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Exploring the protective potential of apple (*Malus domestica*) and kiwi (*Actinidia deliciosa*) against breast cancer: An *in vitro* study

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Despite the frequent and successful use of conventional cancer therapies, the importance of natural resources has grown significantly. *Malus domestica* and *Actinidia deliciosa* were produced and analyzed using HPLC, GC-MS, and FTIR to describe the various amino acids and antioxidants present. Their anticancer efficacy and cytotoxicity were tested on Triple-negative Breast Cancer (MDA-MB231) and breast carcinoma (MCF-7) cell lines, as well as the Wi-38 normal cell line. Flow cytometric analysis for apoptosis and combination index (CI) analysis was performed for both individual and mixed extracts. On the molecular level, the expression of breast cancer-related genes (BAX, CDKN1, E2F4, RB1, TP53, TERT, KRAS1, and KRAS2) was examined. The results indicated that both extracts are rich in antioxidants. The combined extract of *Actinidia deliciosa* (3 parts) and *Malus domestica* (1 part) exhibited the highest anticancer activity, with safe dosages estimated at 2.520 ± 0.125 mg/ml for *Actinidia deliciosa* extract and 0.763 ± 0.176 mg/ml for *Malus domestica* extract. The study's results suggest that extracts of *Malus domestica* and *Actinidia deliciosa*, either alone or in a 3:1 volume ratio, could be beneficial in treating breast cancer.

Keywords: antcancer; antioxidant; breast cancer; extract; gene expression

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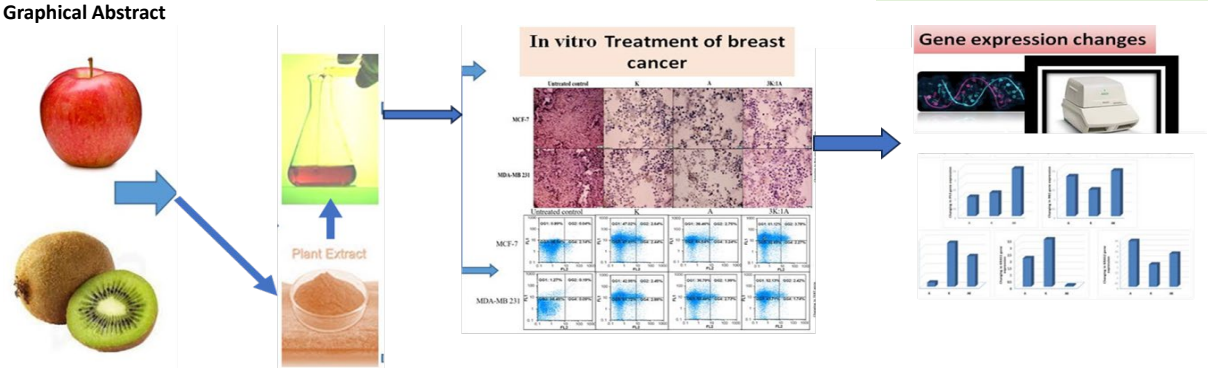
Graphical Abstract



INTRODUCTION

Scientists are diligently working to develop a cure for cancer. Cancerous cells differ from normal cells in their metabolism, nutrient intake, growth rate, and defenses against apoptosis or immune system attacks (Griñan-Lison et al., 2021; Ates et al., 2023). As a result, tumors form both unique and heterogeneous, originating from multiple generations of cells (Díaz-Montero et al., 2021). Due to this diversity, single therapies are unlikely to be universally effective, as different regions of the tumor may respond differently to treatment (Esposito et al., 2021; Song et al., 2023). Consequently, combinatory treatments are necessary to target multiple vulnerabilities across various cancer cell lines simultaneously (Esposito et al., 2021). Since the late 1800s, medical researchers have developed chemotherapy, radiation therapy, targeted therapies, and advanced surgical procedures, laying the foundation for modern cancer care (Esfahani et al., 2020; Schmidt et al., 2020). Despite their efficacy, many traditional treatments come with a slew of negative side effects, including pain, exhaustion, and nausea (Sugerman, 2013; Chattu, 2021; Saman et al., 2024). Some of the negative effects can potentially be fatal. When compared to traditional medicines, many supporters of alternative remedies say that they are more successful and have fewer adverse effects (Johnson et al., 2018; Rahm, 2024).

Breast cancer is the most frequent type of cancer in women globally (Chen et al., 2021; Fuentes et al., 2024). Breast cancer will have surpassed lung cancer as the most frequent kind of cancer by 2020, all over the place 2.3 million individuals were spotted each year, accounting for 11.7 percent of all cancers and the fifth leading cause of death worldwide (Lei et al., 2021). Breast cancer is a heterogeneous illness that affects the female reproductive system (Sun et al.,

2021; Carlino et al., 2024), with luminal A, luminal B, HER2-overexpressing, and triple-negative subtypes being the most generally recognized molecular classifications. The biology, etiology, prognosis, and therapies of these subgroups vary (Carey et al., 2006; Saridakis et al., 2021).

The hypothesis that oxidative stress performs a role in the onset of a variety of human disorders has received a lot of attention (Lei et al., 2021; Yang et al., 2024). It is the outcome of an oxidant/antioxidant imbalance that is revealed by the constant increase in oxygen, which is reactive, and nitrogen species generation (Sun et al., 2021; Kiran et al., 2023). Lipid peroxidation produces a wide range of breakdown end products that are stable (Carey et al., 2006). Antioxidants are endogenous or exogenous substances that help to prevent or reduce oxidative stress's consequences. They have a variety of functions, ranging from scavenging free radicals directly to strengthening antioxidant defenses (Saridakis et al., 2021). Reduced antioxidant intake, increased antioxidant utilization, or increased endogenous enzyme synthesis can all result in antioxidant deficiencies (Halliwell, 2024). Supplementing antioxidants is becoming more popular to keep your body in top shape. Antioxidants, alternatively, can have pro-oxidant action depending on the circumstances. Their dose and metabolic parameters in the cell are particularly important (Juszczyk et al., 2021; Othman and Ali, 2021).

Consumption of vegetables and fruits has been shown to lower the risk of chronic illnesses such as cancer and heart diseases, and phytochemicals found in vegetables and fruits such as flavonoids, phenolics, and carotenoids may play an important role in chronic disease prevention (Wigner et al., 2021; Othman et al., 2022). *Malus domestica* is a common product strong in phytochemicals, and epidemiological studies have connected *Malus domestica* diet to a reduced risk of cardiovascular diseases, cancer, asthma, and diabetes (Rungratanawanich et al., 2021; Tsoupras et al., 2024). *Malus domestica* has been demonstrated in the lab to have limited cancer cell proliferation, significant antioxidant activity, lower cholesterol, and minimized lipid oxidation. Chlorogenic acid, catechin, quercetin, and phloridzin are powerful antioxidant phytochemicals found in *Malus domestica* (Ercan et al., 2021; Raghu et al., 2023). *Malus domestica's* phytochemical composition varies significantly between varieties, and phytochemical composition alters slightly as the fruit matures and ripens. *Malus domestica* phytochemicals are unaffected by storage, but processing has a considerable influence (Kurutas, 2015; Lapuenteet al., 2019; Górnaś et al., 2024).

Actinidia deliciosa fruit Vitamin C is abundant and includes dietary fiber, vitamin E, potassium, and folate, in addition to bioactive components including phytonutrients, antioxidants, and enzymes, all of which have metabolic and functional benefits (Wojdyłoet al., 2021; Li et al., 2024). According to robust findings from human intervention research, the significance of *Actinidia deliciosa* fruit in digestive health is attracting special attention (Tang et al., 2023). The presence of actinides (Wei et al., 2021) and other phytochemicals, as well as the amount and type of fiber, are all likely to work together (Boyer et al., 2004; Ribeiro et al., 2023). Therefore, the present research aimed to determine the active ingredients of both *Malus domestica* and *Actinidia deliciosa* extracts and to evaluate their anticancer effects on various parameters.

MATERIALS AND METHODS

Plant extract

Plant materials were collected, with *Malus domestica* and *Actinidia deliciosa* fruits purchased from a hypermarket in Alexandria, Egypt. The plant material (peels) was prepared for water extraction. Separate samples were finely ground and stored at -20°C until use. The plant components were extracted with distilled water at a ratio of 1:10 (w/v) and heated at 90°C for 20 minutes. After centrifuging the extracts for 10 minutes at 5000 rpm, the extracts were lyophilized and stored at -20°C.

Determination of cytotoxicity of Malus domestica (A) and Actinidia deliciosa (K) fruit peels on human normal cells

The cytotoxicity of the tested extracts was determined using the normal human lung fibroblast Wi-38 cell line. Wi-38 cells were injected in culture containers with 10% fetal bovine serum (FBS), at a stock solution of $5x10^3$ cells per well on a 96-well cell lines plate and maintained at 37°C in a 5% Humidified incubator (BIOBASE, China). After 24 hours of cell attachment, serial doses of these extracts were cultured with Wi-38 cells for 72 hours. Cell viability was determined using the MTT method (Salazar-Bermeo et al., 2021). The mixture was incubated for 3 hours at 37°C just after a well-obtained 20 µl of 5 mg/ml MTT (Sigma, USA). The MTT solution was then removed, 100 µl DMSO was injected, and the intensity of each well was determined using a

spectrophotometric method at 570 nm (BMG LabTech, Germany). The Graph padInstate program was used to calculate the effective safe concentration (EC100) of the tested extracts at 100% cell viability.

Anticancer activity evaluation

Breast cancer cell lines (MDA-MB 231 and MCF-7) were maintained in RPMI (Lonza, USA) with 10% FBS to evaluate the anticancer effects of these extracts. These cancerous cells in the breast ($5x10^3$ cells/well) were seeded in sterile 96-well plates. After 24 hours, cancerous cell cultures were cultivated for 72 hours at 37°C in a 5% CO_2 incubator with repeated doses of A and K (single or combined at varied volume ratios "1:1, 1:2, 1:3, 2:1, and 3:1). As previously stated, the MTT technique was used. The 50 % inhibitory level (IC_{50}) results were computed using the GraphpadInstat tool. Furthermore, cellular morphological changes before and after treatment with the most effective extracts (single or combined) were investigated using a phase contrast inverted microscope with a digital camera (Olympus, Japan) (Awaad et al., 2023).

Apoptosis flow cytometric analysis

MCF-7 and MDA-MB 231 cell lines were cultured for 72 hours with the IC_{50} of the most efficient extracts (single or mixed). Untreated and treated cells were incubated with annexin V/PI for 15 minutes after trypsinization. After that, the cells were frozen and treated with streptavidin-fluorescein (5 g/mL) for 15 minutes. To explore the anticancer impact of apoptosis, researchers employed the FITC signal detector (FL1) detector of phycoerythrin emission signal to quantify annexin-stained apoptotic cells (FL2) (El Fawal et al., 2023).

Combination index (CI) analysis

The combination of K and A may or may not have a synergistic anticancer effect. This possible unique anticancer effect was assessed using the estimated value of CI, which might be 1 (synergistic impact), equal to 1 (additive effect), or 1 (negative effect) (antagonistic effect). The CI and graphs for growth inhibition activity were created by CompuSyn software. 1, and The CI for the measurement of apoptosis was calculated by dividing the anticipated value by the observed value (Bensam et al., 2023).

Immunohistochemical detection of proliferation marker (ki-67)

Untreated and treated breast cancer cells were centrifuged and rinsed with PBS buffer after trypsinization, and then 10 percent formalin in PBS was applied to the cell pellets. The fixed cell specimens were dried in increasing concentrations of alcohol and soaked in xylene for one hour (three times) before being impregnated in molten paraffin to form solid paraffin blocks. A rotator microtome was used to slice the blocks into 3-5 m thick slices, which were subsequently transferred to positively charged slides. The slides were waxed and then dewaxed three times in xylene and rehydrated in decreasing ethanol grades after being dried for 1-2 hours at 60-70°C. After that, the slides were incubated in 3 percent H_2O_2 for 10 minutes, rinsed twice in PBS (Phosphate-buffered saline) buffer for 3 minutes, and placed in 10 mM citrate buffer (pH) before being heated for 10-20 minutes. After cooling, each slide was soaked in primary antibody overnight and then washed in PBS (anti-Ki-67). After rinsing the slides in PBS, they were treated with streptavidin peroxidase before being coated with a biotinylated goat anti-polyvalent secondary antibody for 10 minutes. After 10 minutes, the secondary antibody's substrate (3,3'-diaminobenzidine) was applied, followed by washing in PBS, hematoxylin bathing for 1-4 minutes, and finally washing in PBS (1 minute) and water (3 min). The proportion of immune-stained cells was determined using the imaging analysis cellSens software of a phase contrast microscope (Olympus, Japan) (Bensam et al., 2023).

FTIR analysis

Function groups of the different combinations of extract from different serial concentrations of A (*Malus domestica* extract) and K (*Actinidia deliciosa* extract) (single or combined at different volume ratios “1:1, 1:2, 1:3, 2:1 and 3:1”) using Fourier transform infrared spectrophotometer (Schimadzu FTIR-8400 S- Japan).

Real-time PCR analysis

After treatment with A and K extracts separately, the quantitative gene expression of different genes control breast cancer (BAX, CDKN1, E2F4, RB1, TP53, TERT, KRAS1, and KRAS2) in cancer cells was determined. A Gene JET RNA Kit was used to achieve total RNA from both treated and untreated trials (Thermo Scientific, USA). The primers presented in Table 1 were used to generate genes for each specimen in Real-Time PCR by using TOPrealTM One-step RT qPCR kit (SYBR Green with low ROX) from Korea. A housekeeping gene, B-actin, was also discovered. The relative gene expression estimates

Table 1. Quantitative polymerase chain reaction primer sequences

Gene	Forward	Reverse
BAX	CAAACTGGTGCTCAAGGCCC	GGGCGTCCCAAAGTAGGAGA
CDKN1	TACCCTTGTGCCTCGCTCAG	GGCGGATTAGGGCTTCCTCT
E2F4	GCATCCAGTGGAAGGGTGTG	ACGTTCCGGATGCTCTGCT
RB1	GACCCAGAAGCCATTGAAATCT	GGTGTGCTGGAAAAGGGTCC)
KRAS2	ACTGAATATAAACTTGTGGTAGTTGGACCT	CAAATCACATTTATTTCCTACCAGGACCAT
KRAS1	ACTGAATATAAACTTGTGGTAGTTGGACCT	TCAAAGAATGGTCCTGGACC
TERT	CGGAAGAGTGTCTGGAGCAA	GGATGAAGCGGAGTCTGGA
TP53	GCGTGTTTGTGCCTGTCCTG	TGGTTTCTTCTTTGGCTGGG
B-actin	GCTGTGCTATCCCTGTACGC	TGCCTCAGGGCAGCGGAACC

changes in gene expression of genes (Table 1) before and after treatment of cancer cells with A and K.

Statistical Analysis

The data was represented using the mean and standard error of the mean (SEM). Statistical significance was calculated using the SPSS16 program's multiple comparisons Tukeypost-hoc analysis of variance (ANOVA). At p value <0.05, the differences were judged statistically significant.

RESULTS

Chemical analysis

The estimated compositions of the various extracts, *Malus domestica* (A) and *Actinidia deliciosa* fruit peel (K), dissolved in acetone using GC-MS with calculated error K=2, Confirmed by 95% presented in Figures 1S and 2S. An RP-HPLC system was used to analyze the antioxidant for crude extract of *Malus domestica* and *Actinidia deliciosa* fruits peels (Figures 3S and 4S) at 284 (Agilent1260; Santa Clara, CA, USA).

Determination of cytotoxicity and anticancer activity

The estimated safe doses of K and A were 2.52±0.125 and 0.763±0.176 mg/ml respectively on the growth of human normal cells. Due to the low IC_{50} referring to the high growth inhibition activity, the combined extract of K and A (3:1 v/v) showed the strongest anticancer activity in comparison with single and other extracts' combined volume ratio (Table 2). The best active combined extract is composed of 4.25 µg/ml of A plus 12.75 µg/ml of K. The morphological alterations were more severe in the combined extract (3K:1A v/v)-treated breast cancer cells relative to single extracts (Figure 1).

Flow cytometric analysis of apoptosis and Combination index (CI) analysis

The estimated CI values in all studied ratios of the combined extract were <1, this indicates the synergistic anticancer action between K and A (Table 3). Moreover, the combined extract with volume ratio 3K: 1A v/v recorded the highest synergism which was confirmed by the dose-effect curve (growth inhibition response was proportional to dose) and CI plot (Table 3 and Figure 2I & II). The high percentage of annexin-stained cells in the treated wells with A, K, and 3K: 1A v/v, indicated these extracts induced anticancer effect via apoptosis. In compared to solo extracts, the combined extract (3K: 1A v/v) showed the greatest apoptosis percentage (>56%) in the tested breast cancer cell lines (Table 4 and Figure 3). Furthermore, immunohistochemistry revealed that the studied extracts suppressed the proliferative marker (Ki-67). As demonstrated in Figure 4A, B, the combined extract (3K: 1A v/v) revealed a higher inhibitory effect on Ki-67 than the single extract (K and A). This is illustrated by decreasing brown color stained-Ki-67+ MCF-7 and –MDA-MB 231 cells by 75.084 and 69.528%, respectively in 3K: 1A v/v while it was less than 62% and 50%, respectively in the case of single extract.

Table 2. Anticancer activities of K and A (single or combined extracts) against breast cancer cell lines in the term of IC_{50} (µg/ml)

CI	MCF-7	MDA-MB231
K	68.62 ± 1.28^{d}	54.18 ± 0.72^{e}
A	99.50 ± 2.54^{e}	85.58 ± 1.55^{d}
1k:1A	95.46 ± 3.14^{e}	95.92 ± 2.49^{e}
1K:2A	73.78 ± 2.15^{d}	86.60 ± 1.83^{d}
1K:3A	59.20 ± 1.98^{c}	62.96 ± 1.98^{c}
2K:1A	36.35 ± 0.04^{b}	45.27 ± 2.36^{b}
3K:1A	16.41 ± 0.42^{a}	17.59 ± 0.256^{a}

All values were expressed as mean±SEM. Different letters in the same column are significantly difference at p<0.05.

Table 3. CI values for the growth inhibition effect of the combined extract at different volume ratios

CI	MCF-7	MDA-MB231
1k:1A	0.853	0.268
1K:2A	0.539	0.376
1K:3A	0.391	0.292
2K:1A	0.199	0.094
3K:1A	0.157	0.027

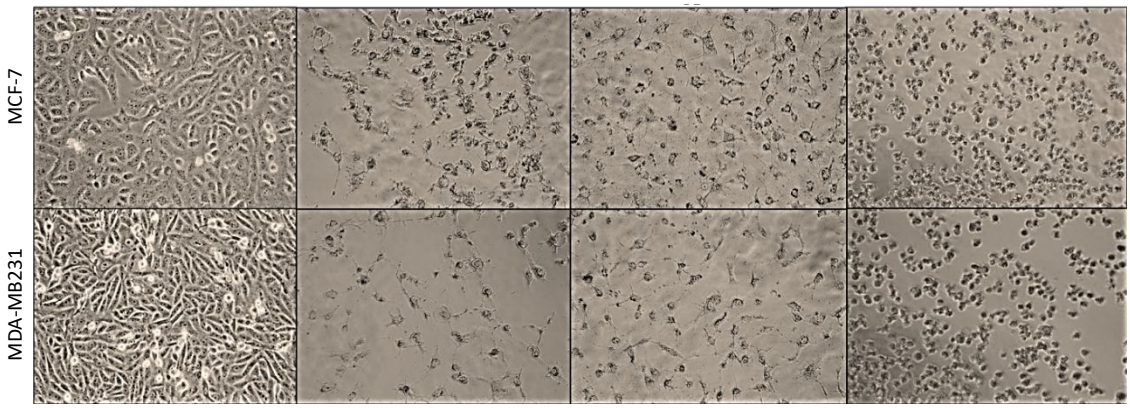


Figure 1. Morphological alteration of MCF-7 and MDA-MB 231 cell lines after treatment with the most active combined extract in comparison

Table 4. Percentage of apoptosis-dependent death of extract-treated cancer cells using flow cytometry

	MCF-7	MDA-MB231
Untreated control	1.215±0.285[d]	1.27±0.19[d]
K	51.74±2.08[b]	47.50±2.10[b]
A	42.63±1.42[c]	35.43±3.35[c]
3K:1A	65.66±0.76[a]	56.95±2.40[a]

All values were expressed as mean±SEM. Different letters in the same raw are significantly difference at p<0.05.

FTIR analysis

As shown in Figure 5, a wide peak characteristic for the polyhydroxy compounds assigned as stretch hydroxyl group was observed at about 3200-3400 cm^{-1}, while the peaks at 615, 1017, 1100, 1250, 1440 and 1730 cm^{-1} were assigned to =C-H alkenes, bending -C-O alcohols, stretching C-O-H alcohols,-OH aromatic, C-H alkanes and C=C stretch which assigned to the ester and derived from acetyl ($COCH_3$) group, respectively.

Real-time assay of apoptosis-related genes

Gene expression levels for BAX, CDKN1, E2F4, RB1, TP53, TERT, KRAS1, and KRAS2 genes which control the level of cancer were detected using a specific primer and analyzed (Figure 6). *Actinidia deliciosa* extract was more effective via increasing the level of expression of BAX, CDKN1, E2F4, TERT and KRAS1 genes, *Malus domestica* extract induced up-regulation of KRAS2 gene while the mixture of both extracts (*Malus domestica* and *Actinidia deliciosa*) elevated the expression in cases of RB1and TP53 genes.

DISCUSSION

Cancer is an illness that affects people with many facets and a genomically complicated genome (Satpalet al., 2021; Krupina et al., 2024). Genetic/epigenetic mutations, overexpression of

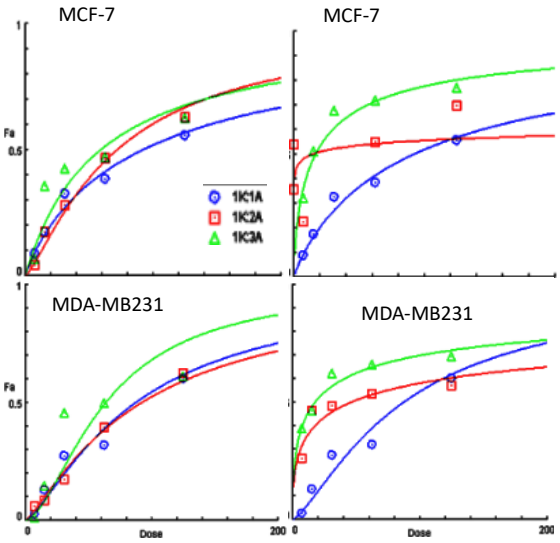


Figure 2I. Dose-effect curve for K (*Actinidia deliciosa*) and A (*Malus domestica*) combination at different volume ratios.

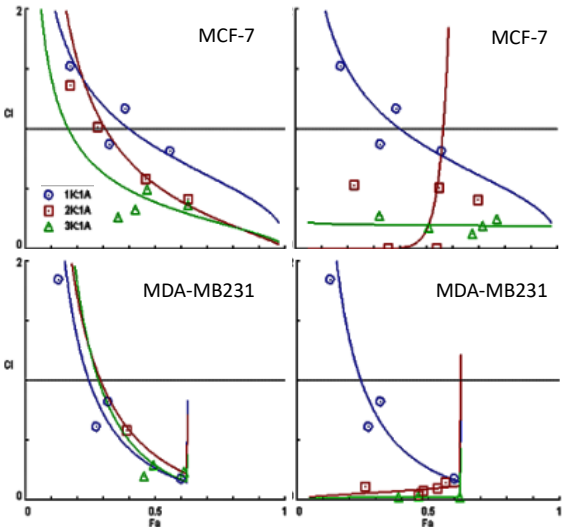


Figure 2II: CI plot (II) for K (*Actinidia deliciosa*) and A (*Malus domestica*) combination at different volume ratios.

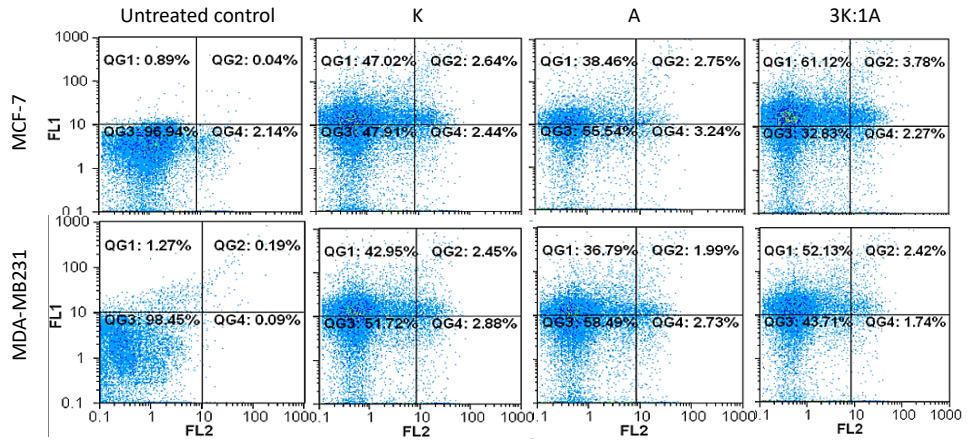


Figure 3. Dot plot of flow cytometry analysis for the untreated and treated breast cancer cells after staining with annexin and propidium iodide.

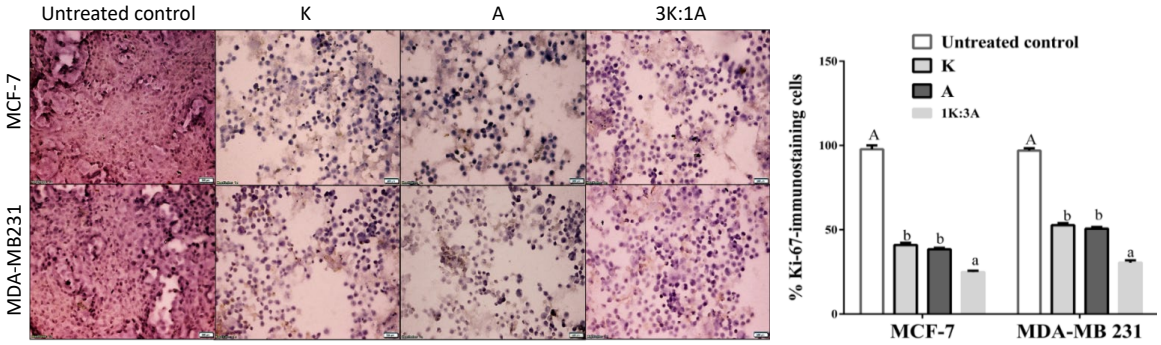


Figure 4. Ki-67 immunostaining the untreated and treated breast cancer cell lines. (A) Immunostaining image for Ki-67 of the untreated and treated cells (magnification ×400) with (B) the representative percentage of positive immunostaining cancer cells. Different letters in the same cell line are significantly difference at p<0.05.

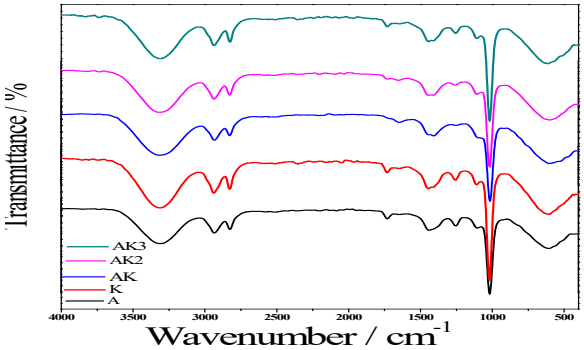


Figure 5. FTIR spectra of A (*Malus domestica* extract) and k (*Actinidia deliciosa* fruit extract) and different combinations between the *Malus domestica* and *Actinidia deliciosa* extract. AK: (V/V), AK2: 1 volume of A and 2 volumes from K, AK3: 1 volume of A and 3 volumes of K.

oncogenes, inactivation of tumor suppressors, epithelial to mesenchymal transition (EMT), spatiotemporally dyes regulated intracellular signaling cascades, metastasis, and loss of apoptosis are some of the most extensively studied biological mechanisms that underpin cancer development and progression (Kaur et al., 2010; Göransson, 2023).

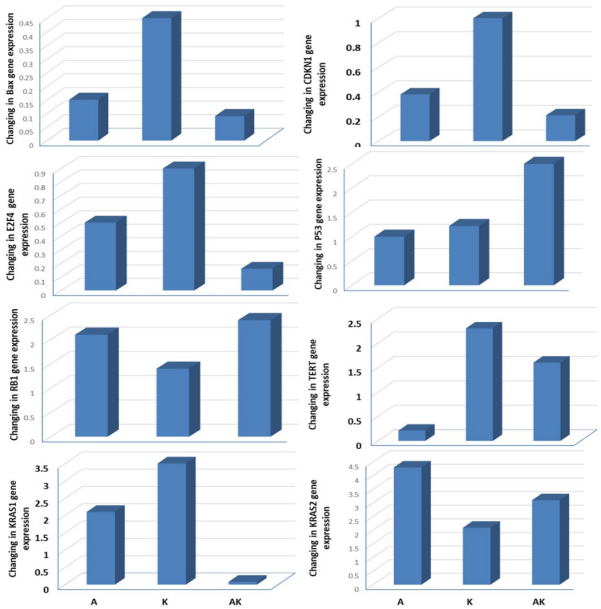


Figure 6. The consequence of the observed *Malus domestica* and *Actinidia deliciosa* extracts on quantitative gene expression of BAX, CDKN1, E2F4, RB1, TP53, TERT, KRAS1, and KRAS2 In breast cancer cell lines.

The variety of tumors necessitates a multidisciplinary approach and quickly rising medication resistance, it is becoming increasingly clear that conventional treatment strategies are inadequate (Edsjö et al., 2023). Bioactive substances derived from nature have exerted significant biological activity, revolutionizing the field of natural product chemistry, and quick progress in preclinical investigations is encouraging. An improved and better understanding of oncogenic signaling cascades will aid in the evolution of customized treatment (Ciardiello et al., 2008).

The current study evaluated several antioxidants in both extracts that exhibited an anti-breast cancer impact. Long-term antioxidant intake through diet or supplements, according to (Ferrari et al., 1990) and (Menon, 2021), may protect women from developing breast cancer. In lab trials, antioxidants have been discovered to neutralize or trap oxygen-reactive molecules, reducing cellular DNA damage that may lead to illnesses like cancer. Vitamin E included in *Actinidia deliciosa* peel helps to enhance cell health by avoiding free radical damage. Vitamin E levels are increased by 34% when *Actinidia deliciosa* peel is consumed. MCF7 and MDA-MB-231 cells are good examples since they are both invasive ductal/breast cancer cells, yet their phenotypic/genotypic traits differ significantly: MCF7 is hormone-dependent (it expresses estrogen and progesterone receptors—ER and PR), whereas MDA-MB-231 is triple negative. MDA-MB-231 is resistant to antiestrogen therapies, for instance, tamoxifen, an estrogen receptor modulator was chosen (Attar et al., 2015; Fu et al., 2021; Farghadani & Naidu, 2023), which is extensively utilized in breast cancer chemoprevention, additionally acting as an adjuvant to primary illness (Michels, 2007). MCF7 cells are more Pasteur-like, relying on oxidative phosphorylation for ATP production in normoxic conditions but increasing glycolytic activity in hypoxia, whereas MDA-MB-231 cells are more Warburg-like, relying on glycolysis for ATP production in both hypoxic and normoxic conditions(Sheng et al., 2021). In conclusion, MCF7 cells show an epithelial phenotype, as opposed to MDA-MB-231 cells (Osborne, 1998; Giordano et al., 2023), which are more mesenchymal, were used in this study and have been linked to multidrug resistance (Jordan, 2021).

The anticancer efficacy of both extracts was demonstrated in this investigation using these cell lines. The opposite connection exists between consuming *Malus domestica* and the many possibility formulae of cancer, according to studies. *Malus domestica* has been shown to contain high amounts of antioxidants and are frequently discarded. Its therapy led to a clear reduction in concentration-dependent proliferative protein levels of nuclear antigen in cells, which is a proliferation marker. A considerable rise in maspin, a tumor suppressor protein that inhibits cell infiltration, metastasis, and angiogenesis, was further noticed. Their findings show that *Malus domestica* has a substantial antiproliferative impact on cancer cells and should not be eliminated from the diet (Radmacher and Simon, 2000; Vuran et al., 2023; Pal et al., 2024). Ethanol extracted from the root of *Actinidia deliciosa* (Hardy Kiwi) was found to have anticancer properties. Activation of Caspase 3, Caspase 8, and Poly (ADP-ribose) polymerase (PARP) reduced cell viability and led to apoptosis in a variety of cell types. They discovered that it had anti-cancer properties both in vitro and in vivo. These findings show that it might be a viable anti-cancer drug that could help with therapy (Sakamoto et al., 2011).

On the molecular level, the increased expression of BAX, CDKN1, E2F4, RB1, TP53, TERT, KRAS1, and KRAS2 genes in the current study indicated an increase in apoptosis and necrosis. The BAX gene (Bcl-2 Associated X-protein) is a member of the Bcl-2 gene family that generates BAX-alpha, a pro-apoptotic protein, a 21-kDa protein that researchers think would regulate intrinsic apoptosis through its interaction with Bcl-2 (Arisan et al., 2021). Apoptotic dysfunction caused by Baxdysregulation raises the risk of numerous diseases. Bax is a tumor suppressor gene that plays an important role in tumor prevention (Shirley et al., 2021; Wu et al., 2024), and its loss of function is common in human cancers. Incomplete negative selection and tolerance failing in the outskirts can result from loss of function mutations, resulting in autoimmune problems (Ávila-Románet al., 2021). In humans, the CDKN1B gene encodes the enzyme inhibitor cyclin-dependent kinase inhibitor 1B (p27Kip1). It is a member of the Cip/Kip family of cyclin-dependent kinase (Cdk) inhibitor proteins. The encoded protein binds to cyclin D-CDK4 complexes or cyclin E-CDK2 and prevents them from activating, therefore controlling the cell cycle's G1 phase (Zhao et al., 2019). It's known as a cell cycle inhibitor protein since its principal purpose is to interrupt or slow down the cell division cycle (Lee and Fairlie, 2021).One of pRb's functions is to suppress cell proliferation by stopping the cell cycle from progressing until the cells are ready to divide (Merlin et al., 2021). The KRAS gene is referred to as a proto-oncogene in the cellular

genome (Kelly and Strasser, 2011; Chhichholiya et al., 2023). KRAS uses protein dynamics to operate as a molecular switch that turns things on and off. It mobilizes and activates the proteins essential for growth factor proliferation when activated allosterically(Matthews et al., 2021; Wang et al., 2023). However, the bands in FTIR at 2932, 2827, 1440 and 1100 cm^{-1} in *Actinidia deliciosa* fruit and the combined extract (3K: 1A v/v) showed more intensive peaks than in the other samples (Polyaket al., 1994; Nagasakaet al., 2021; Roufayelet al., 2021). As a result, the anticancer effects demonstrated in the current study might be explained by the elevation in their regulations generated by the two extracts

CONCLUSION

From the previous data and discussion, it was proved that both *Malus domestica* and *Actinidia deliciosa* extracts are natural extracts that are rich in bioactive compounds that were proved to be strong antioxidants and thereby recommended to be used separately or in combination as anticancer agents.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies involving animals or human participants performed by any of the authors.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

All data generated or analyzed during this study are included in this published article.

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DECLARATION OF COMPETING INTEREST

The authors declare no competing financial interests.

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Supplementary Files

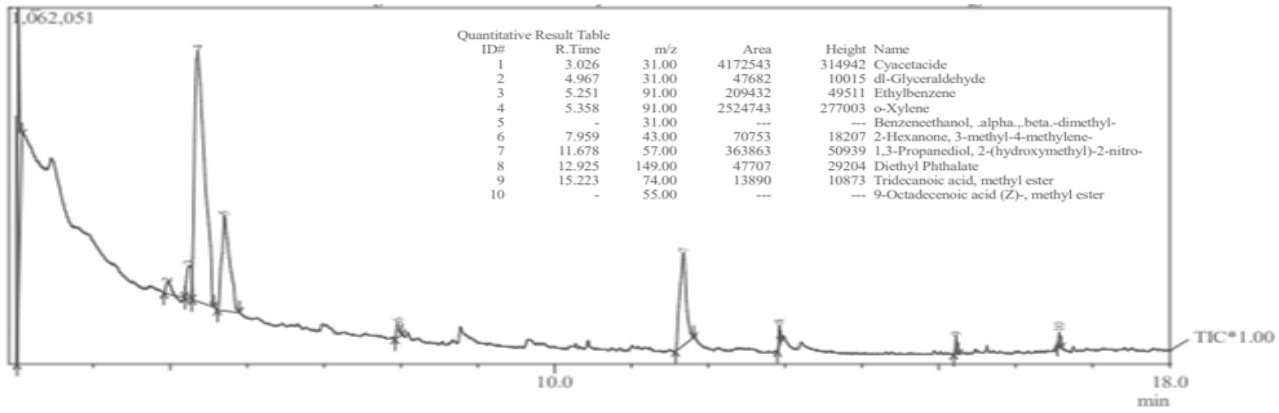

Figure S1. Compositions of Apple peel extract using GC-MS

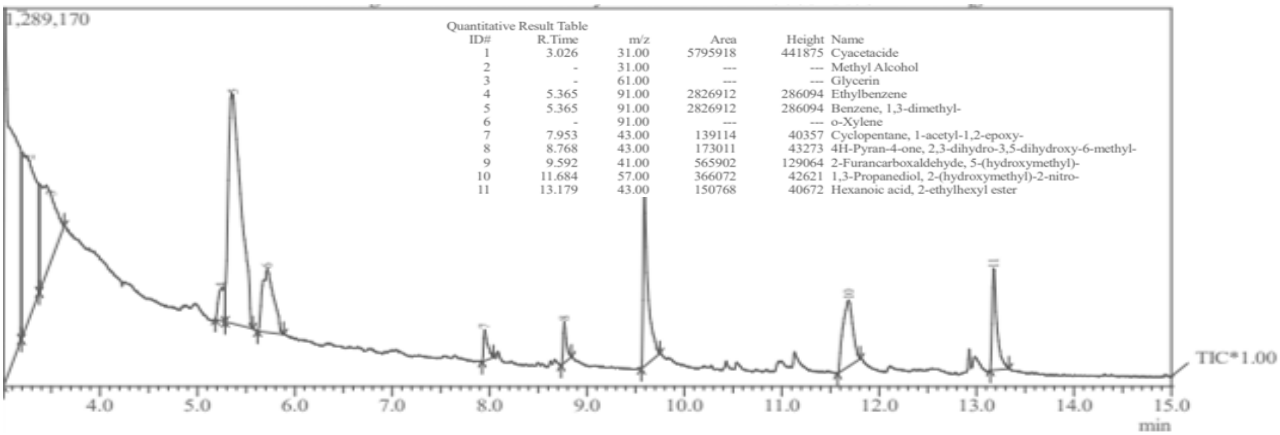

Figure S2. Compositions of kiwi fruit peel extract using GC-MS.

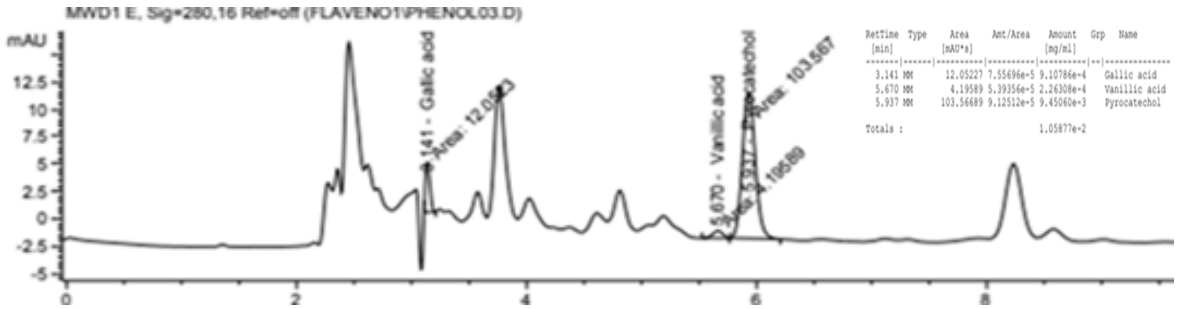

Figure S3. HPLC chromatogram of Apple peel extract, recorded.

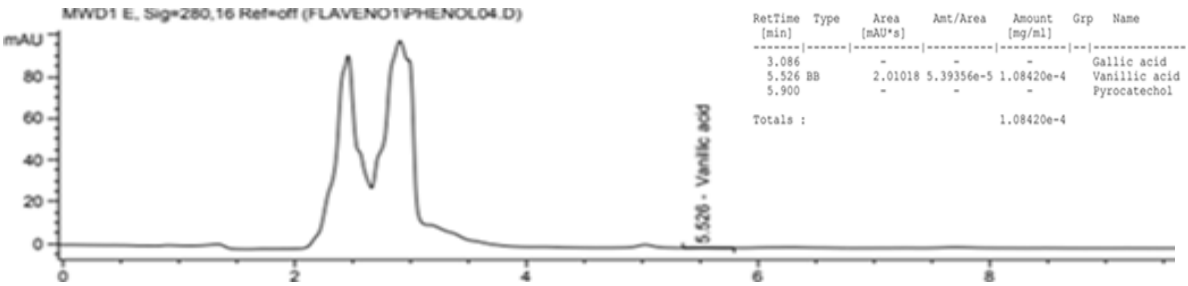

Figure S4. HPLC chromatogram of kiwi extract, recorded