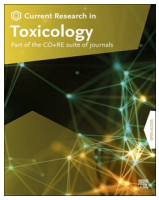
Current Research in Toxicology 8 (2025) 100230

Contents lists available at ScienceDirect

Current Research in Toxicology

journal homepage: www.journals.elsevier.com/current-research-in-toxicology



Research Paper

Bioinformatics study and cytotoxicity of several curcumin analogues in ovarian cancer

Retno Murwanti [a,b,*], Ritmaleni [c,b], Navista Sri Octa Ujiantari [c,b], I Made Rhamandana Putra [d], Aliffian Farhan Wahyudi [d], Vigha Ilmanafi Arifka [d]

[a] Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia
[b] Curcumin Research Center, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia
[c] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia
[d] Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia

ARTICLE INFO

Keywords:
Ovarian cancer
Curcumin analogues
Dibenzylidene-cyclopentanone
Cytotoxicity
Bioinformatics

ABSTRACT

Ovarian cancer ranks as Indonesia's third-leading cause of cancer-related death, emphasising the need for innovative treatments. This study combined bioinformatics, molecular docking, and experimental assays to tackle this challenge. We identified 166 ovarian cancer-related genes, with MYC standing out as a key target. Analysis of MYC mutations revealed prevalent alterations, though no significant survival differences were observed in patients with or without the mutations. Molecular docking pinpointed compound B155 as a promising MYC inhibitor. A preliminary cytotoxicity assay revealed compound B155′s notable activity, with an 87.19 % inhibition of cell viability at 50 μM. Most of the other curcumin analogues only caused more than 50 % inhibition at the same concentration. This result suggests alternative mechanisms of action, possibly antioxidant effects, warranting further exploration. In summary, this study unveiled MYC as a prime target for ovarian cancer treatment, with curcumin analogues like B155 showing potential. Nonetheless, the complex factors affecting cytotoxicity underscore the need for deeper investigation into these compounds' mechanisms in ovarian cancer cells.

Introduction

In 2020, there were an estimated 313,959 new cases and 207,252 deaths worldwide from ovarian cancer. Overall, Asia is the leading region with a death rate higher than in Europe and Northern America. In high-income countries like Northern Europe and North America, the incidence has declined over the past two decades. By contrast, low-income countries like Eastern Europe and parts of Asia have the highest incidence, particularly in women under 50 years of age (Webb and Jordan, 2024). Specifically in Indonesia, ovarian cancer is a significant gynaecologic malignancy, with a high mortality rate ranking third after cervical and uterine cancers. It accounts for approximately 4.3 % of all cancer cases in the country, with about 13,310 new cases yearly. Despite its relatively low prevalence, ovarian cancer has a much higher fatality rate than breast cancer, claiming around 7,842 lives annually and ranking as the eighth leading cause of cancer-related deaths (Sung et al., 2021).

The risk of developing ovarian cancer for women is 1 in 75, with a mortality risk of 1 in 100. The global 5-years relative survival rate for ovarian cancer is only 30 to 40 %, with only minimal improvement since 1995 (Brett et al., 2017). Common causes of ovarian cancer include BRCA1 and BRCA2 gene mutations and several non-genetic factors such as reproductive hormonal stability. Current treatment strategies involve surgery, drugs, radiotherapy, and chemotherapy. However, since ovarian cancer cells experience certain molecular changes over time, chemotherapy may not be a wise choice due to cancer cell resistance (Chandra et al., 2019) and often comes with severe side effects that can impact both survival and quality of life. As a result, there is growing interest in a molecular approach that targets specific signalling pathways to inhibit ovarian cancer progression (Vallianou et al., 2015).

Indonesia's rich biodiversity offers diverse potential therapeutic compounds like curcumin, which has garnered attention for its

* Corresponding author at: Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta 55281, Indonesia.
E-mail addresses: retno_murwanti@ugm.ac.id (R. Murwanti), ritmaleni@ugm.ac.id (Ritmaleni), navista.sri.o@mail.ugm.ac.id (N.S.O. Ujiantari), maderhamandana@mail.ugm.ac.id (I.M.R. Putra), aliffianfarhan35@mail.ugm.ac.id (A.F. Wahyudi), vighailmanafi@mail.ugm.ac.id (V.I. Arifka).

https://doi.org/10.1016/j.crtox.2025.100230
Received 13 September 2024; Received in revised form 15 March 2025; Accepted 17 March 2025
Available online 27 March 2025

anticancer properties. Highlighted among these properties is its tumor growth inhibition by inhibiting the cell cycle, inducing apoptosis, and inhibiting angiogenesis. Moreover, curcumin has no significant toxicity and has been found to increase the efficiency of chemotherapeutics. Therefore, curcumin has been extensively studied in various cancer types, such as breast, lung, colorectal, and ovarian cancers, with different mechanisms of action involving various signalling pathways (Panda et al., 2017; Yu et al., 2016; Liu et al., 2016). Nevertheless, curcumin's effectiveness is limited by challenges related to oral bioavailability and low aqueous solubility, hindering its delivery. Consequently, researchers have explored modified curcumin analogue compounds to overcome these limitations and enhance its efficacy (Tomeh et al., 2019; Gogineni et al., 2021). This research aimed to screen the most appropriate target gene and the most active novel curcumin analogue compounds using in silico and in vitro approaches.

Materials and methods

In silico study

Ovarian cancer-related target gene determination

Ovarian cancer-related genes were retrieved from the DISGENET web-based tool using 'Epithelial ovarian cancer' data (CUI: C0677886) (Pinero et al., 2015). The genes were selected based on a Gene Disease Association (GDA) score above 0.1. The selected genes' Protein-Protein Interaction (PPI) were then identified using STRING v12.0 database with default setting (Szklarczyk et al., 2015). The resulting networks were then ranked using the Cytohubba plugin from Cytoscape v3.10.0 to find the best target gene for ovarian cancer. The mutation and survival profile of the gene based on ovarian cancer studies were also profiled using the cBioPortal database (Gao et al., 2013).

Molecular docking

The 3D structure of MYC was retrieved from Protein Data Bank (PDB) with PDB-ID: 1NKP (Nair and Burley, 2003). Molecular docking was carried out using Molecular Operating Environment (MOE) v2022 (Environment, 2024). The protein structure was prepared with all the issues corrected, 3D protonated, and the energy minimisation was calculated using the AMBER forcefield. The binding site was identified first using Site Finder feature in MOE since there is no ligand bound to the protein. Eleven curcumin analogues were sketched and then built with the Builder feature from MOE. The MOPAC (Molecular Orbital Package) system with the PM3 method was assigned to charge these analogues. Flexible docking was carried out using the Dock feature with Triangle Matcher and London DG as placement method and scoring function, respectively. The docking results were analysed based on the poses of the curcumin analogues and docking scores, and their interaction with the protein was visualised both in 2D and 3D.

In vitro study

Chemicals and reagents

Dulbecco's modified Eagle's medium (DMEM) high glucose, dimethylsulfoxide (DMSO), and trypsin were purchased from Sigma-Aldrich (Germany). Fetal bovine serum (FBS) was purchased from Sigma-Aldrich (USA). Antibiotic-antimycotic containing penicillin, streptomycin, and amphotericin B was purchased from Sigma-Aldrich (Israel). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was purchased from Biobasic (USA). Sodium dodecyl sulfate (SDS) and hydrochloric acid were procured from Merck (Germany). All curcumin analogs samples (B103, B115, B118, B126, B127, B129, B143, B145, B148, B149, and B155) were synthesized by Ritmaleni, Curcumin Research Center (CRC), Faculty of Pharmacy, Universitas Gadjah Mada, and have not yet been registered at CASRN.

Cell culture

SK-OV-3 cancer cells (ECACC, catalogue no. 91091004) were cultured in DMEM-high glucose medium supplemented with 10 % FBS and 1 % antibiotic–antimycotic. Maintaining the culture in an incubator, an atmosphere of 5 % CO_2 and 95 % O_2 was used at a temperature of 37 °C.

Cytotoxicity assay

SK-OV-3 cancer cells were cultured until they reached more than 80 % confluence, were then harvested using trypsin, and were put into a 96-well plate at 10^4 cells/well. The cells were then incubated for 24 h and treated with the samples at concentrations of 50 μM, previously dissolved in 1 % dimethyl sulfoxide (DMSO). Subsequently, the cells were incubated in a CO_2 incubator for 24 h. The test solution was removed, and the cells were washed with phosphate buffer saline (PBS). MTT reagent was added, followed by a 4-hour incubation, and then a 10 % SDS stopper reagent was added. After overnight incubation in the dark, the well plate was placed on a shaker for 5 min. Following this, absorbance was measured using an ELISA reader at a wavelength of 595 nm. Cell viability percentage was then calculated based on the absorbance results.

Results

Ovarian cancer-related target gene determination

Data mining results from the DISGENET database (https://www.disgenet.com) show that 2841 genes have been associated with ovarian cell cancer. Subsequently, data were selected based on a Gene Disease Association (GDA) value greater than 0.1, resulting in the identification of 166 genes predicted to have the highest association with ovarian cancer. The genes were then analysed for their interactions using the STRING v12.0 database (https://string-db.org/) to determine the genes with the highest interactions with other genes (Fig. 1).

These interactions were then quantified using the Cytohubba plugin in Cytoscape, revealing the TP53 gene to have the highest degree of interaction with a value of 123, followed by MYC with a value of 112

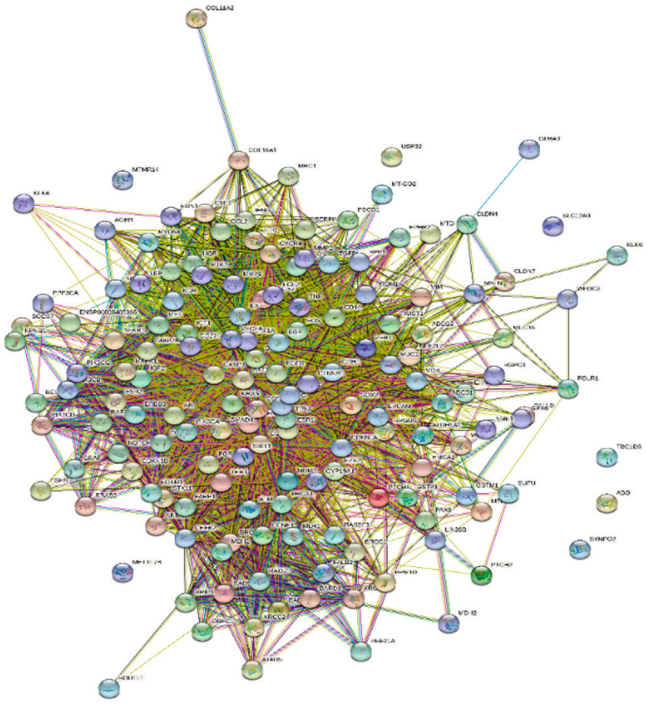


Fig. 1. PPI Result of 166 Ovarian Cancer-Related Genes with GDA Over 0.1.

Table 1
Top 10 Ranked Genes with Highest Connection (Degree) From STRING Network.

Gene	Gene Name	Degree
TP53	Tumor Protein P53	123
MYC	MYC Proto-Oncogene	112
EGFR	Epidermal Growth Factor Receptor	110
AKT1	AKT Serine/Threonine Kinase 1	110
CTNNB1	Catenin Beta 1	106
PTEN	Phosphatase and Tensin Homolog	104
ERBB2	Erb-b2 Receptor Tyrosine Kinase 2	103
ESR1	Estrogen Receptor 1	97
KRAS	KRAS Proto-Oncogene	94
CCND1	Cyclin D1	93

(Table 1). TP53 is a tumor suppressor gene, and its expression is crucial in preventing cancer. Mutations leading to the inactivation of TP53 are frequently observed in cancer cases (Brett et al., 2017). Therefore, inhibiting TP53 is not a viable option for improving the prognosis of ovarian cancer patients. Hence, the best candidate gene for targeted inhibition in ovarian cancer cases is MYC, an oncogenic protein.

Analysis of survival curve and gene mutation profile

From the cBioPortal database (https://www.cbioportal.org/), the study used as a reference for determining the gene mutation profile of MYC in ovarian cancer originates from 7 different studies, comprising a total of 1949 samples and 1892 patients. Based on these multiple studies, the MYC alteration profile varies from 10 to 40 %, with an average of 32 % across all cases (Fig. 2). Nearly all alterations observed in the MYC gene are amplifications, with the remainder being mixed alterations consisting of amplifications along with mutations.

The survival curve of ovarian cancer patients with variations in the MYC gene alterations is displayed graphically using data collected from the seven prior studies. The outcomes derived from the analysis indicate the absence of statistically significant disparities between the survival curves of the patient cohort exhibiting MYC gene alterations in comparison to the cohort lacking such alterations.

Molecular docking of test compounds with the target protein

The 3D structure of MYC was obtained from the Protein Data Bank (PDB) with the PDB-ID: 1NKP. This protein is a heterodimer bound to a common DNA target (Enhancer or E box hexanucleotide, 5′-CACGTG-3′) (Nair and Burley, 2003). The compound MYCMI-6, previously recognised for its MYC inhibitory activity with a Kd value of 1.6 ± 0.5 μM, was employed as a reference compound (Vallianou et al., 2015). The site finder found a binding site between the protein and DNA similar to that described in other studies, suggesting that the compounds might have transcription blocker features (Feng et al., 2021). The docking scores represent the binding affinity prediction (kcal/mol). All compounds exhibited relatively similar docking scores, suggesting a similar potential effect when compared to MYCMI-6 (Table 2). Compound B155 displayed the highest docking score, meaning it is predicted to have higher binding affinity than MYCMI-6, so B155 may act as a potent MYC inhibitor.

All curcumin analogues could occupy the binding site, interacting with amino acid residues and nucleotides located in the intercalation section of MYC and DNA (Table 3). Each analogue exhibited a specific interaction with certain amino acid residues and/or nucleotides. The 2D visualisation in Fig. 3 indicates that the specific interactions of B155 and MYCMI-6 with MYC are slightly different. B155 undergoes hydrogen bonding with Ala937 and Arg913 of the protein, while MYCMI-6 exhibits hydrogen bonding with DAB309 of DNA (Fig. 3). The detailed interaction can be seen in Fig. 4. The 3D visualisation illustrates the poses of B155 and MYCMI-6 in the binding site located in the intercalation section of MYC and DNA. Despite subtle differences in interaction,

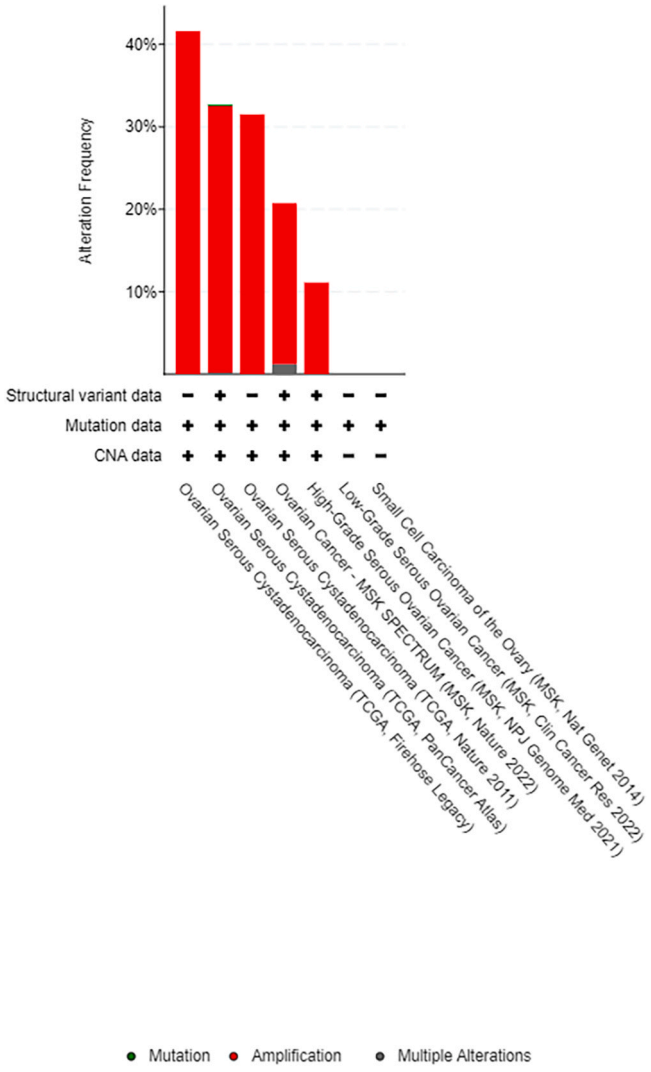


Fig. 2. The MYC Gene Alteration Profile in Multiple Ovarian Cancer Studies from the cBioPortal Database.

Table 2
MYC binding affinity predictions.

Compounds	Docking score (ΔG) Kcal/mol
B103	−9.9873
B115	−11.1495
B118	−9.1953
B126	−9.6448
B127	−9.5456
B129	−9.6971
B143	−9.5207
B145	−7.0176
B148	−10.1526
B149	−8.8263
B155	**−11.8257**
MYCMI-6	−10.9839

all the curcumin analogues could potentially interfere with the binding of MYC to the DNA target.

Cytotoxic profile against SK-OV-3 ovarian cancer cells using MTT assay

A cytotoxicity assay was performed following the bioinformatics and molecular docking results on human epithelial ovarian cancer cell line

Table 3
Interaction of Curcumin Analogues and MYCMI-6 in the binding site located between MYC and DNA.

Compounds	Amino acid residues and nucleotides in the binding site	Specific interaction	Interaction type
B103	Nucleotide of DNA:	DCB310	Aromatic-H
B115	DAA109, DCA110, DGA111, DCA108, DCB308, DAB309,	DAA109, DAB309	H
B118	DCB310, DGB311	DCB310	Aromatic-H
B126	Myc protein:	DCB310	Aromatic-H
B127	Glu211, Glu910, Arg913,	DCB310	H
B129	Arg914, Leu917, Lys918,	DCB310	H
B143	Phe921, Phe922, Glu935, Ala937, Lys936, Pro938, Lys939,	DCB310, DAA109	H
B145	Ile942	DCB310, DAA109	H
B148		DCB310	Aromatic-H
B149		DCB310	Aromatic-H
B155		Arg913, Ala937	H
MYCMI-6		DAB309	H

H = hydrogen bond.

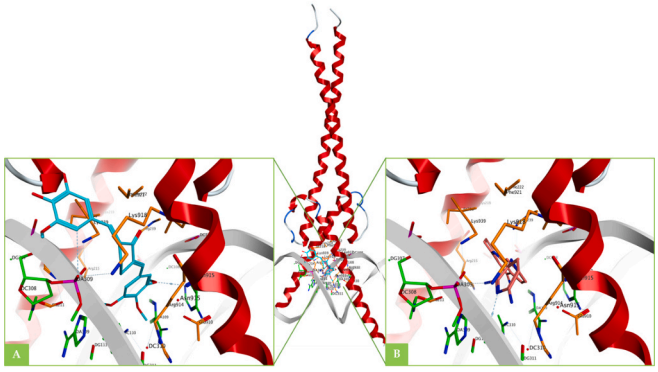


Fig. 3. The 2D Visualisation of B155 (A) and MYCMI-6 (B) with MYC.

SK-OV-3 (Fig. 5). In this stage, all the curcumin analogues (dibenzylidene-cyclopentanones) were tested at a concentration of 50 μM in a preliminary screen for the compounds with the highest potential as anticancer agents for future evaluation. Most of the compounds exhibited low or negligible cytotoxic activity except for B143 and B155. The lowest cell viability value (12.81 %) was obtained with B155 and it was remarked as the most potent cytotoxic effect on the cell line SKOV-3. This result correlates fairly well with the molecular docking, although most of the analogues failed to reduce the viability of the cancer cells. Additional cytotoxicity assay was performed to determine IC_{50} values of the B155 compound which has the lowest cell viability value (Fig. 6). The IC_{50} value of B155 is 1.81 μM.

Discussion

Despite having the highest degree of connection with ovarian cancer based on STRING Network analysis, gene TP53 is not a good target for curcumin analogue inhibition. This gene reportedly acts as a 'guardian of the genome' with a role as a tumor suppressor, directly and indirectly suppressing unconstrained neoplasia and proliferation. Mutation or alteration in such tumor suppressor genes, including TP53, could lead to the inactivation of its main function to restrict tumorigenic potential (Pietragalla et al., 2020; Schuijer and Berns, 2003). Therefore, MYC was selected as the target for inhibition as it presented the second highest degree of connection (112; Table 1). As the best candidate for ovarian cancer inhibition in this study, and MYC is indeed an ideal target for cancer therapy, as its oncogenic c-MCY plays a pivotal role as a stimulant in cancer growth and maintenance, and is associated with drug resistance (Massó-Vallés and Soucek, 2020; Meyer and Penn, 2008; Vita and Henriksson, 2006). c-MYC also plays a crucial role as a transcription factor for FOXM1, particularly in High-Grade Serous Carcinoma (HGSC) (Liu et al., 2021). This topic is further discussed in a recent review on major oncogenic pathways in ovarian cancer (Lliberos et al., 2024).

From the analysis of survival and MYC gene mutation data, there was no significant difference between the survival curves of the patient cohort exhibiting MYC gene alterations and those of the cohort lacking such alterations. This result aligns with a previous report, which stated that the expression of MYC is not significantly correlated with the survival rate of ovarian cancer patients. Meanwhile, MYC status is associated with tumor grade, where differentiated tumors are usually positive for c-MYC. Moreover, a patient's ability to survive ovarian cancer is strongly aligned with the expression of p53 protein, which is expressed by TP53 gene mutations (86 % of all primary tumors and 91 % of all serous tumors. Expression of p53 in epithelial ovarian carcinoma has been related to lower survival rates, either alone or combined with p27 and c-MYC (Skírnisdóttir et al., 2011). These observations are strengthened by the fact that, in cases positive for c-MYC and negative for p53, the survival of ovarian cancer patients increases.

To predict the compound with highest inhibitory MYC pathway activity, molecular docking and cytotoxic assay were carried out. The docking scores reflect binding affinity of the curcumin analogues compared to MYCMI-6, a recognised MYC inhibitor (Duffy et al., 2021). Compound B155, both in silico and in vitro assay, had the highest binding affinity prediction with MYC and the highest cytotoxic activity in cancer cells. Based on the concept that 'similar ligands bind to similar targets,' evaluating the similarity between a ligand of interest and a target compound is a straightforward means to predict novel target-ligand interactions, even in a condition of low specific binding affinity (Meslamani et al., 2012; Yang et al., 2011; Vidal et al., 2011). Thus, there was a high probability of identifying a compound with high prediction confidence of inhibition capability, with suitable docking score and binding affinity values.

The interactions of the curcumin analogues and MYCMI-6 listed in Table 3 were used to identify the most similar interaction profile between them. Interestingly, B155 showed a different interaction profile to MYCMI-6. Despite its lower inhibitory activity, only B115 showed a similarity to MYCMI-6 in terms of interaction. Key for selective interaction between protein and ligand is the unusual amino acid composition in the binding site, which has a crucial role in the catalysis or recognition process (Salentin et al., 2014). These specific binding amino acids present a specific location and orientation. Thus, a ligand compound with a binding site similar to the reference compound may not correlate in terms of docking score. In summary, the prime cytotoxic activity of the novel curcumin analogues was obtained with compound B155, which resulted in 12.81 % of cell viability at 50 μM or exhibited 87.19 % suppression of viability. Moreover, this compound has quite promising IC_{50} value, which is 1.81 μM.

Conclusions

MYC was identified as a crucial target for ovarian cancer treatment. Analysis of MYC mutations revealed prevalent alterations, though no significant survival differences were observed in patients with or without the MYC mutations. Molecular docking pinpointed compound B155 as a promising MYC inhibitor. In addition, cytotoxicity assays revealed the notable activity of compound B155 as the most potent cytotoxic effect on the cell line SKOV-3 with 12.81 % of cell viability at 50 μM. This research also show that B155 has promising IC_{50} value, which is 1.81 μM.

Institutional Review Board Statement

This study was approved by the Institutional Review Board (or Ethics Committee) of Faculty of Medicine, Public Health, and Nursing

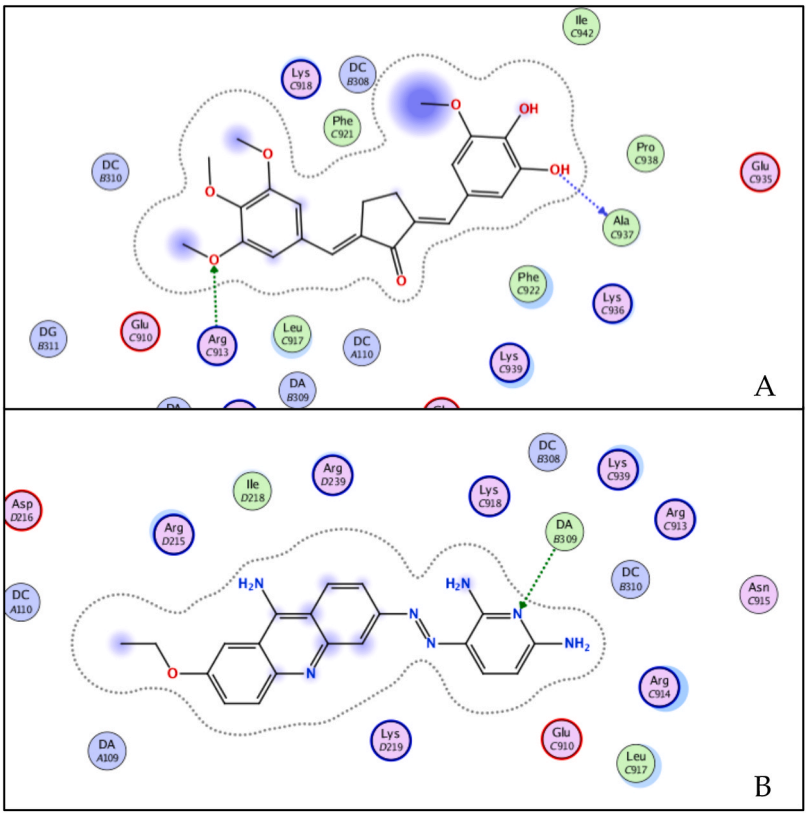


Fig. 4. 3D Visualisation of B155 (blue-A) and MYCMI-6 (pink-B) with MYC (orange = amino acid residues of MYC; green = DNA). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

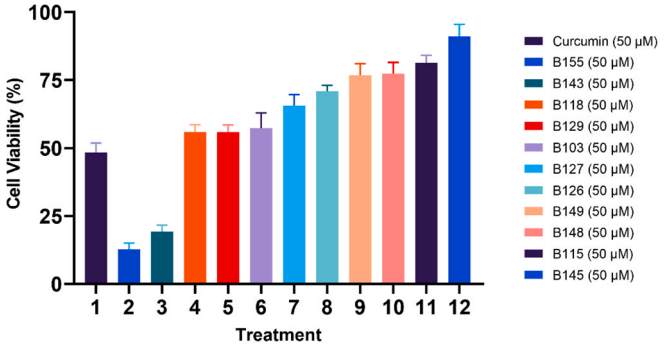


Fig. 5. Cytotoxicity Activity of Curcumin and Curcumin Analogues.

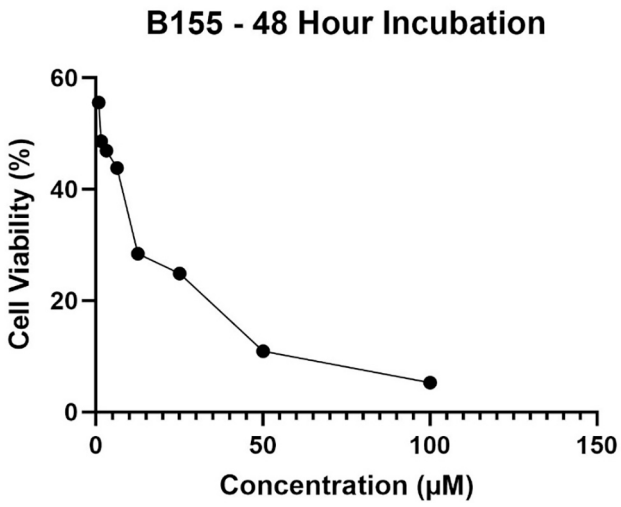


Fig. 6. Cytotoxicity Activity of B155 Curcumin Analogues.

Universitas Gadjah Mada, Yogyakarta, Indonesia (Ethical Clearance number: KE/0526/03/2023).

CRediT authorship contribution statement

Retno Murwanti: Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data curation, Supervision, Project administration, Funding acquisition, Writing – original draft, Writing – review & editing. **Ritmaleni:** Methodology, Software, Validation, Investigation, Resources, Data curation, Supervision. **Navista Sri Octa Ujiantari:** Investigation, Data curation, Visualization, Formal analysis. **I Made Rhamandana Putra:** Investigation, Data curation, Visualization, Formal analysis. **Aliffian Farhan Wahyudi:** Investigation, Data curation, Visualization, Formal analysis. **Vigha Ilmanafi Arifka:** Writing – original draft, Writing – review & editing.

Funding

This research was funded by Penelitian Fundamental Reguler, Ministry of Education, Culture, Research, and Technology, Republic of Indonesia, grant number 3130/UN1/DITLIT/Dit-Lit/PT.01.

Declaration of competing interest

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

Acknowledgment

The authors would like to thank the Ministry of Education, Culture, Research, and Technology, Republic of Indonesia for funding this research through the scheme of Penelitian Fundamental Reguler [Grant Number 3130/UN1/DITLIT/Dit-Lit/PT.01] and Faculty of Pharmacy, Universitas Gadjah Mada, for providing the licensed-MOE software.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crtox.2025.100230.

Data availability

No data was used for the research described in the article.

References

Brett, M.R., Jennifer, B.P., Thomas, A.S., Brett, M.R., Jennifer, B.P., Thomas, A.S., 2017. Epidemiology of ovarian cancer: a review. *Cancer Biol. Med.* 14, 9–32. https://doi.org/10.20892/j.issn.2095-3941.2016.0084.

Chandra, A., Pius, C., Nabeel, M., Nair, M., Vishwanatha, J.K., Ahmad, S., Basha, R., 2019. Ovarian Cancer: Current Status and Strategies for Improving Therapeutic Outcomes. *Cancer Med.* 8, 7018–7031. https://doi.org/10.1002/cam4.2560.

Duffy, M.J., O'Grady, S., Tang, M., Crown, J., 2021. MYC as a Target for Cancer Treatment. *Cancer Treat. Rev.* 94, 102154. https://doi.org/10.1016/j.ctrv.2021.102154.

Molecular Operating Environment (MOE) 2024.

Feng, L., Sun, C., Sun, X., Zhao, Y., Yu, R., Kang, C., 2021. Identification of Inhibitors Targeting HIF-2α/c-Myc by Molecular Docking and MM-GBSA Technology. *J. Recept. Signal Transduction* 41, 511–519. https://doi.org/10.1080/10799893.2020.1825493.

Gao, J., Aksoy, B.A., Dogrusoz, U., Dresdner, G., Gross, B., Sumer, S.O., Sun, Y., Jacobsen, A., Sinha, R., Larsson, E., et al., 2013. Integrative Analysis of Complex Cancer Genomics and Clinical Profiles Using the cBioPortal. *Sci. Signal.* 6. https://doi.org/10.1126/scisignal.2004088.

Gogineni, V., Morand, S., Staats, H., Royfman, R., Devanaboyina, M., Einloth, K., Dever, D., Stanbery, L., Aaron, P., Manning, L., et al., 2021. Current Ovarian Cancer Maintenance Strategies and Promising New Developments. *J. Cancer* 12, 38–53. https://doi.org/10.7150/jca.49406.

Liu, C., Barger, C.J., Karpf, A.R., 2021. FOXM1: a multifunctional oncoprotein and emerging therapeutic target in ovarian cancer. *Cancers* 13, 3065. https://doi.org/10.3390/cancers13123065.

Liu, W., Zhai, Y., Heng, X., Che, F.Y., Chen, W., Sun, D., Zhai, G., 2016. Oral Bioavailability of Curcumin: Problems and Advancements. *J. Drug Target.* 24, 694–702. https://doi.org/10.3109/1061186X.2016.1157883.

Lliberos, C., Richardson, G., Papa, A., 2024. Oncogenic pathways and targeted therapies in ovarian cancer. *Biomolecules* 14, 585. https://doi.org/10.3390/biom14050585.

Massó-Vallés, D., Soucek, L., 2020. Blocking Myc to Treat Cancer: Reflecting on Two Decades of Omomyc. *Cells* 9, 883. https://doi.org/10.3390/cells9040883.

Meslamani, J., Li, J., Sutter, J., Stevens, A., Bertrand, H.-O., Rognan, D., 2012. Protein–Ligand-Based Pharmacophores: Generation and Utility Assessment in Computational Ligand Profiling. *J. Chem. Inf. Model.* 52, 943–955. https://doi.org/10.1021/ci300083r.

Meyer, N., Penn, L.Z., 2008. Reflecting on 25 Years with MYC. *Nat. Rev. Cancer* 8, 976–990. https://doi.org/10.1038/nrc2231.

Nair, S.K., Burley, S.K., 2003. X-Ray Structures of Myc-Max and Mad-Max Recognizing DNA. *Cell* 112, 193–205. https://doi.org/10.1016/S0092-8674(02)01284-9.

Panda, A.K., Chakraborty, D., Sarkar, I., Khan, T., Sa, G., 2017. New Insights into Therapeutic Activity and Anticancer Properties of Curcumin. JEP 9, 31–45. https://doi.org/10.2147/JEP.S70568.

Pietragalla, A., Arcieri, M., Marchetti, C., Scambia, G., Fagotti, A., 2020. Ovarian Cancer Predisposition beyond BRCA1 and BRCA2 Genes. *Int J Gynecol Cancer* 30, 1803–1810. https://doi.org/10.1136/ijgc-2020-001556.

Pinero, J., Queralt-Rosinach, N., Bravo, A., Deu-Pons, J., Bauer-Mehren, A., Baron, M., Sanz, F., Furlong, L.I.D., 2015. A Discovery Platform for the Dynamical Exploration of Human Diseases and Their Genes. *Database* 2015, bav028–bav028. https://doi.org/10.1093/database/bav028.

Salentin, S., Haupt, V.J., Daminelli, S., Schroeder, M., 2014. Polypharmacology Rescored: Protein–Ligand Interaction Profiles for Remote Binding Site Similarity Assessment. *Progr. Biophys. Mol. Biol.* 116, 174–186. https://doi.org/10.1016/j.pbiomolbio.2014.05.006.

Schuijer, M., Berns, E.M.J.J., 2003. TP53 and Ovarian Cancer. *Hum. Mutat.* 21, 285–291. https://doi.org/10.1002/humu.10181.

Skírnisdóttir, I.A., Sorbe, B., Lindborg, K., Seidal, T., 2011. Prognostic Impact of P53, P27, and C-MYC on Clinicopathological Features and Outcome in Early-Stage (FIGO I-II) Epithelial Ovarian Cancer. *Int J Gynecol Cancer* 21, 236–244. https://doi.org/10.1097/IGC.0b013e31820986e5.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F., 2021. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA A Cancer J. Clin.* 71, 209–249. https://doi.org/10.3322/caac.21660.

Szklarczyk, D., Franceschini, A., Wyder, S., Forslund, K., Heller, D., Huerta-Cepas, J., Simonovic, M., Roth, A., Santos, A., Tsafou, K.P., et al., 2015. STRING V10: Protein–Protein Interaction Networks, Integrated over the Tree of Life. *Nucl. Acids Res.* 43, D447–D452. https://doi.org/10.1093/nar/gku1003.

Tomeh, M.A., Hadianamrei, R., Zhao, X., 2019. A Review of Curcumin and Its Derivatives as Anticancer Agents. *IJMS* 20, 1033. https://doi.org/10.3390/ijms20051033.

Vallianou, N.G., Evangelopoulos, A., Schizas, N., Kazazis, C., 2015. Potential Anticancer Properties and Mechanisms of Action of Curcumin. *Anticancer Res* 35, 645–651.

Vidal, D.; Garcia-Serna, R.; Mestres, J. Ligand-Based Approaches to In Silico Pharmacology. In Chemoinformatics and Computational Chemical Biology; Bajorath, J., Ed.; Methods in Molecular Biology; Humana Press: Totowa, NJ, 2011; Vol. 672, pp. 489–502 ISBN 978-1-60761-838-6.

Vita, M., Henriksson, M., 2006. The Myc Oncoprotein as a Therapeutic Target for Human Cancer. *Semin. Cancer Biol.* 16, 318–330. https://doi.org/10.1016/j.semcancer.2006.07.015.

Webb, P.M., Jordan, S.J., 2024. Global epidemiology of epithelial ovarian cancer, May 01. *Springer Nature*. https://doi.org/10.1038/s41571-024-00881-3.

Yang, L., Wang, K., Chen, J., Jegga, A.G., Luo, H., Shi, L., Wan, C., Guo, X., Qin, S., He, G., et al., 2011. Exploring Off-Targets and Off-Systems for Adverse Drug Reactions via Chemical-Protein Interactome — Clozapine-Induced Agranulocytosis as a Case Study. *PLoS Comput Biol* 7, e1002016. https://doi.org/10.1371/journal.pcbi.1002016.

Yu, Z., Wan, Y., Liu, Y., Yang, J., Li, L., Zhang, W., 2016. Curcumin Induced Apoptosis via PI3K/Akt-Signalling Pathways in SKOV3 Cells. *Pharm. Biol.* 54, 2026–2032. https://doi.org/10.3109/13880209.2016.1139601.