic properties. Analysing the data from Table 1, it can be seen that among the obtained biomaterials, the best cytotoxic effect for the Caco-2 cell line is achieved by the biomaterial containing polysaccharides isolated from the brown algae *Undaria pinnatifida* (A2), followed by the bioproduct containing polysaccharides isolated from the red algae *Porphyra umbilicalis* (A1).

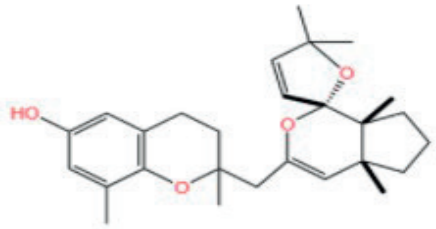

Figure 7. Demethoxy cystoketal chromane structure

Regarding the biomaterials with gold, the best effect is obtained for the bioproduct (A1+Au), derived from the red algae *Porphyra umbilicalis* (45% cytotoxicity), followed by the bioproduct (A3+Au) derived from the brown algae *Cystoseira barbata* (41% cytotoxicity). In the case of the bioproducts A4 and A4+Au, the mathematical model used generates IC50 values for very high bioproduct concentrations in the culture media (10-30%) (Figure 8, Table 1).

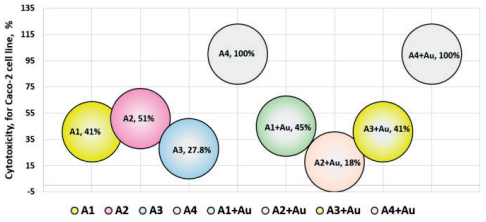

Figure 8. Maximum cytotoxicity predicted of bioproducts derived from seaweed for the tumoral cell line Caco-2

The results obtained through math predictions are useful for selecting the concentration range for studies on the mechanisms involved in the cytotoxicity process. The observed cytotoxic effects on CaCo-2 cells a standardized colorectal cancer cell line-offer preliminary evidence that the algal extracts may contain specific bioactive compounds with anticancer activity. Although algal polysaccharides are already recognized for their biological effects, including anti-inflammatory and immunomodulatory properties, their application as

anticancer agents remains in the early stages of investigation. Emerging research suggests that these compounds can reduce tumour cell viability through mechanisms such as apoptosis induction, oxidative stress generation in cancercells, and inhibition of key signalling pathways involved in tumour survival (Toader et al, 2025). Marine algae such as *Undaria pinnatifida, Porphyra umbilicalis, Cystoseira barbata*, and *Chlorella* sp. are known to produce a range of unique water-soluble secondary metabolites including polysaccharides, proteins, peptides, free amino acids, and pigments like phycoerythrin as well as hydrophilic phenolic compounds. These constituents are present in the aqueous crude extracts analyzed in this study (Toader et al., 2025). The preliminary results presented here pave the way for further investigation into the molecular mechanisms underlying the observed cytotoxic effects, including apoptosis induction, oxidative stress, and cell cycle arrest. This research underscores the pharmaceutical potential of marine algae, highlighting them as a renewable and sustainable source for novel anticancer drug discovery and development. Regarding the limitations of this study, they are due, on the one hand, to the program used, and on the other hand, to the assumptions underlying the generation of the obtained results. In this case, mathematical functions characterised by a single maximum of cytotoxicity and a high correlation coefficient (R^2) were predominantly preferred. As for the future perspectives of this study, it can be appreciated that the use of more sophisticated algorithms, such as Fuzzy (Caramihai et al., 2019), will allow the highlighting of the dependence between the bioproduct concentration in the culture medium and the cytotoxicity generated on normal and tumour cell lines. Our preliminary studies suggest that the algae-based bioproducts may exhibit selective cytotoxicity. Specifically, the aqueous extracts did not show cytotoxic effects on normal cells but may exert cytotoxic activity against the tumour cell line. If future research confirms this selective cytotoxicity, these bioproducts could serve as promising raw materials for novel nutraceuticals or dietary supplements with antitumour potential.

CONCLUSIONS

The results obtained through mathematical prediction demonstrate the potential of marine-derived sources in developing new bioproducts with antitumor properties. The math predictions performed on the data obtained in vitro tests from eight marine algae-derived bioproducts, applied to two standardised tumour cell lines, revealed differences in the cytotoxicity profiles. The results obtained from the math modelling studies indicate: 1) In the case of the Caco-2 cell line, the bioproduct (A1+Au) (polysaccharides from *Porphyra umbilicalis*+gold) showed greater cytotoxicity (45% at c=7.5 µL/mL) in comparison with the polysaccharides extract. The A2 bioproduct (obtained from *Undaria pinnatifida*) showed higher cytotoxicity (51%) than its gold-containing counterpart. For *Cystoseira barbata*, the presence of gold enhanced cytotoxicity: the bioproduct with gold reached a cytotoxicity of 41%, compared to a cytotoxicity of 27.8% for the bioproduct without gold. In the case of *Chlorella* sp., the model predicts 100% cytotoxicity at c=105 µL/mL for A4 and, respectively, at c=385 µL/mL for (A4+Au); 2) In the case of the HEPG2 cell line, predictions indicate as following: in the case of the bioproduct A3 was obtained a cytotoxicity of 48 cytotoxicity at c=80 µL/mL; for the bioproduct (A3+Au), was obtained a cytotoxicity of 14.5% at c=83 µL/mL; in the case of the bioproduct A4 was obtained a cytotoxicity of 5.1% at c=68 µL/mL; for the bioproduct (A4+Au) a cytotoxicity of 34% was obtained at c= 92.5 µL/mL.

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