Cancer, which is characterized by uncontrolled cell growth and division, was the cause of 1 in every 6 deaths worldwide in 2018 and rank the 2nd among all diseases that cause death. The findings show that there will be 27.5 million new cancer cases every year by 2040. The most common cause of cancer-related deaths in 2020 is lung cancer, followed by colon and rectal cancer. These data show the fundamental importance and necessity of intensive research for anti-cancer drugs and treatments.
for its potential anti-cancer activity in human lung and colon cancer.

Chalcone and chalcone derivatives are compounds that have been studied for use in both medicine and agriculture in recent years.[4-6] Chalcone compounds are one of the non-heterocyclic C-ring members of the flavonoid family. The presence of an α,β-unsaturated carbonyl group on the propane chain in the main structure of flavonoids, or in other words, the presence of a double bond and a ketone group forms chalcones.[7] Chalcone term is used for all compounds with 1,3-diaryl-2-propen-1-one structure.[8] It is known that chalcones are found in edible plants and fruits in nature and are very beneficial compounds for health. They can be obtained by methods such as extraction from plants and fruits, or they can be synthesized chemically. It has been determined that chalcone and flavonoid derivatives show more than 90% inhibition against tuberculosis, an infectious and fatal disease.[10] Chalcones and their synthetic derivatives have a wide range of biological properties such as anti-hypertensive, anti-diabetic, antiretroviral, anti-histaminic, anti-inflammatory, anti-oxidant, anti-tuberculosis, anti-fungal, anti-ulcer and anti-cancer.[11] In a study, newly synthesized compounds based on chalcone and sulfonamide derivatives were examined and they were shown to have anticancer effects in MCF-7 breast cancer cells.[12] Similarly, in another study, a number of synthesized chalcone-derived compounds were tested in five different human tumor cell lines (HL-60, SMMC-7721, A549, MCF-7, and SW480), and some of the compounds had significant cytotoxic effects by inducing cell cycle arrest and apoptosis.[13] In a previous study done by our group, the cytotoxic and apoptotic effects of a series of chalcone compounds in breast cancer (MCF-7), non-small cell lung cancer (A549) and prostate cancer (PC-3) cells were investigated and results showed that they induce apoptosis via caspase-dependent pathway.[14] Curcumin is a polyphenolic compound extracted from the turmeric rhizome and is a promising candidate as an effective anti-cancer drug when used alone or in combination with other drugs.[15] It has been shown to have an effect on proliferation, apoptosis, signalling pathways and invasion in many cancer types, including lung and colon cancer.[15-17] Curcumin is involved in tumor control through multiple signalling pathways, including PI3K/Akt, JAK/STAT, MAPK, Wnt/β-catenin, p53, NF-kB, and apoptosis-related signalling pathways. It is also known to affect the expression of relevant signalling pathway genes/proteins by regulating the expression of non-coding RNAs (ncRNAs). Thus, it inhibits tumor cell proliferation and increases sensitivity to chemotherapy drugs by promoting cell apoptosis.[18] Most of the studies done by the Kok Wai lam group suggested that the unsymmetrical form of demethoxycurcumin derivative might possess greater biological profile compared to the symmetrical form of bisdemethoxycurcumin.[19-22] These mentioned findings encouraged us to was to find new, potent anticancer agents with higher efficacy and better safety profiles, herein, we have synthesized a derivative of unsymmetrical diarylpentadienone.

In the light of this information, in this study, the cytotoxic/apoptotic effect of the new chalcone derivative compound, (2E,4E)-1-(7-ethoxy-1-benzofuran-2-yl)-5-(4-hydroxy-3-methoxyphenyl) penta-2,4-dien-1-one which was synthesized based on the curcumin structure, was investigated in human lung (A-549, H1299) and colon cancer (HCT-116, HT-29) cells.

Methods

Chemistry

Chemicals were purchased from Sigma-Aldrich and used without further purification. Melting points were determined on a differential scanning calorimeter (Shimadzu DSC-50) apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were detected with a Bruker Avance (400-MHz) spectrometer, with tetramethylsilane (TMS) as the internal standard in CDCl$_3$ as solvent. IR spectra were recorded on a FT-IR Thermo Spectroscopy. Compound purity was determined by elemental analysis and was confirmed to be >95% for the tested compound. The starting compound 1-(7-ethoxy-1-benzofuran-2-yl) ethanone (1) was synthesized following the procedure previously described.[14] (2E,4E)-1-(7-ethoxy-1-benzofuran-2-yl)-5-(4-hydroxy-3-methoxyphenyl) penta-2,4-dien-1-one (3) were synthesized by base-catalyzed reaction of 4-hydroxy-3-methoxy cinnamaldehyde (2) and 1-(7-ethoxy-1-benzofuran-2-yl) ethanone (1). The condensation was performed in methanol using sodium hydroxide as base (Fig. 1).

**Synthesis of (2E,4E)-1-(7-ethoxy-1-benzofuran-2-yl)-5-(4-hydroxy-3-methoxyphenyl) penta-2,4-dien-1-one**

Equimolar quantities of 1-(7-ethoxy-1-benzofuran-2-yl) ethanone (2 mmol) and 4-hydroxy-3-methoxycinnamaldehyde (2 mmol) were mixed in methanol (10 ml). The temperature of the solution was cooled to 0-5 °C. Then, NaOH (1M, 3 ml) solution was added dropwise onto the cooled solution and the reaction mixture was stirred at room temperature for 8 hours. The reaction was monitored by TLC. When the reaction was completed, the reaction mixture was neutralised with 10 % HCl. The organic layer was dried, concentrated under reduced pressure and recrystallised
from EtOH. The analysis results were: bordeaux colour solid, yield: 67%, mp 183–185 °C; FT-IR (in ATR, cm−1): 3170 (-OH), 1641 (C=O). 1H NMR (400 MHz, CDCl 3): δ (ppm) 7.74 (dd, 1H, Hβ, Jα-β = 14.8 Hz, J β-γ = 10.4 and 9.6 Hz), 7.59 (s, 1H, H3), 7.27 (d, 1H, Hα, Jα-β = 15.2 Hz), 7.31-7.21 (m, 2H, H4, H5), 6.97 (dd, 1H, Hγ , Jγ-δ = 14.6 Hz, Jβ-γ = 10.4 and 10.0 Hz), 7.10-6.94 (m, 5H, H6, H6’ , Hδ, H2’ , H5’), 5.89 (s, 1H, OH), 4.33 (q, 2H, J = 7.2 and 6.8 Hz, OCH 2), 3.98 (s, 3H, OCH 3), 1.58 (t, 3H, J = 7.2 and 6.8 Hz, CH 3). 13C NMR (CDCl 3): δ (ppm) 179.93 (C=O), 154.18 (C2), 147.25 (C7), 146.80 (C3’), 145.49 (C8), 145.30 (C4’), 145.11 (Cβ), 143.01 (Cδ), 129.15 (C1’), 128.83 (C1’), 124.81 (C6’), 124.51 (Cα), 123.62 (Cy), 122.09 (C5), 114.87 (C4), 114.81 (C6), 112.75 (C2’), 110.32 (C3), 108.91 (C5’), 64.68 (OCH 2), 55.97 (OCH 3), 14.91 (CH 3). Anal. calcd. for C21H 19O 3: C, 72.52; H, 5.49; found: C, 73.61; H, 5.61.

**Cell Culture**

Lung cancer (A549, H1299) and colon cancer (HCT116, HT29) cell lines were cultured in RPMI 1640 medium (Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (Lonza, Verviers, Belgium), 1% Penicillin-G (100 U/ml)-Streptomycin (100 μg/ml) (Gibco, Grand Island, NY, USA) and 1% L-glutamine (Gibco, Grand Island, NY, USA) at 37 °C in a humidified atmosphere containing 5% CO₂.

**Sulforhodamine B (SRB) Viability Assay**

SRB cell viability assay was applied to determine the cytotoxic effect of the newly synthesized Chalcone compound at different concentrations. After the cells were seeded in 96-well plate at a density of 1x10⁴ cells/well, they were treated with 0.39-25 µM concentration of Chalcone compound for 48 hours. SRB test and calculation of cell viability were performed as method described before.[23]

**Combination of Chalcone Compound with 5-Fluorouracil**

In order to increase the effectiveness of a clinically used chemotherapy drug (5-Fluorouracil, 5-FU) and to compare the anticancer activity of the newly synthesized Chalcone compound, combination study was done. The determined concentrations of Chalcone compound (0.39 and 0.78 μM) and different doses of 5-FU (2-172 μM) were combined and effects on the viability of colon cancer cells after 48 hours of treatment were examined by SRB method.

**Fluorescence Imaging for Cell Death Visualization**

Determination of the cell death mode were performed by fluorescent imaging method with Hoechst 33342, Annexin-V-FITC and Propidium iodide (PI) triple staining. Cells were seeded in 6-well plate at a density of 1x10⁵ cells/well and the treatment was applied with the determined concentrations of Chalcone compound for 24 h. At the end of the treatment time, cells were incubated with a working solution consisting of 5 μg/ml Hoechst 33342, Annexin-V-FITC and 1 μg/ml PI dyes. After the incubation for 20 min in the dark, cell nuclear morphology and membrane integrity

![Figure 1. General synthesis of (2E,4E)-1-(7-ethoxy-1-benzofuran-2-yl)-5-(4-hydroxy-3-methoxyphenyl)penta-2,4-dien-1-one Reagants and conditions: (i) NaOH was added at 0-5 °C in methanol and then 8 h r.t.](image-url)
were examined and death mode of the cells was evaluated by fluorescence imaging.

**Statistical Analysis**

All statistical analyses were performed using SPSS 22.0. The significance was calculated using one-way analysis of variance (ANOVA). A value of $p<0.05$, $p<0.01$ and $p<0.001$ was considered statistically significant.

**Results and Discussion**

**Characterization**

In $^1$H-NMR, the signals at $\delta$H 7.31-7.21 (Hα) and 7.74 (Hβ) ppm ($dd$, $J = 14.8$ Hz), and 7.10-6.94 (Hγ) and (Hδ) ppm were attributed to doublets referring to α,β-unsaturated hydrogens, whose coupling constant ($J$) confirms the stereochemistry E. The singlet peak seen at 7.59 ppm belongs to H3. The singlet observed at $\delta$H 5.89 ppm refers to hydrogen attached to the hydroxyl group. In addition, the signals at $\delta$H 4.33 ppm ($q$, $J = 7.0$ Hz, CH$_2$), 3.98 ppm (s, OCH$_3$), and 1.58 ppm (t, CH$_3$) support the structure.

The $^{13}$C NMR spectrum showed a peak at $\delta$C 179.9 ppm corresponding to an α,β-unsaturated carbonyl. The peaks of Cα-Cγ and Cβ-Cδ carbon atoms of the α,β-unsaturated carbonyl system resonated at 124.51–123.62 and 145.11–143.01 ppm, respectively (Fig. 2).

**Effect of Chalcone Compound on Cell Viability**

The effect of newly synthesized Chalcone compound at different concentrations (0.39-25 µM) on cell viability in human lung (A549 and H1299) and colon cancer (HCT116 and HT29) cell lines was evaluated by SRB viability assay. It was observed that cell viability was significantly decreased depending on the concentration in all four cell lines (A549, H1299, HCT116, HT29) in the treatment group compared to the control group, and colon cancer cells were observed to be more sensitive to Chalcone compound.

The lowest concentration (0.39 µM) of Chalcone compound applied to A549 and H1299 cells reduced cell viability to 81% and 72%, respectively ($p<0.05$ and $p<0.01$). At 6.25 µM concentration, cell viability decreased to 26% in A549 cells, while 9% cell viability was observed at 25 µM concentration in H1299 cells ($p<0.001$) (Fig. 3). The $IC_{50}$ value is calculated 2.85 µM for the A549 cells and 1.46 µM for the H1299 cells (Table 1).

In HCT116 and HT29 colon cancer cells, it was observed that 0.39 µM Chalcone compound application reduced cell viability to 64% and 48%, respectively ($p<0.01$ and $p<0.001$). At 12.5 µM concentration cell viability decreased to 8% in HCT116, while 20% viability was observed at 25 µM concentration in HT29 cells ($p<0.001$) (Fig. 3). $IC_{50}$ values were calculated as 0.59 µM for HCT116 and 0.35 µM for HT29 (Table 1).

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**Figure 2.** (a) FT-IR Spectrum, (b) 1H-NMR Spectrum, (c) 13C-NMR Spectrum of (2E,4E)-1-(7-ethoxy-1-benzofuran-2-yl)-5-(4-hydroxy-3-methoxyphenyl)penta-2,4-dien-1-one.
SRB results show that the cytotoxic effect of increasing concentrations of the Chalcone compound in human lung (A549, H1299) and colon cancer (HCT116, HT29) cell lines. Naturally occurring chalcones and chalcone-derived compounds are known to have therapeutic potential against various types of cancer, including lung and colon cancer. For example, Isoliquiritigen (2',4',4-trihydroxychalcone, ISL), one of the most important bioactive compounds with chalcone structure isolated from licorice roots, suppresses cell proliferation, induces apoptosis and autophagy, arrests the cell cycle, inhibits angiogenesis, and inhibits metastasis. Also, it has been shown in various studies that it can increase chemosensitivity.\textsuperscript{[24-29]} Similarly, it has been shown that Butein compound, one of the biologically active chalcones, has an anticarcinogenic effect in non-small cell lung cancer by inducing apoptosis, and isobavacalcone compound inhibits cell proliferation and induces apotosis by suppressing the AKT/glycogen synthase kinase 3β (GSK3β)/β-catenin pathway in colorectal cancer cells.\textsuperscript{[30,31]}

The fact that they are natural compounds with anticancer properties has increased the importance of studies on the development of new synthetic chalcones by improving their physicochemical properties and biological profiles through molecular modification of chalcones. In the study by Padhye et al.,\textsuperscript{[32]} it was found that 2'-hydroxychalcones synthesized by bioisosteric substitution of fluoro groups showed antiproliferative activity in human pancreatic BxPC-3 cancer cells and breast cancer BT-20 cells, and \textit{IC}_{50} values were shown as 18.67 μM and 26.43 μM, respectively. In another study, a series of chalcone-derived compounds were synthesized and their anticancer activities have been researched in Leukemia (HL-60), myeloid liver carcinoma (SMMC-7721), lung cancer (A549), breast cancer (MCF-7), and colon cancer (SW480) cell lines. It was shown that some chalcone derivatives have cytotoxic effects in all five human cancer cell lines (\textit{IC}_{50} values 0.83 μM for HL-60; 1.57 μM for MCF-7; 2.92 μM for SW480).\textsuperscript{[13]} In addition, in human oral squamous cell carcinoma (OSCC) cell lines, it was reported that phenothiazine derived methoxylated chalcones have cytotoxic and apoptotic effect with the tumor-specificity.\textsuperscript{[33]}

In a study done by our group, investigating the anticancer effects of 10 different chalcone-derived compounds, it was shown that chalcone compounds inhibited cell growth in breast cancer (MCF-7), non-small cell lung cancer (A549) and prostate cancer (PC-3) cell lines at a concentration of 20 μM, and \textit{IC}_{50} values have calculated as 9.2 and 10 μM for A549, MCF-7 and PC-3 cells for 72h.\textsuperscript{[14]}

In the current study, the new Chalcone derivative compound was synthesized based on curcumin structure that another natural compound with known anticancer effect,

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**Table 1.** \textit{IC}_{50} values of cancer cells treated with different doses (0.39–25 μM) of Chalcone compound for 48 hours. \textit{IC}_{50} was defined as the dose that inhibited 50% of cell viability.

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>\textit{IC}_{50} (μM) Chalcone Compound</th>
<th>\textit{IC}_{50} (μM) Curcumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A549</td>
<td>2.85</td>
<td>18.25</td>
</tr>
<tr>
<td>H1299</td>
<td>1.46</td>
<td>12.46</td>
</tr>
<tr>
<td>HCT116</td>
<td>0.59</td>
<td>20</td>
</tr>
<tr>
<td>HT29</td>
<td>0.35</td>
<td>26.70</td>
</tr>
</tbody>
</table>

**Figure 3.** Viability of A549, H1299, HCT116 and HT29 cells after treatment with Chalcone compound for 48h measured by the SRB viability assay. *Denotes statistically significant differences in comparison with control: * (p< 0.05); ** (p<0.01); *** (p<0.001). Data are presented as mean± SD (n=3). SD, standard deviation; SRB, sulforhodamine B.
and it was tested for the first time in human lung and colon cancer cell lines. According to our previous results in A549 cells and other similar studies in the literature, it was seen that this modification of structure (curcumin-like structure) allowed to effectively inhibit cell viability at low concentrations (Table 1). This means that the new Chalcone compound showed higher potency at lower doses than its parent compounds. The use of lower doses in anticancer agent studies is important as it may reduce the risk of systemic toxicity in patients.

Studies to date show that curcumin-derived compounds increase the cytotoxic potential. It is known that curcumin compounds, alone or in combination with other anticancer drugs, inhibit the clonogenicity of cancer cells, increase cytotoxicity by inducing antiproliferative and apoptotic effects, suppress cellular transformation and thus prevent cancer cell proliferation. In a study focused on curcumin analogues, it was revealed that one of the agents, named J1, induced growth arrest and apoptosis, changed level of cyclin A, CDK2 and cyclin E, and decreased the phosphorylation of AKT, mTOR and PKC-theta in breast cancer cells. These results demonstrate enhanced anti-tumor effects of compounds based on the curcumin structure.

When we look at the literature, it is seen that the IC_{50} values of curcumin alone are higher than the Chalcone-derived compound (Table 1). Accordingly, we think that the curcumin-like structure of the newly synthesized Chalcone derivative compound that we used in our study may be effective in increasing cytotoxicity.

**Combination Effect of Chalcone Compound with Anti-Cancer Drug**

The effects of Chalcone compound in combination with 5-FU, which is used as an effective chemotherapy drug especially in colon cancer, on the viability of HCT116 and HT29 colon cancer cells were investigated by SRB test. Thus, it was evaluated whether the efficacy of common chemotherapy drugs could be increased and the cytotoxic effect of Chalcone compound was compared with 5-FU. Cell viability was evaluated after 48 hours of administration of different concentrations of 5-FU (2-172 μM) and Chalcone (0.39 and 0.78 μM) alone and in combination.

It was observed that the Chalcone compound alone resulted in approximately 2 times more cytotoxicity in cancer cells than the administration of 5-FU, especially at low doses. This indicates a higher cytotoxic potential of the Chalcone compound at lower doses than a clinically used chemotherapy agent. Although it was observed that the combination with Chalcone compound significantly reduced cell viability compared to 5-FU alone, this effect was seen as the effect of chalcone alone rather than a synergistic effect (Fig. 4).

5-FU is a drug widely used alone or in combination with other chemotherapeutic agents in the treatment of a number of cancer types, especially colorectal cancer. Although response rates to 5-FU-based chemotherapy as first-line treatment in advanced colorectal cancer are only 10-15%, response rates increase to 40-50% in combination with other anticancer drugs. In addition, 5-FU is known as the second most common chemotherapeutic drug associated with cardiotoxicity. There is a need for new treatment strategies in chemotherapy to increase the response to treatment and reduce the toxic side effects of drugs in patients.

The results of our study show that the combination of newly synthesized Chalcone compound and 5-FU is not highly effective in increasing cytotoxicity in cancer cells, however, Chalcone compound at 0.39 and 0.78 μM concentrations reduces cancer cell viability more effectively than low doses of 5-FU. Similarly, in a study investigating the cytotoxic and antiproliferative activity of chalcone derivatives containing morpholine ring in Rat glioma (C6) and human cervical adenocarcinoma cells (HeLa), it was found that some...
Chalcone derivatives showed higher cytotoxicity than cisplatin used as a chemotherapy drug.[44]

**Fluorescence Imaging for Determination of Cell Death Mode**

After observing the cytotoxic potential of Chalcone compound in cancer cells, fluorescent staining was performed to determine the mode of cell death. The doses at which the Chalcone compound showed the highest cytotoxic activity (16.25 μM for A549 cells; 12.5 μM for H1299; 1.56 μM for HT29; 3.12 μM for HCT116) were used for 24 hours. After incubation time, cells were stained with Hoechst 33342, Annexin-V-FITC and PI fluorescent dyes for evaluating the nuclear morphology and membrane integrity.

Hoechst 33342 is a fluorescent dye that can bind to DNA in both dead (apoptotic and necrotic) and living cells (blue). In the early phase of apoptotic cell death, phosphatidylserine (PS) translocated from the inner side of the plasma membrane to the outer layer. Annexin-V-FITC binds to PS, making apoptotic cells visible, so detection of PS translocation is a marker for apoptotic cell death. However, since Annexin-V-FITC can also bind to necrotic cells, PI staining is used to distinguish between apoptotic and necrotic cells. PI is a dye that can only pass through the damaged membrane, so it can only stain primary necrotic and late apoptotic (secondary necrosis) cells.[45] At the end of the incubation time, primary necrotic or late apoptotic cells stained positively with both Annexin-V-FITC (green) and PI (red), while early apoptotic cells only stained Annexin-V-FITC positive (Fig. 5a, 5b). The results indicate that the Chalcone compound induces apoptotic cell death in A549, H1299, HT29 and HCT116 cells. The presence of Annexin-V-FITC positive staining (green) with pyknotic nuclei and chromatin condensation in cells is considered evidence of apoptotic cell death. In the H1299 and HCT116 cell lines, some of the cells were observed positively stained both Annexin-V-FITC (green) and PI (red), thus implying late stage of apoptosis (Fig. 5a).

There are many studies reporting that different chalcone-derived compounds have anticancer activity and induce apoptosis in various cancer cell lines. The results of a study in breast cancer (T47D) and cervical cancer cell line (HeLa) revealed that a chalcone-derived compound caused cell death via apoptosis pathway. In addition, it has been reported that 1.09% early apoptosis and 2.35% late apoptosis stage in HeLa cells, 18.14% early apoptosis and 48.73% late apoptosis stage in T47D cells were observed.[46]

![Figure 5](image-url)

**Figure 5.** (a) Fluorescence staining of A549, H1299, HCT116 and HT29 cells with Hoechst 33342 (blue), Annexin-V-FITC (green) and PI (red) after treatment with Chalcone compound for 24h. Untreated cells were used as control. (b) Quantitative early apoptotic measurement by Annexin V/PI staining in A549, H1299, HT29 and HCT116 cells after treatment of Chalcone compound for 24 h. Data were expressed as mean ± SE of three independent experiments. *(p<0.05); ** (p<0.01).
In previous studies conducted by our group, which investigated the anticancer effects of a number of chalcone-derived compounds, it was shown that some of the chalcone derivatives induce apoptosis in prostate, lung and breast cancer cells via the caspase-dependent pathway, resulting in an increase in reactive oxygen species (ROS) levels with a decrease in mitochondrial membrane potential.[14] In another study, it has been reported that the chalcone derivative compound synthesized by Williamson etherification and Claisen-Schmidt condensation method up-regulates DR5 expression in gastric cancer cells and induces apoptosis via the mitochondrial pathway and increases ROS production with the activation of the keap1/Nrf2 pathway. In the same study, it was shown that intraperitoneal administration of chalcone compound inhibited tumor growth in xenograft mouse model.[47] Various chalcones are also known to induce apoptosis through c-Myc15-mediated ROS induction.[48-50]

Similarly, curcumin and its analogues have the potential to induce cell death in many different types of cancer. It has been reported in various studies that curcumin analogues induce apoptosis through several pathways such as caspase activation, Bcl-2 and PARP down-regulation, and ROS induction.[39, 51-54]

In conclusion, in this study, the anti-cancer properties of new Chalcone-derived compound, which was newly synthesized based on the curcumin structure was investigated in human lung (A549, H1299) and colon cancer (HT29, HCT116) cells. It was observed that the Chalcone compound had a significant cytotoxic effect on all four cell lines and was more effective in colon cancer cells. In combination studies in HT29 and HCT116 cells, it was observed that Chalcone compound inhibited cell viability more effectively than especially low doses of the 5-FU drug used in chemotherapy. In addition, it was determined that Chalcone compound induced cell death in lung and colon cancer cells via apoptotic pathway. The results obtained show that this newly synthesized Chalcone-derived compound may have a potential anticancer activity in lung and colon cancer when it is supported by elucidation of its main mechanism of action, cellular targets and in-vivo studies.

Disclosures

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Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.


References

39. Baddr G, Gul HI, Yamali C, Mohamed AAM, Baddr BM, Gul M, et al. Curcumin analogue 1,5-bis(4-hydroxy-3-{[(4-methylpiperazin-1-yl)methyl]phenyl}penta-1,4-dien-3-one mediates growth arrest and apoptosis by targeting the PI3K/AKT/mTOR and PKC-theta signaling pathways in human breast carcinoma.