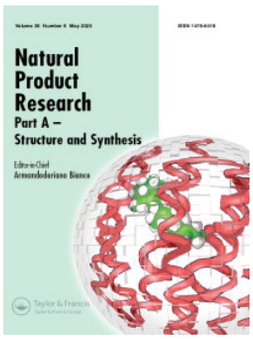

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Cytotoxic and anti-migratory effects of polyphenolic compounds on breast cancer cells by altering *Jam-A*, *LFA-1*, and *VLA-4* gene expression

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ABSTRACT

This study represents the initial research of the effects of a combination of the largest number (13) of different polyphenic substances (PFK^{5120}), formulated based on the propolis content on cell viability, migration and expression of *lymphocyte function-associated antigen-1 (LFA-1), very late antigen-4 (VLA-4)* and *junction adhesion molecule A (Jam-A*) in breast cancer (BC) cells. PFK^{5120} negatively affected cell viability at a 5% concentration as compared with unexposed ones ($p < 0.001$). Treatment with 20% PFK^{5120} for 48h down-regulated *Jam-A* in MCF-7 and MCF-10A, up-regulated *LFA-1* in MCF-10A and MDA-MB-231, and down-regulated *VLA-4* in MCF-10A and MDA-MB-231 ($p < 0.001$). Furthermore, migration was found to be inhibited by PFK^{5120} at varying doses and times. Migration was completely inhibited by 35% PFK^{5120} treatment in MDA-MB-231, while even lower concentrations (10%) were effective in MCF-7. Current findings indicate that PFK^{5120} represents a valuable natural component of BC therapy through its cytotoxic and anti-migratory effects.

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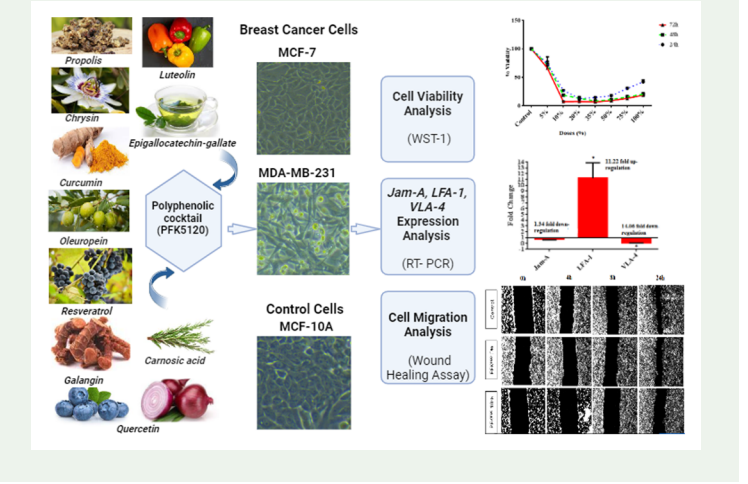

Impact statement

This study is the first to demonstrate that PFK^{5120}, a novel polyphenol-rich formulation comprising 13 bioactive compounds, exhibits cytotoxic and anti-migratory effects in breast cancer cells. By modulating key adhesion molecules (Jam-A, LFA-1, VLA-4), PFK^{5120} shows potential not only as a preventive agent but also as a promising adjuvant in breast cancer therapy.

1. Introduction

Cell adhesion molecules, involving integrins and some junctional proteins are pivotal regulators during the formation and subsequent course of breast cancer (BC) (McSherry et al. 2011). Jam (junctional adhesion molecule) proteins, one of the tight junctions function in diverse immune and adhesion events, including cell polarity, permeability, and migration (McSherry et al. 2011; Zhao et al. 2014). Although previous reports have linked *Jam-A* expression with many cancer types (Naik et al. 2008; McSherry et al. 2009, 2011; Brennan et al. 2013; Cao et al. 2014; Czubak-Prowizor et al. 2022), its association with BC remains controversial. Some studies demonstrated an inverse relationship between *Jam-A* expression and BC cell migration (Naik et al. 2008; Wang and Lui 2012; Cao et al. 2014). Conversely, others reported a positive correlation between *Jam-A* expression and BC migration (McSherry et al. 2009, 2011; Brennan et al. 2013). Lymphocyte function-associated antigen-1 (LFA-1), a β2 integrin predominantly expressed on leukocytes (Hyun et al. 2019), regulates leukocyte adhesion and migration at the site of inflammation by acting as a receptor for intercellular adhesion molecule-1 (ICAM-1) and interacting with Jam-A (Filippi 2016; Vazquez Rodriguez et al. 2017). A close relation between LFA-1 expression and BC survival has been reported (Byrne et al. 2021; Wu et al. 2023). Very late antigen-4 (VLA-4), a member of the β1-integrin family, has been shown to act on endothelial cells to interact with Jam-B, fibronectin, and vascular cell adhesion molecule-1 (VCAM-1) (Strell and Entschladen

2008; Filippi 2016) and moves with LFA-1 during leukocyte migration (Wang et al. 2005). Previous studies in lung, bone, and brain metastasis of BC have up-regulation of *VLA-4* (Schlesinger and Bendas 2015; Sharma et al. 2017) in tumor tissues.

Dietary polyphenols have been identified as potential fighters against BC due to their pleiotropic and epigenetic effects (Selvakumar et al. 2020; Nguyen and Osipo 2022). Polyphenols exhibit beneficial biological features against inflammation, cancer, allergies and atherosclerosis by scavenging oxygen radicals, inhibiting various oxidases, and stimulating antioxidant enzymes (Nijveldt et al. 2001). There is also evidence from previous studies that different polyphenols exert anti-migratory and anti-metastatic effects by altering different molecular pathways (Borawska et al. 2016; Masadah et al. 2021; Sari et al. 2022; Yu et al. 2023). In our previous study, propolis with high polyphenol content was also shown to have significant apoptotic-inducing cytotoxic activities on BC cells (Seyhan et al. 2017, 2019). The scope of this study was to further explore the cytotoxic and anti-migration properties of a polyphenolic cocktail (PFK^{5120}) formulated on the basis of the most effective propolis content identified in our previous studies on BC cells. Therefore, the current study aimed to evaluate the effects of the PFK^{5120} polyphenolic cocktail on both *LFA-1*, *VLA-4,* and *Jam-A* gene expression and anti-migration effects in BC cell lines and also to investigate its potential role in BC metastasis for the first time.

2. Results and discussion

2.1. Cell viability

The cell viability results are given in Table S1 and Figures S1A–C. Accordingly, cytotoxic effects of the PFK^{5120} were observed in all cell lines, depending on concentration and time. The viability was affected negatively with the treatment of PFK^{5120} beginning from 5% concentration compared to controls at 24h, 48h, and 72h ($p < 0.001$). The cell viability was decreased dramatically following treatment with 20% PFK^{5120} in MCF-7 (Figure S1A) and MCF-10A (Figure S1C). The cytotoxic effect of PFK^{5120} was started at 24h in MDA-MB 231, and the IC50 concentration was determined as 20-35% at 48h (Figure S1B). The cell viability assay demonstrated that 13.2% of MCF-7, 57.5% of MDA-MB-231, and 12.4% of MCF-10A remained viable following 20% PFK^{5120} treatment for 48h (Table S1). When the treatment (20% PFK^{5120}) was applied for 72h, the cell viability was 7.49% for MCF-7, 36.68% for MDA-MB-231 and 8.15% for MCF-10A. These outcomes indicate a slight tendency for cell selectivity against MCF-7 than for MCF-10A. The effects of PFK^{5120} on MCF-10A mammary epithelial cells modelling fibrocystic breast disease are consistent with the findings of our previous research, which demonstrated the antiproliferative activities of propolis samples and the polyphenolic compounds ferulic acid, pinostrobin, and galangin on these cells (Çelik et al., 2024).

2.2. Cell migration

PFK^{5120} had an anti-migratory effect on the MCF-7 and MDA-MB-231 at varying doses and times. In MCF-7, a significant decrease in migration was observed at 4h, 8h, and 24h with 5% PFK^{5120} and at all hours with 10% PFK^{5120} (Table S2, Figures S2A and

S5A). In MDA-MB-231, 5% PFK^{5120} resulted in a notable decrease in migration at 24h ($p < 0.05$), whereas 10% PFK^{5120} affected cell migration at 4h ($p < 0.05$), 24h ($p < 0.0001$), and 48h ($p < 0.05$) (Table S2, Figures S2B and S5B). Similarly, 35% of PFK^{5120} caused migration arrest in MDA-MB-231 at 48h. In MCF-10A, migration was inhibited by all concentrations of PFK^{5120} for up to 24h. However, cells migrated again after 24h and the scratch was almost closed within 48h as in untreated MCF-10A (Table S2, Figures S2C and S5C).

Our results are consistent with the previous reports of cytotoxic, antiproliferative, and anti-migratory properties of phenolic substances which are the components of PFK^{5120} including luteolin (Wu et al. 2021), epigallocatechin (Marín et al. 2023), apigenin (Sudhakaran et al. 2023), caffeic acid (Rezaei-Seresht et al. 2019), CAPE (caffeic acid phenethyl ester) (Fang et al. 2023), chrysin (Yang et al. 2014), quercetin (Wu et al. 2018), oleuropein (Messeha et al. 2020), and resveratrol (Kowsari et al. 2023) and our previous research in which the antiapoptotic and cytotoxic effects of Anatolian honey (Seyhan et al. 2017) and propolis samples rich in polyphenolic compounds on BC cells, both hormone-positive (+) and hormone-negative (–) were demonstrated (Seyhan et al. 2019).

2.3. Influence of PFK^{5120} treatment on cell morphology

After 48h of treatment with 20% PFK^{5120}, apoptotic morphological changes previously reported (Willingham 1999), were detected in the cells, such as a decrease in cell number and the amount of cytoplasm, blebbing, and impaired membrane integrity. PFK^{5120} led to the disruption of cell attachment and the floating of cells on the surface of the culture medium (Figure S3). These morphological changes related to apoptosis were also observed in our previous study with Anatolian propolis in BC cells (Seyhan et al. 2017).

2.4. Gene expression

2.4.1. Comparison of expression levels between non-invasive and invasive cells without PFK^{5120} treatment

Jam-A was reported to modulate cell migration as well as apoptosis and cell proliferation in BC (Murakami et al. 2011; Wang and Lui 2012; Brennan et al. 2013; Goetsch et al. 2013). The association of *Jam-A* expression with BC is controversial. While an inverse correlation was reported between *Jam-A* and BC cell migration by some researchers (Naik et al. 2008; Wang and Lui 2012; Cao et al. 2014), others reported that higher levels of *Jam-A* are favourably associated with tumor aggressiveness and poor prognosis (McSherry et al. 2009, 2011; Brennan et al. 2013). It was suggested that a down-regulated *Jam-A* reduced tumor progression through induction of apoptosis, suggesting that it may be a survival factor in BC (Murakami et al. 2011). *In vivo* studies in xenografts of various cancers (breast, lung, kidney, prostate) showed that Jam-A antibody treatment significantly reduces tumor progression (Goetsch et al. 2013; Walker et al. 2021). Recent research suggests that Jam-A has a potential molecule for cancer therapy as it participates in multiple signalling pathways that drive tumor progression, cell proliferation, migration, angiogenesis, apoptosis, etc. (Smith

et al. 2022; Bednarek et al. 2023). In the current research, the highest *Jam-A* expression (lowest ΔCt value) was found in MCF-10A, followed by MCF-7 and MDA-MB-231 cells (Figure S4). Significant differences in *Jam-A* expression (ΔCt) were observed between MCF-7 cells and MDA-MB-231, and MCF-10A ($p = 0.013$ and $p = 0.003$, respectively) (Figure S4A). Accordingly, *Jam-A* expression was 5.77-fold and 12.46-fold lower in MCF-7 and MDA-MB-231, respectively, than in MCF-10A. The present findings are in agreement with the findings of previous research, which expressed an inverse correlation between Jam-A and cell aggressiveness in BC (Naik et al. 2008; Wang and Lui 2012; Cao et al. 2014; Bednarek et al. 2020).

Metastasis and poor prognosis-related alterations in integrin gene expression have previously been reported (Seguin et al. 2015; Sökeland and Schumacher 2019). However, studies investigating *VLA-4* and *LFA-1* expression in BC are limited. In this study, the highest *LFA-1* expression was detected in untreated MCF-7, followed by MCF-10A and MDA-MB-231. *LFA-1* expression was 2.26-fold higher in untreated MCF-7, and 6.32-fold lower in MDA-MB-231 than MCF-10A. However, when ΔCt values were compared, no significant difference in *LFA-1* expression was observed between untreated MCF-7 and MDA-MB-231 versus MCF-10A ($p > 0.05$) (Figure S4B). Budinsky et al. previously reported very low *LFA-1 alpha* and *LFA-1 beta* expression in MCF-7 (Budinsky et al. 1997). Wang et al. suggested that increased CD44 expression which leads to the up-regulated *LFA-1* and *VLA-4 via* crosslinking and increased integrin-mediated cell migration contributes to tumor metastasis in MDA-MB-435S BC cells. (Wang et al. 2005). Vasse et al. demonstrated higher *LFA-1* expression in MDA-MB-231 than in MCF-7 (Vasse et al. 2001). Unlike the previous findings (Vasse et al. 2001), *LFA-1* expression in PFK^{5120} untreated MCF-7 and MDA-MB-231 was not significantly different from that in MCF-10A and among untreated cells, the highest *LFA-1* expression was observed in MCF-7, followed by MCF-10A and MDA-MB-231 in the current research (Figure S4B).

VLA-4 was found lower in MCF-7, ZR-75-1, and SK-BR-3 cells than in normal epithelial cells previously (Budinsky et al. 1997). Up-regulation of *VLA-4* has been shown in metastasis of BC (Schlesinger and Bendas 2015; Sharma et al. 2017). In basal-like and HER2 (+) BC, *VLA-4* expression was related to good prognosis (Rojas et al. 2021). In recent research, up-regulated *VLA-4* in MDA-MB-231 showed an association with brain metastasis *in vitro* (Zhang et al. 2023). Compatible with earlier studies (Budinsky et al. 1997), the current study presented that *VLA-4* expression was 125.36-fold lower in MDA-MB-231 compared to MCF-10A ($p = 0.007$) (Figure S4C). Conversely, no *VLA-4* expression was detected in MCF-7 in our study.

2.4.2. The influence of 20% PFK^{5120} treatment (48h) on Jam-A, LFA-1, and VLA-4 expressions

20% PFK^{5120} led to down-regulation of the *Jam-A* after 48h, which was ~7644-fold in MCF-7 ($p = 0.0001$) and 49.45-fold in MCF-10A ($p < 0.0001$). However, the down-regulation of *Jam-A* in MDA-MB-231 did not reach statistical significance (1.34-fold) (Figure S5A). As no *Jam-A* expression was observed in MCF-7 after 48h 20% PFK^{5120} treatment, the fold-change was calculated using the accepted value of 45 Ct (Yamashita et al. 2023). In this study, no *Jam-A* expression was detected in MCF-7 after 20% PFK^{5120} treatment for 48h, whereas it was observed in control cells

(7644-fold down-regulation ($p < 0.0001$)). There was also a 49.24-fold down-regulation of the *Jam-A* in MCF-10A at 48h for control cells (without treatment) ($p < 0.001$). In MDA-MB-231, a slight down-regulation of *Jam-A* (1.34-fold) was observed ($p > 0.05$). Current findings reveal that PFK^{5120} caused a notable down-regulation of *Jam-A* in both MCF-7 and MCF-10A, and this effect of PFK^{5120} was stronger in MCF-7 cells (~7644 vs 49.45-fold down-regulation, respectively). Although the mechanism underlying the observed effects in this study is not fully understood, the fact that PFK^{5120} decreased both cell viability and migration and downregulated *Jam-A* in MCF-7 and MCF-10A may be attributable to rendering the cells sensitive to apoptosis as suggested in previous studies (Murakami et al. 2011). The fact that 20% concentrations of PFK^{5120} did not significantly affect the down-regulation of *Jam-A* in MDA-MB-231 but the viability and migration, suggests that higher than 20% concentrations of PFK^{5120} may be required to reduce *Jam-A* levels as the viability assay shows IC50 of PFK^{5120} treatment for MDA-MB-231 is higher than MCF-7 (IC50 for 48h: 20-35% vs 7-10%, respectively) or the cell migration in these highly invasive cells may be driven by factors other than Jam-A. The present findings show consistency with the results of Bednarek et al. which showed that peptide 4D, an antagonist of Jam-A, exhibited a more pronounced inhibiting effect on the transendothelial migration of high *Jam-A* expressing MCF-7 compared with MDA-MB-231, suggesting that the migration of MDA-MB-231 may be enhanced compared to MCF-7 since MDA-MB-231 had decreased *Jam-A* than MCF-7 (Bednarek et al. 2020). Conversely, the recent study of Bednarek et al. showed that peptide 4D did not affect MDA-MB-231 migration, but effectively inhibited metastasis in the triple-negative BC (TNBC) 4T1 mouse model suggesting that Jam-A antagonist may inhibit new tight junction formation, but not destroy the existing ones (Bednarek et al. 2023). In the present study, while *Jam-A* is down-regulated in both MCF-7 and MCF-10A cells by the 20% PFK^{5120} treatment, inhibition of the cell migration was only observed in MCF-7. In MCF-10A, migration was inhibited by PFK^{5120} treatment until 24h, however, cells initiated to migrate again after 24h. These findings support the results of Bednarek et al. which show an increased cell migration in MCF-10A cells after Jam-A antagonist application suggesting the previously supported idea that MCF-10A could not be a good model to represent the non-tumorigenic mammary epithelium (Qu et al. 2015; Bednarek et al. 2023). Moreover, in the mice study of Murakami et al. transgenic mice without *Jam-A* expression showed less tumour growth and increased susceptibility to apoptosis in the TNBC 4T1 model (Murakami et al. 2011). As with another antagonist of Jam-A, it has been demonstrated that Tetrocarcin-A and tetraspanin inhibit the proliferation and invasion of TNBC cells, concomitantly reducing Jam-A levels (Vellanki, Cruz, Jahns, et al. 2019; Vellanki, Cruz, Richards, et al. 2019; Vences-Catalán et al. 2021). Our study provides further evidence for the hypothesis that Jam-A plays a significant role in BC metastasis, and secondly, similar to the effects of Jam-A antagonists, it can be predicted that PFK^{5120} may prevent the early stages of metastasis or induce apoptosis by modulating Jam-A expression. Considering that PFK^{5120} may be a natural alternative as a Jam-A antagonist without toxic side effects, it is obviously worth further investigation.

Recent studies have suggested LFA-1 (ITGB2) as a target for immunotherapy (Wei et al. 2021). There is evidence that the overexpression of ITGB4 is associated

with hematological malignancies (Wei et al. 2021), oral squamous-cell cancer (Zhang et al. 2020), and TNBC (Puerkaiti et al. 2020). Liu et al. showed that ITGB2-AS1, a long non-coding RNA, could promote migration and invasion by increasing the levels of ITGB2 (LFA-1) in MCF-7 cells. (Liu et al. 2018). In the current research, 20% PFK^{5120} caused an 11.22-fold ($p < 0.0001$) up-regulated *LFA-1* in MDA-MB-231 and an 8.33-fold ($p < 0.001$) up-regulation in MCF-10A. On the contrary, it caused a slight down-regulation of *LFA-1* (1.37-fold ($p > 0.05$)) in MCF-7 (Figure S5B). Contrary to our findings, Soto et al. reported the prevention of brain metastasis *via* the knockdown of *LFA-1* expression of TNBC MDA-MB-231 in mice (Soto et al. 2016). Furthermore, Niu et al. demonstrated that *LFA-1* knockdown showed a decreased number of Treg cells (regulatory T cells) and inhibited intestinal tumor growth in mice (Niu et al. 2023). Conversely, Vasse et al. showed that NaPa (sodium phenylacetate) led to up-regulation of *LFA-1* and reduced the invasiveness of both MCF-7 and MDA-MB-231 (Vasse et al. 2001). Overall, our results imply that the anti-migratory effects of PFK^{5120} in MCF-7 may not be directly mediated by LFA-1, whereas it may inhibit cell invasion by up-regulating *LFA-1* in MDA-MB-231 similarly to the study of Vasse et al. (2001). The findings of the current study do not demonstrate inconsistency with the majority of previous studies with respect to the *LFA-1* gene expression and invasiveness of the BC cells, which may be because LFA-1 is predominantly expressed in leucocytes and the integrin family exerts a direct effect on cell migration through interaction with the extracellular matrix (ECM). Therefore, the exact effect of PFK^{5120} needs to be studied in more detail including the ECM effect on cell migration.

ITGB1 (VLA-4) is another potential target for metastasis (Liu et al. 2024). Liu et al. demonstrated that USP22, a deubiquitinase, promoted ITGB1 (VLA-4) transcription and USP22 inhibition prevented BC lung metastasis in mice (Liu et al. 2024). Avtanski et al. detected that *VLA-4* is up-regulated in MCF-7 after resistin treatment which induces cell migration and indicated that VLA-4 is associated with cell migration in MCF-7 cells (Avtanski et al. 2019). Vahdanikia et al. demonstrated that the *VLA-4* expression and cell migration in MDA-MB-231 were inhibited by Wharton's Jelly Stem Cells (Vahdanikia et al. 2022). Supporting this, in the present study, the administration of 20% PFK^{5120} resulted in the down-regulation of *VLA-4* in MDA-MB-231 and MCF-10A, with *a* ~14.06-fold ($p < 0.0001$, Figure S5B) and ~500-fold ($p < 0.0001$, Figure S5B), respectively. However, in contrast to the findings of Avtanski et al. *VLA-4* expression was not detected in MCF-7 (both PFK^{5120} treated and control) in our study (Avtanski et al. 2019). These results indicate that PFK^{5120} may impede cell migration by down-regulating the *VLA-4* exclusively in MDA-MB-231 with invasive characteristics, not MCF-7. This observation suggests that PFK^{5120} could serve as a promising inhibitor of VLA-4 as a component of a therapeutic approach for TNBC.

3. Experimental

The online supplementary data provides comprehensive methods for cell culture conditions, PFK5120 preparation, cell viability assay, gene expression, cell migration and statistical analysis, along with the relevant tables, graphs and figures.

4. Conclusions

Current results indicate that PFK^{5120}, a unique polyphenol-rich cocktail with 13 different compounds (apigenin, galangin, caffeic acid phenethyl ester (CAPE), chrysin, curcumin, luteolin, epigallocatechin-gallate (EGCG), oleuropein, quercetin, resveratrol, pinocembrin, carnosic acid), cytotoxic and anti-migratory effects through modulation of *Jam-A, LFA-1* and *VLA-4* expressions in both hormone (+) and (-) BC cells. These results suggest that PFK^{5120} may be not only preventive against BC but also a powerful adjuvant in its treatment, which remains to be examined in future *in vivo* studies.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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