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Natural inhibitors of PTP1B: Caffeic acid, cinnamic acid, and cinnamaldehyde as promising agents against triple-negative breast cancer

Michał Suchecki [a], Maria Denise Amico [b], Joanna Herkt [a], Giuseppe Vergilio [b], Francesca Rappa [b,c], Magdalena Gorska-Ponikowska [a], Alicja Kuban-Jankowska [a,d,*]

[a] Medical University of Gdansk, Department of Medical Chemistry, Gdansk, Poland
[b] Department of Biomedicine, Neuroscience and Advanced Diagnostics, University of Palermo, Palermo, Italy
[c] Institute of Translational Pharmacology, National Research Council of Italy (CNR), Palermo 90146, Italy
[d] Medical University of Gdansk, Department of Medical Chemistry, Debinki 1 Street, Gdansk 80-211, Poland

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ABSTRACT

Background: and Aim: Natural substances have always been used to treat various diseases and cancers. Cinnamaldehyde has been previously reported to have antioxidant, antidiabetic and anticancer potential. This study aims to investigate the effect of caffeic acid and cinnamic acid compared to cinnamic aldehyde on the viability of MCF-7 and MDA-MB-231 cell lines in correlation with the effect on the non-cancerous cell line: HB-2.
Materials and Methods: Cell viability assays were conducted using the MCF-7 and MDA-MB-231 breast cancer cell lines in correlation with the HB2 cell line. The migration assay has been done using all three cell lines using the scratch assay. Molecular docking was achived using SwissDock SwissDrugDesign of method AutoDock Vina 1.2.0 docking parameters of the full protein binding ligand samling exhaustivity of 4 (Molecular Modeling Group, University of Lausane and Swiss Insisute of Bioinformatics. Schematics was created using BioRender © 2024. Images of proteins and ligands were rendered using BIOVIA, BIOVIA, Dassault Systèmes, Discovery Studio Visualizer, v17.2, San Diego: Dassault Systèmes, 2016. The PTP inhibitory effect was calculated using PNPP as the substrate, with compounds serving as inhibitors in correlation with the non-inhibited control.
Results: Both Caffeic acid and cinnamic acid had an inhibitory effect on the cell viability of the MDA-MB-231 cell line. MCF-7 studies showed that caffeic acid had an inhibitory effect on cells, but cinnamic acid had this effect only on MCF-7 cells. HB2 cells have shown reduced viability, which is significantly higher than that of MCF-7 cell lines.

1. Introduction

Breast cancer remains one of the most prevalent malignancies affecting women worldwide, with continuing challenges [1]. According to GLOBOCAN 2022 data [2], breast cancer is the most commonly diagnosed cancer in women globally with approximately 2.3 million new cases annually, and the leading cause of cancer-related death in women with approximately 662,500 deaths annually. The treatment of breast cancer is based on a multidisciplinary approach that integrates surgery, radiotherapy and systemic therapies, including chemotherapy, hormonal therapy and targeted treatments, selected based on the biological subtype (hormone receptor positive, HER2 positive or triple negative) and the risk of recurrence [3]. In treatment and prognosis, despite advances in clinical interventions. The search for novel therapeutic agents has increasingly turned towards natural compounds, which may offer enhanced efficacy and reduced toxicity.[3]In this context, cinnamic aldehyde, cinnamic acid, and caffeic acid have emerged as promising candidates due to their diverse biological activities observed in preclinical studies and can also play a role as adjuvants in cooperation with classical oncology [4,5].

These naturally occurring phenolic compounds (Fig. 1) are found in a variety of plants and have been historically recognised for their antioxidant, anti-inflammatory, and anticancer properties [9]. Cinnamic aldehyde, the principal component of cinnamon oil, has demonstrated potential in modulating several signalling pathways associated with tumor growth and metastasis [10]. Similarly, cinnamic acid has been

* Corresponding author at: Medical University of Gdansk, Department of Medical Chemistry, Gdansk, Poland.
E-mail addresses: michal.suchecki@gumed.edu.pl (M. Suchecki), magdalena.gorska-ponikowska@gumed.edu.pl (M. Gorska-Ponikowska), alicja.kuban-jankowska@gumed.edu.pl (A. Kuban-Jankowska).

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noted for its ability to induce apoptosis in cancer cells while exhibiting minimal effects on normal tissues [11]. Caffeic acid, a well-known hydroxycinnamic acid, further complements these effects through its free radical scavenging activity and its role in inhibiting angiogenesis, a critical process in cancer progression [9,12,13].

Recent studies have begun to elucidate the mechanisms underlying the anticancer properties of these compounds, pointing to their capacity to interfere with key cellular processes such as cell cycle regulation, apoptosis, and metastatic behaviour [11,14]. The integration of these compounds into novel therapeutic strategies could potentially lead to more effective and less toxic treatments for breast cancer [5,10]. This article aims to explore the molecular basis of these effects and evaluate the translational potential of cinnamic aldehyde, cinnamic acid, and caffeic acid as adjuncts to conventional breast cancer therapy [15].

Protein phosphorylation is a key regulatory mechanism in cell signaling, with protein tyrosine kinases and phosphatases acting in concert to modulate and fine-tune a wide range of cellular processes, including proliferation, differentiation, and apoptosis. Dysregulation of these enzymes is often implicated in the development and progression of cancer [16]. The human genome Protein Tyrosine Phosphatases (PTP) superfamily is divided into four different families (Class I, II, III, and IV) [17–19] depending on sequence and their catalytic domains. The function of the PTP family has wide potential through its role in angiogenesis of cancer and regulation of the mTORC pathway in cancer cells, promoting cell proliferation and cancer aggression [18,19].

Protein Tyrosine Phosphatase 1B (PTP1B) is a critical regulator of cellular signalling (Fig. 2), acting predominantly through the dephosphorylation of phosphotyrosine residues on its substrates [18,19]. As a member of the (PTP) family, PTP1B plays an essential role in modulating key signal transduction pathways, including Ras/ERK, mTORC, AKT, and signalling pathways for immune cells and oncogenic signalling [24–26].

The enzyme contains an active-site cysteine residue (Cys 215) that is highly susceptible to reversible oxidation, which temporarily inactivates its phosphatase activity. Susceptibility to oxidation may be one of the mechanisms regulating the overexpression of this enzyme, among others, in cancers [27]. This oxidative regulation serves as a natural cellular mechanism to regulate signaling pathways [28].

Despite the broad involvement of PTP1B in multiple signaling cascades, its regulatory influence appears to be highly context-dependent [29]. Recent studies suggest that PTP1B activity is modulated not only by expression levels but also by subcellular localization, oxidative modifications, and interactions with specific adaptor proteins [30]. Moreover, dysregulation of PTP1B has been implicated in diverse pathological conditions, including metabolic disorders, cancer, and immune dysfunction [31]. Focusing on these unresolved aspects is therefore essential to elucidate the precise contribution of PTP1B to cellular homeostasis and to identify potential therapeutic strategies targeting its activity as adjunctive therapy to classical chemotherapy [32].

2. Methods

Reagents: MCF-7 and MDA-MB-231, HB-2 cells were purchased from the European Collection of Cell Cultures (ECACC). Dulbecco Modified Eagle Medium (DMEM) (D6429), cinnamaldehyde (W228613), cinnamic acid (8.00235), caffeic acid (C0625) were obtained from Sigma Aldrich.

Cell Culture: MCF-7 and MDA-MB-231 cells were cultured in DMEM medium supplemented with 10 % fetal bovine serum and 1 % penicillin/streptomycin solution, maintained at 37°C in a 5 % CO2 atmosphere. Cell confluency was kept at a maximum of 2 × 10^6 cells/ml, with medium changes every two days to maintain recommended density. HB-2 cells were cultured with DMEM medium supplemented with 10 % FBS, 1 % PEN/STR, 5 µg/ml hydrocortisone and 10 µg/ml insulin.

2.1. Cell viability test

Untreated cells (1 ×10^6 cells/ml) served as control, while treated cells with 1 mM, 0.5 mM, 0,25 mM, 0,125 mM, 0.0625 mM, 0,03175 mM, 0,016 mM and 0,008 mM solutions of: caffeic acid, cinnamic acid, and cinnamaldehyde and incubated for 24 h. MTT(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) in DMEM was added for 3 h at 37°C in 96-well plates. After the formazan formation, a visible purple precipitate formation, the medium was discarded, and the crystals were dissolved in DMSO. Absorbance was measured at 595 nm

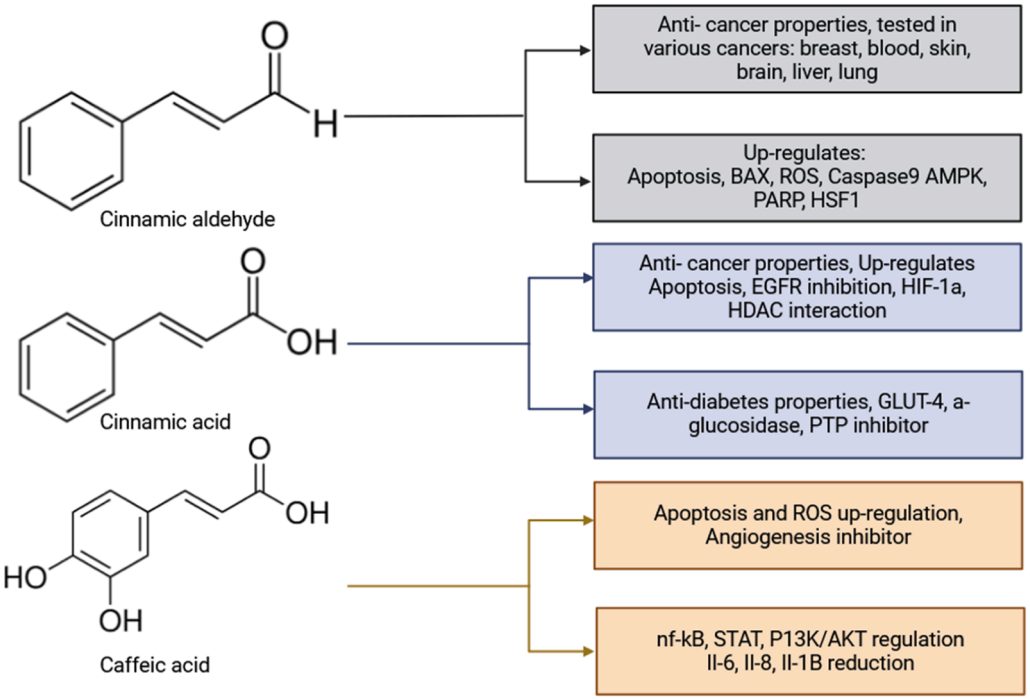

Fig. 1. Structure of the molecules of cinnamic aldehyde, cinnamic acid and caffeic acid with selected mechanisms of action of the substances [6–8].

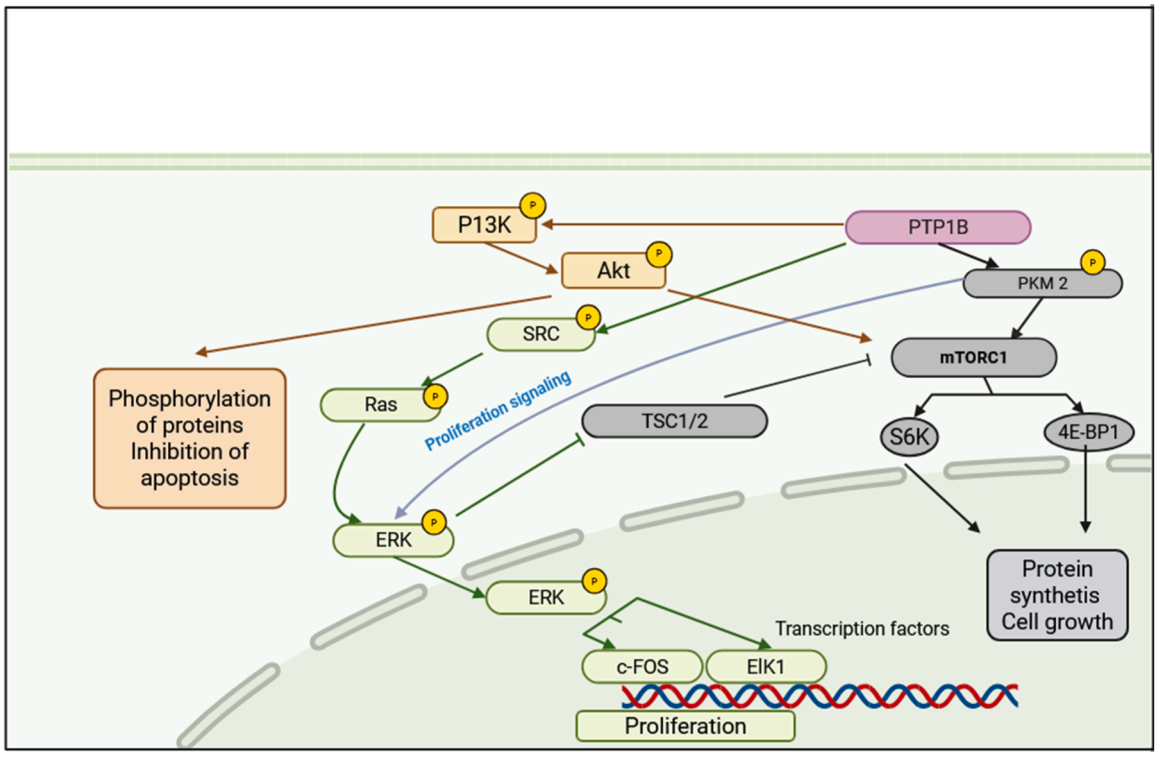

Fig. 2. Schematic diagram of the mechanism of PTP1B-dependent phosphorylation on the cell signaling pathway [20–23].

using a microplate reader. All tests were performed in triplicate.

2.2. PTP1B activity assay

Recombinant PTP1B phosphatase was prepared in 10 mM Tris-HCl buffer containing 2 mM β-mercaptoethanol and 1 mM DTT, to a final concentration of 0.02 mg/ml. The tested compounds were initially dissolved in DMSO at concentrations 1000 times higher than the final assay concentrations. These stock solutions were then diluted with distilled water to obtain working concentrations ranging from 200 μM to 6.125 μM. The experiment was carried out using 96-well immuno microplates. The assay was performed for 30 min, and the percentage of enzyme inhibition was calculated relative to the positive control.

2.3. Statistical analysis

Experiments were performed at least three times, and data were analysed using GraphPad Prism. Statistical significance was determined using ANOVA with Tukey's test or T test with Wilcoxon test, with $p < 0.05$ considered significant. Statistical calculations of PTP1b inhibition was achived using non-linear regression with 95 % of likelihood method of IC_{50} calculation.

2.4. Molecular modeling

Molecular docking was achived using SwissDock SwissDrugDesign of method AutoDock Vina 1.2.0 supporting Auto Dock 4.0 docking parameters of the full protein binding ligand area, samling exhaustivity of 4 (Molecular Modeling Group, University of Lausane and Swiss Insisute of Bioinformatics. The best model and rotation was chosen by most energy Schematics was created using BioRender © 2024. Images of proteins and ligands was rendered using BIOVIA, BIOVIA, Dassault Systèmes, Discovery Studio Visualizer, v17.2, San Diego: Dassault Systèmes, 2016.

2.5. Ligand docking and in-silico based analysis

The interactions between PTP1B and ligands are was visualized using SwissDrugDesign of method AutoDock Vina 1.2.0 4 (Molecular Modeling Group, University of Lausane and *sapiens* has resolution of 2.50 Å, obtained by X-ray diffraction bounded with inhibitor complex used in this experiment. Control of this experiment was phosphorylated nitro-phenol (pNPP)

2.6. Multiple ligand docking and analysis

The molecules used in the studies were selected according to their known receptor binding site in control of known receptor binding-side inhibitor and allosteric inhibitor. The interactions between molecules and most favorable model location was virualised using BIOVIA, BIOVIA, Dassault Systèmes, Discovery Studio Visualizer, v17.2, San Diego: Dassault Systèmes, 2016. Detailed informations regarding types and quantity of interactions are provided in Table 1.

3. Results and discussion

3.1. Overview of experimental findings

The enzymatic activity assays reveled that the tested phenolic compounds exhibited a concentration-dependent inhibition of PTP1B (Fig. 3). Caffeic acid shows the highest inhibitory potency among the evaluated molecules reaching the IC_{50} of 11,82 μM. This result indicates a strong affinity of caffeic acid for the PTP1B catalytic site, suggesting that its hydroxyl and carboxyl functional groups play a critical role in enzyme binding and inhibition [35]. Compared to cinnamic aldehyde and cinnamic acid obtaining the IC_{50} value 44,09 and indeterminate value consecutively. Comparing the obtained values, they confirm the results obtained previously for cinnamic acid reaching $IC_{50} = 57,6$ μM [36]. The result for cinnamic aldehyde outside the limit of quantification indicates our previous research articles a weak affinity of this substance to the PTP1B receptor, confirming the $IC_{50} > 100$uM [36].

Table 1
The type and quantity of docking interactions between the PTP1B receptor and ligands with specific amino acid interactions [33,34].

Compounds	Docking score (kcal/mol	Docking details			Interacting amino acids
		Conventional H-bond	Alkyl and pi-alkyl	Others	
Caffeic Acid	- 7575	1	2	3	Tyr 46, Val 49, Phe 182, Ser 216, Arg 221,
Cinnamic aldehyde	- 5865	0	3	4	Met 74, Glu 76, Ala 77, Leu 234, Asp 245, Val 249, Glu 252,
Cinnamic acid	- 5625	1	2	3	Tyr 46, Val 49, Phe 182, Ser 216, Ala 217, Arg 221,
pPNP	0,288	3	3	7	Tyr 46, Val 49, Phe 182, Cys 215, Ile 219, Arg 221,

3.2. Correlation with molecular modeling

The experimental results were consistent with molecular modelling predictions, confirming that the studied compounds can effectively bind to the catalytic pocket of PTP1B through interactions with key active-site residues such as Tyr 46, Val 49, Phe 182, Cys 215, Ile 219, Arg 221 (Fig. 4.) confirming affinity to enzyme catalytic domain achieving this by comparing the substrate binding site residues [35,37].

Molecular docking analysis of the four ligands to the protein model reveals significant differences in binding strength and the amino acid residues involved. (Fig. 4) The strongest and most stable binding was observed at the catalytic domain of protein, where the ligand forms multiple interactions with residues Tyr46, Cys215, Arg221, Ala217, and Phe182 (Table 1). The presence of these residues, including potentially catalytic ones, suggests that caffeic acid (ΔG = –7.575 kcal/mol) and cinnamic acid (ΔG = –5.625 kcal/mol), serves as inhibitors of active site (Fig. 5). Control modeling showed caffeic acid, cinnamic acid and pNPP are binding to the active side of protein, but significant differences for binding energy (Table 1). The results obtained by molecular modeling confirm the in-vitro PTP1B experiments, proposing the hypothesis of competitive inhibition [38].

3.3. Mechanistic interpretation

The observed inhibitory activity can be mechanistically explained by the suppression of PTP1B-mediated dephosphorylation of the PMK2 Y105 residue, which induces a metabolic blockade that disrupts cancer cell proliferation pathways [29]. The inhibition of PTP1B by caffeic acid, cinnamic acid translated into a measurable reduction in the proliferation of breast cancer cell lines MCF-7 and MDA-MB-231, suggesting a functional link between enzymatic inhibition and antiproliferative outcomes [39]. This functional link between enzymatic inhibition and antiproliferative outcomes suggests that blocking PTP1B activity disrupts downstream signaling cascades that are essential for tumor cell survival and growth. Mechanistically, PTP1B inhibition prevents the dephosphorylation of key regulatory residues, leading to a “metabolic jam” that compromises the energetic and proliferative capacity of cancer cells. Furthermore, recent studies have demonstrated that PTP1B inhibition can interfere with multiple oncogenic kinases, such as HER/EGFR, JAK, and STAT, which act as central initiators of tumor formation and progression [17,40–42]

Collectively, these findings indicate that experimental compounds confirm previous reports of substances used in this article as substances reducing breast tumor proliferation [39,43,44].

3.4. Biological significance

In the present study, we evaluated the effects of natural products, including caffeic acid, cinnamic acid, and cinnamic aldehyde, on the proliferation of breast cancer cell lines MCF-7 and MDA-MB-231, as well as the non-tumorigenic HB-2 cell line. Cinnamic aldehyde was included as a reference compound due to its well-documented inhibitory activity against multiple molecular targets involved in cancer, including PTP1B [45]. All compounds reduced viability of the breast cancer cells (Figs. 6–8), confirming the inhibition of the enzyme due to the over-expression of PTP1B in cancer cells, leading to a reduction in cell viability.

Cinnamic acid showed concentration-dependent cytotoxicity against both breast cancer cell lines. In particular, significant cytotoxicity was observed against MCF-7 cells (Figs. 6a,7a,8a), with IC_{50} around 31,75 μM in contrast to MDA-MB-231, HB 2 cell line with IC_{50} around

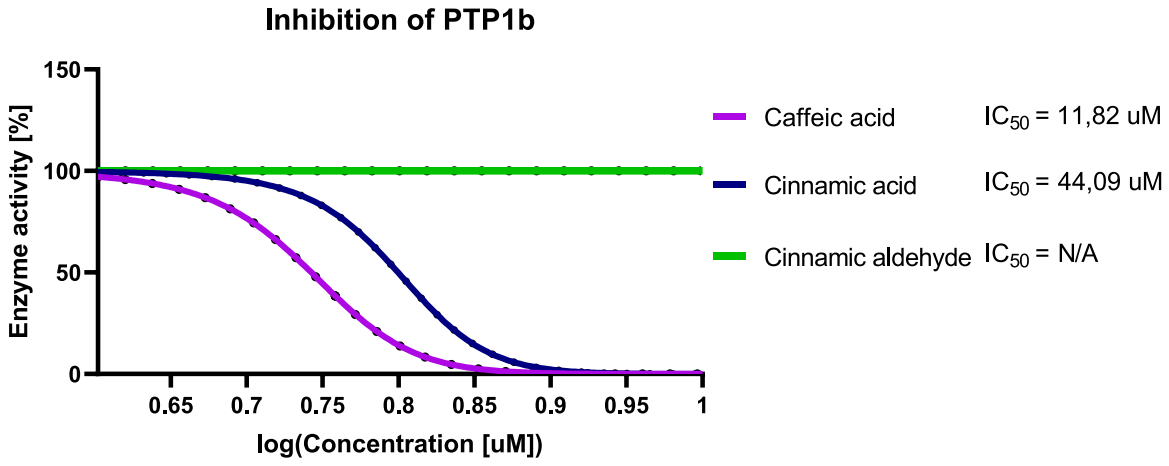

Fig. 3. Enzymatic activity of PTP1B phosphatase after 30 min of treatment. Data are presented as enzymatic activity [%] and calculated relative to the control (enzyme with substrate).

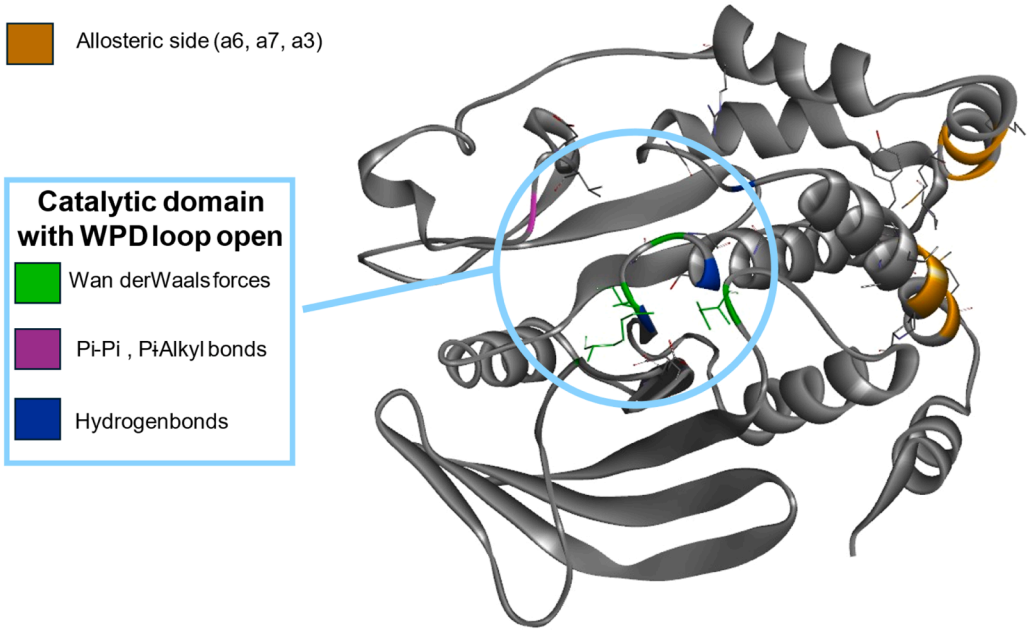

Fig. 4. Crystal structure of PTP1B with the WPD loop and the enzyme catalytic domain and allosteric site highlighted.

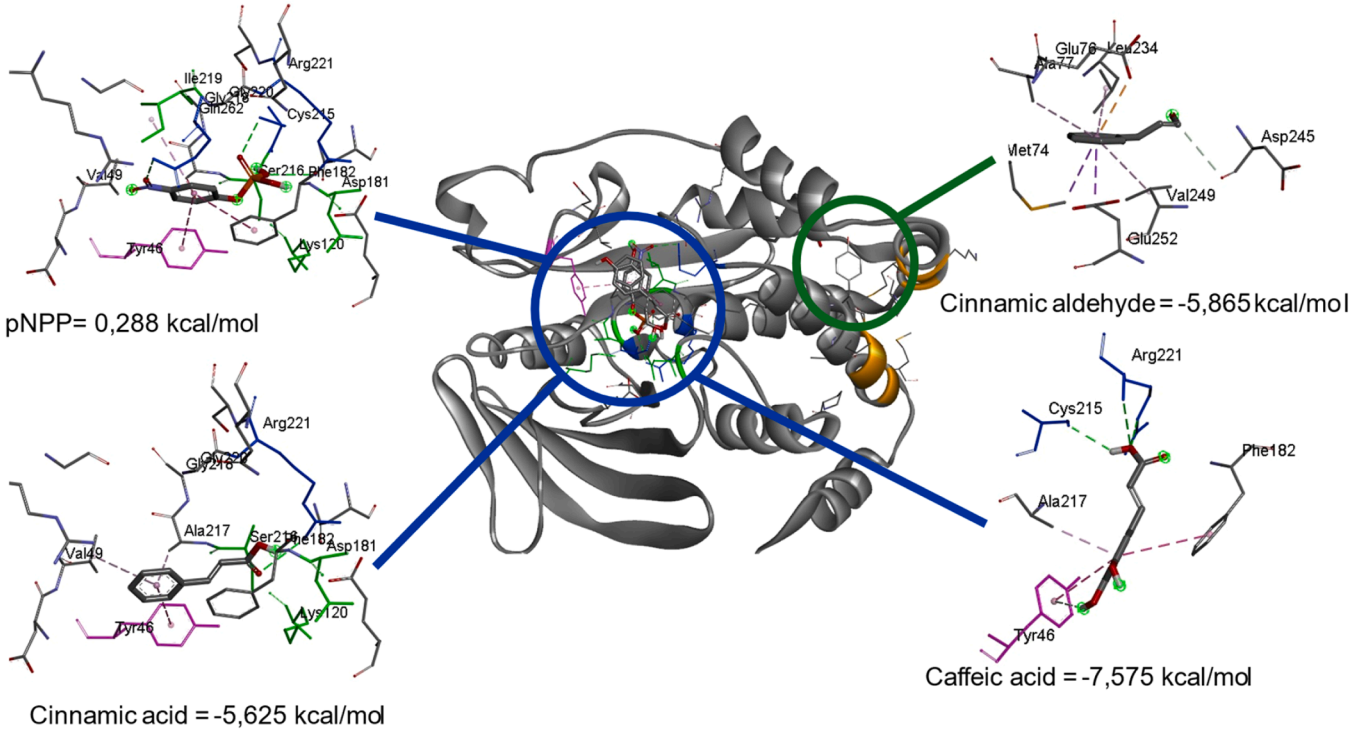

Fig. 5. 3D Molecular modeling and docking with tested molecules. pNPP – paranitrophenyl phosphate control docking of substrate, Cinnamic acid, Cinnamic aldehyde, and Caffeic acid with binding affinity as kcal/mol.

1 mM. The result obtained is promising for the effects on the MCF-7 breast cancer cell line, notoriously less aggressive and more responsive to chemotherapy and hormonal treatments [25], in which a reduction in cell viability was observed at very low concentrations of cinnamic acid. The data obtained suggests the potential of cinnamic acid as an anti-cancer candidate against some subtypes of breast cancer.

Caffeic acid showed, compared to cinnamic acid, more significant cytotoxicity of both cancer cell lines. In particular, in MCF-7 cells subjected to treatment an IC_{50} about 0,08 mM is found (Fig. 6a), in MDA-MB-231 cells an IC_{50} of around 0.125 mM, while in non-tumor HB-2 cells an IC_{50} of about 0.5 mM (Fig. 8a). The data obtained show that there is a marked effect on the cellular viability of tumor cells at very low concentrations, on the contrary at the same concentrations no significant reduction of cellular viability is observed in non-tumor cells. These results contrast with previous publications on caffeic acid used against MDA-MB-231 cells, which achieved an IC50 of $>$ 10,000 μM [46].

Based on the data obtained, caffeic acid shows the potential of an effective and promising candidate to be used in the modeling of anti-

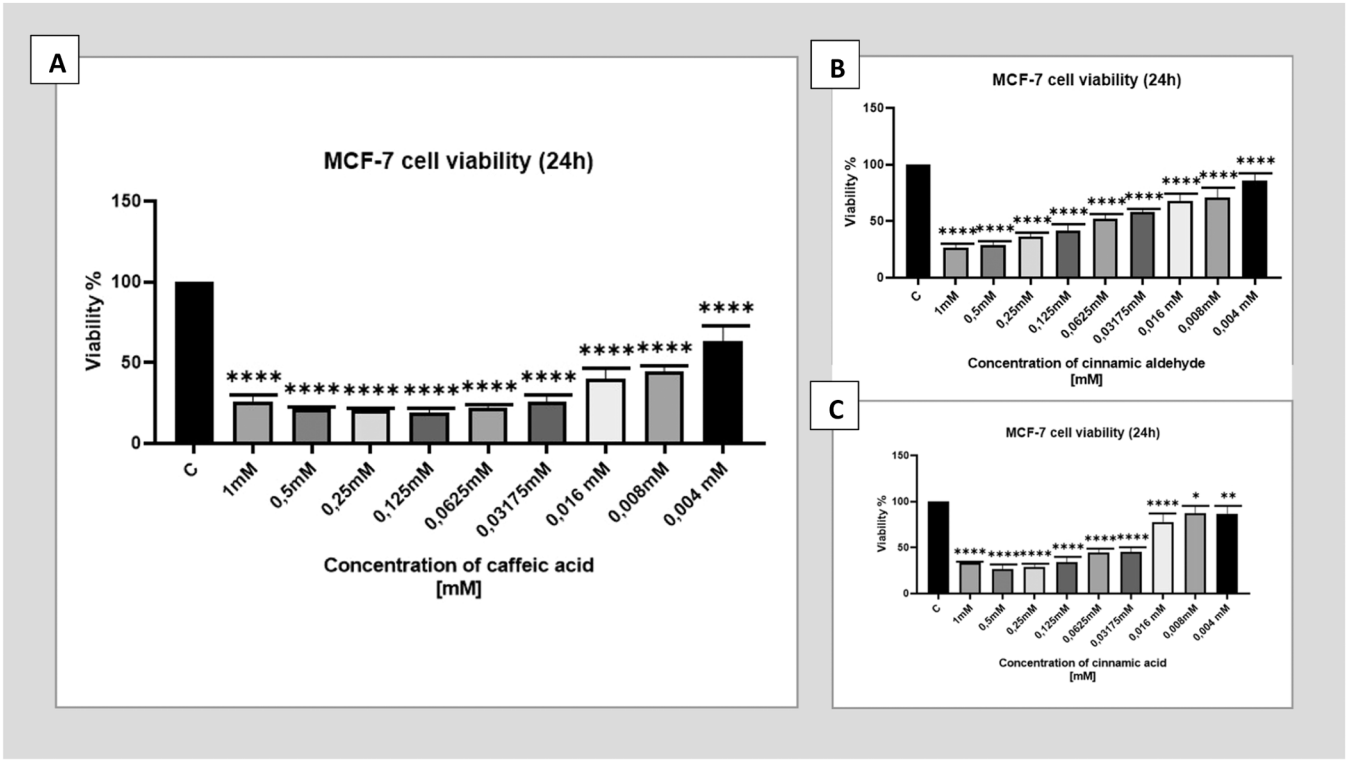

Fig. 6. A,B,C - Cell viability of MCF-7 breast cell line after treatment for 24 h with 3 molecules, measured with MTT-based test. Data presented as a percentage of the untreated control calculated from the absorbance (570 nm) vs the control. ****p < 0,0001, ***p < 0,001, **p < 0,01, *p < 0,1 vs control.

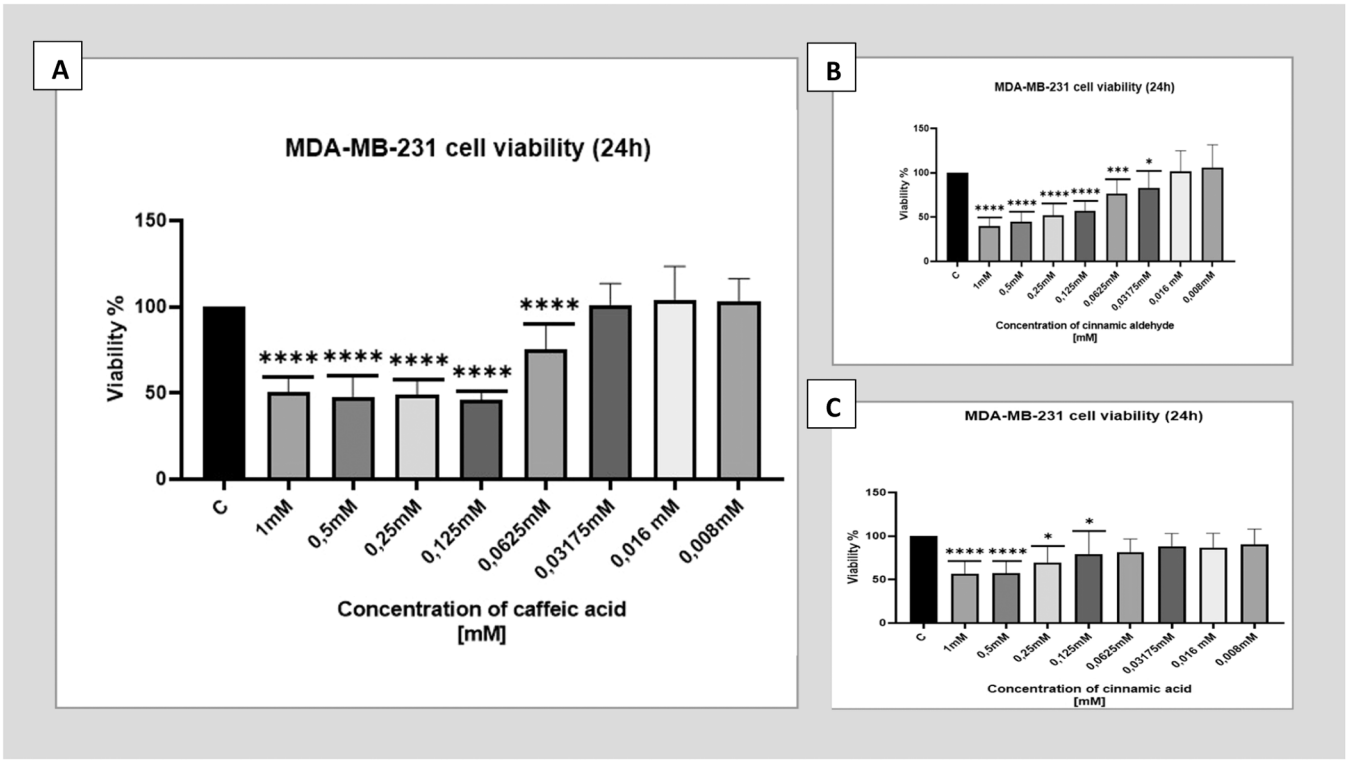

Fig. 7. A,B,C- Cell viability of MDA-MB-231 breast cell line after treatment for 24 h with 3 molecules, measured with MTT-based test. Data presented as a percentage of the untreated control calculated from the absorbance (570 nm) vs the control. ****p < 0,0001, ***p < 0,001, **p < 0,01, *p < 0,1 vs control.

tumor therapies that specifically target tumor cells, while sparing healthy cells. However, further studies are needed to better understand and expand the knowledge on this subject [39,47].

Based on the obtained results, it can be concluded that the combination of vincristine (Fig. 9) with natural phenolic compounds (caffeic acid, cinnamic acid, and cinnamaldehyde) leads to a significant

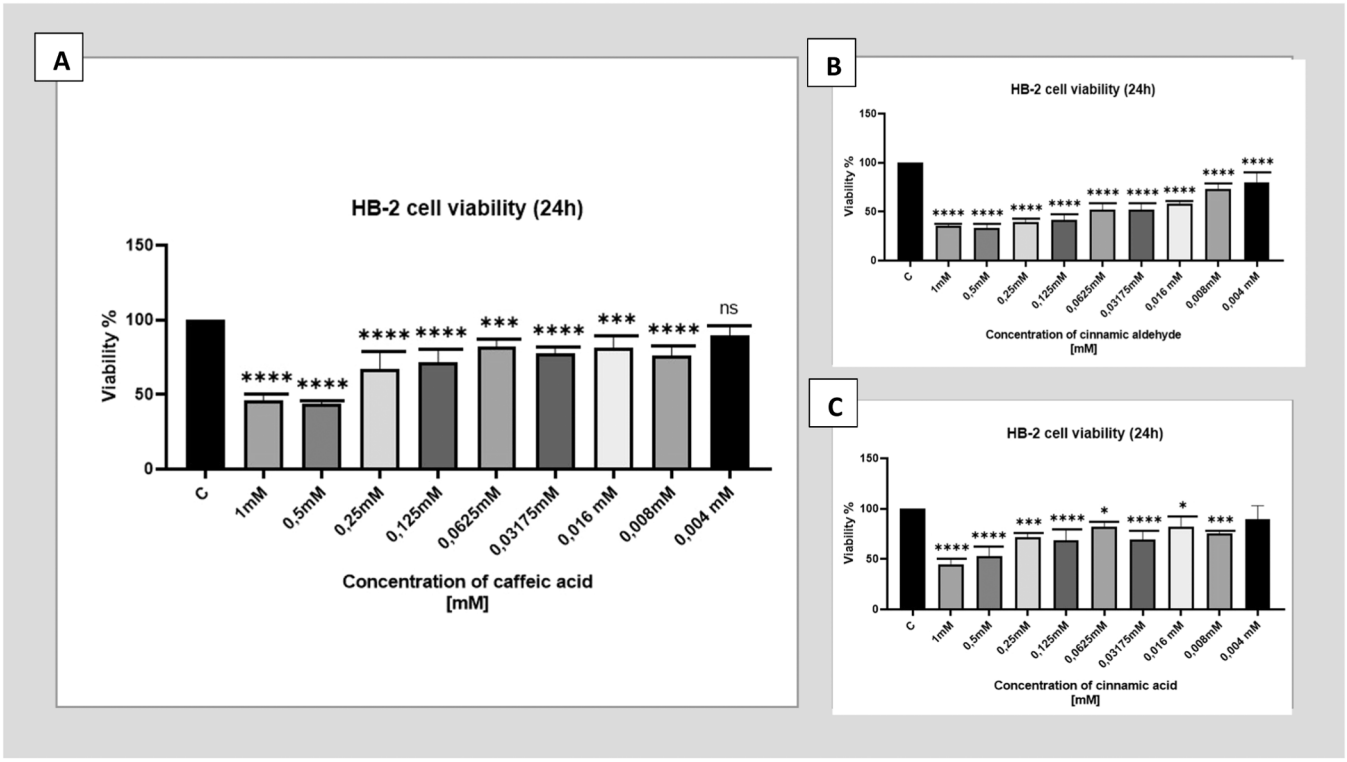

Fig. 8. A,B,C- Cell viability of MDA-MB-231 breast cell line after treatment for 24 h with 3 molecules, measured with MTT-based test. Data presented as a percentage of the untreated control calculated from the absorbance (570 nm) vs the control. ****p < 0,0001, ***p < 0,001, **p < 0,01, *p < 0,1 vs control.

reduction in the survival of cancer cells from the MCF-7 (HER+) and MDA-MB-231 (triple-negative breast cancer) lines, while having a

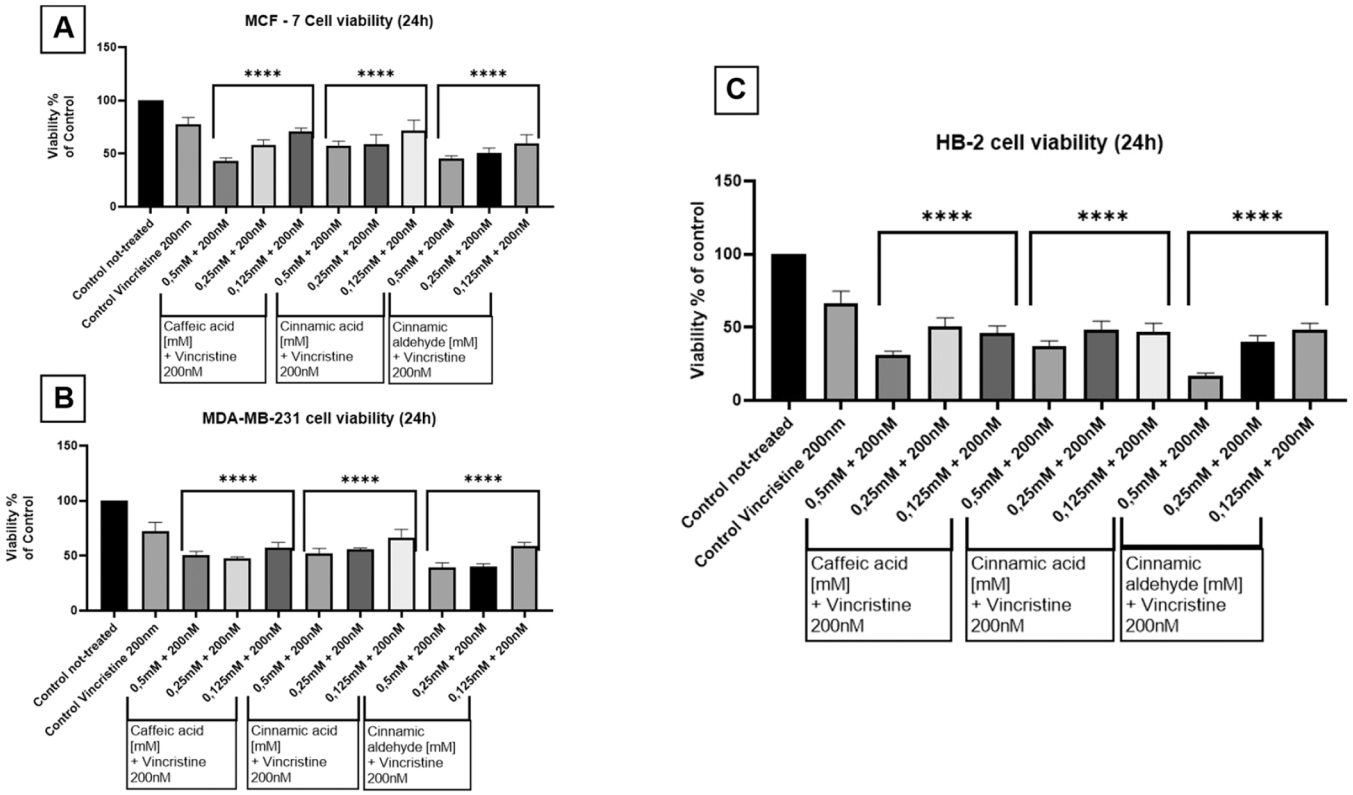

Fig. 9. Comparison of the Cell viability of the MCF-7 (a), MDA-MB-231 (b), HB-2 (c) breast cell lines after treatment for 24 h with three bioactive compounds in coincubation with Vincristine, measured with an MTT-based test. Data presented as a percentage of the untreated control calculated from the absorbance (570 nm) vs the control. ****p < 0,0001.

smaller, though still noticeable, toxic effect on normal breast epithelial cells (HB-2 line). The strongest anticancer effect was observed for cinnamaldehyde in combination with vincristine, which caused the greatest decrease in cancer cell survival. In HB-2 cells, a decrease in survival was also observed after the combination. Previous experiments on these cell lines have shown that vincristine reduced the proliferation of the cancer cells used, which shows the potential use of the substances used as an adjuvant therapy to classical oncological therapy [48,49].

4. Conclusion

In summary, this study demonstrates that natural compounds such as caffeic acid, cinnamic acid, and cinnamaldehyde effectively inhibit PTP1B enzymatic activity, leading to a reduction in the proliferation of breast cancer cell lines MCF-7 and MDA-MB-231. Cinnamic acid exhibited concentration-dependent cytotoxicity, particularly against MCF-7 cells, highlighting its potential selectivity toward specific breast cancer subtypes. The observed antiproliferative effects are consistent with molecular modelling predictions and can be mechanistically attributed to the suppression of PTP1B-mediated dephosphorylation of key regulatory residues, resulting in metabolic blockade and disruption of oncogenic signaling pathways, including HER/EGFR, JAK, and STAT. Collectively, these findings underscore the relevance of PTP1B as a therapeutic target and support the potential of these natural products as lead compounds for anticancer drug development. Further studies are warranted to fully elucidate their mechanism of action, optimize their potency, and assess their efficacy in in vivo models.

CRediT authorship contribution statement

Joanna Herkt: Writing – review & editing. **Giuseppe Vergilio:** Writing – review & editing, Investigation. **Alicja Kuban-Jankowska:** Writing – review & editing, Validation, Supervision, Project administration, Formal analysis, Conceptualization. **Magdalena Gorska-Ponikowska:** Supervision, Funding acquisition. **Francesca Rappa:** Supervision. **Michał Suchecki:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Maria Denise Amico:** Writing – review & editing, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

Data will be made available on request.

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