

## DAFTAR PUSTAKA

- Abdal Dayem, A., Hossain, M., Lee, S., Kim, K., Saha, S., Yang, G.-M., Choi, H., Cho, S.-G., 2017. The Role of Reactive Oxygen Species (ROS) in the Biological Activities of Metallic Nanoparticles. *Int. J. Mol. Sci.* 18, 120. <https://doi.org/10.3390/ijms18010120>
- Adina, A.B., Goenadi, F.A., Handoko, F.F., Ana, D., Hermawan, A., Jenie, R.I., Meiyanto, E., 2014. Combination of Ethanolic Extract of *Citrus aurantifolia* Peels with Doxorubicin Modulate Cell Cycle and Increase Apoptosis Induction on MCF-7 Cells 8.
- Al-Ashaal, H.A., El-Sheltawy, S.T., 2011. Antioxidant capacity of hesperidin from *Citrus* peel using electron spin resonance and cytotoxic activity against human carcinoma cell lines. *Pharm. Biol.* 49, 276–282. <https://doi.org/10.3109/13880209.2010.509734>
- Allocati, N., Masulli, M., Di Ilio, C., Federici, L., 2018. Glutathione transferases: substrates, inhibitors and pro-drugs in cancer and neurodegenerative diseases. *Oncogenesis* 7, 8. <https://doi.org/10.1038/s41389-017-0025-3>
- Anderson, D.H., 2021. Luminal A breast cancer resistance mechanisms and emerging treatments, in: *Biological Mechanisms and the Advancing Approaches to Overcoming Cancer Drug Resistance*. Elsevier, pp. 1–22. <https://doi.org/10.1016/B978-0-12-821310-0.00010-3>
- Arora, S., Tandon, S., 2015. DNA fragmentation and cell cycle arrest: a hallmark of apoptosis induced by *Ruta graveolens* in human colon cancer cells - PubMed [WWW Document]. URL <https://pubmed.ncbi.nlm.nih.gov/25576270/> (accessed 7.2.22).
- Banjerdpongchai, R., Wudtiwai, B., Khaw-on, P., Rachakhom, W., Duangnil, N., Kongtawelert, P., 2016. Hesperidin from *Citrus* seed induces human hepatocellular carcinoma HepG2 cell apoptosis via both mitochondrial and death receptor pathways. *Tumor Biol.* 37, 227–237. <https://doi.org/10.1007/s13277-015-3774-7>
- Bannister, A.J., Zegerman, P., Partridge, J.F., Miska, E.A., Thomas, J.O., Allshire, R.C., Kouzarides, T., 2001. Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain. *Nature* 410, 120–124. <https://doi.org/10.1038/35065138>
- Beausejour, C.M., 2003. Reversal of human cellular senescence: roles of the p53 and p16 pathways. *EMBO J.* 22, 4212–4222. <https://doi.org/10.1093/emboj/cdg417>
- Birsu Cincin, Z., Unlu, M., Kiran, B., Sinem Bireller, E., Baran, Y., Cakmakoglu, B., 2015. Anti-proliferative, apoptotic and signal transduction effects of hesperidin in non-small cell lung cancer cells. *Cell. Oncol.* 38, 195–204. <https://doi.org/10.1007/s13402-015-0222-z>

Birt, D., Wang, W., Pavia, N., Au, A., Chung, C., Schmitt, L., Jiang, Y., 2003. Cancer Prevention by Phytochemicals, Modulation of Cell Cycle. <https://doi.org/10.1201/9780203506332.ch5>

Bozko, P., Larsen, A.K., Raymond, E., Skladanowski, A., 2002. Influence of G2 arrest on the cytotoxicity of DNA topoisomerase inhibitors toward human carcinoma cells with different p53 status. *Acta Biochim. Pol.* 49, 109–119. [https://doi.org/10.18388/abp.2002\\_3827](https://doi.org/10.18388/abp.2002_3827)

Brett, J.O., Spring, L.M., Bardia, A., Wander, S.A., 2021. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res.* 23, 85. <https://doi.org/10.1186/s13058-021-01462-3>

Burdelski, C., Strauss, C., Tsourlakakis, M.C., Kluth, M., Hube-Magg, C., Melling, N., Lebok, P., Minner, S., Koop, C., Graefen, M., Heinzer, H., Wittmer, C., Krech, T., Sauter, G., Wilczak, W., Simon, R., Schlomm, T., Steurer, S., 2015. Overexpression of thymidylate synthase (TYMS) is associated with aggressive tumor features and early PSA recurrence in prostate cancer. *Oncotarget* 6, 8377–8387. <https://doi.org/10.18632/oncotarget.3107>

Campisi, J., 2013. Aging, Cellular Senescence, and Cancer. *Annu. Rev. Physiol.* 75, 685–705. <https://doi.org/10.1146/annurev-physiol-030212-183653>

Campisi, J., d'Adda di Fagagna, F., 2007. Cellular senescence: when bad things happen to good cells. *Nat. Rev. Mol. Cell Biol.* 8, 729–740. <https://doi.org/10.1038/nrm2233>

Cao, R., Zhang, Y., 2004. The functions of E(Z)/EZH2-mediated methylation of lysine 27 in histone H3. *Curr. Opin. Genet. Dev.* 14, 155–164. <https://doi.org/10.1016/j.gde.2004.02.001>

Carrasco-Torres, G., Monroy-Ramírez, H.C., Martínez-Guerra, A.A., Baltiérrez-Hoyos, R., Romero-Tlalolini, M. de los Á., Villa-Treviño, S., Sánchez-Chino, X., Vásquez-Garzón, V.R., 2017. Quercetin Reverses Rat Liver Preneoplastic Lesions Induced by Chemical Carcinogenesis. *Oxid. Med. Cell. Longev.* 2017, 1–8. <https://doi.org/10.1155/2017/4674918>

Chandrashekar, D.S., Bashel, B., Balasubramanya, S.A.H., Creighton, C.J., Ponce-Rodriguez, I., Chakravarthi, B.V.S.K., Varambally, S., 2017. UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. *Neoplasia* 19, 649–658. <https://doi.org/10.1016/j.neo.2017.05.002>

Chandrashekar, D.S., Karthikeyan, S.K., Korla, P.K., Patel, H., Shovon, A.R., Athar, M., Netto, G.J., Qin, Z.S., Kumar, S., Manne, U., Creighton, C.J., Varambally, S., 2022. UALCAN: An update to the integrated cancer data analysis platform. *Neoplasia* 25, 18–27. <https://doi.org/10.1016/j.neo.2022.01.001>

- Chang, M.-S., 2012. Tamoxifen Resistance in Breast Cancer. *Biomol. Ther.* 20, 256–267. <https://doi.org/10.4062/biomolther.2012.20.3.256>
- Chen, C., Huang, H., Wu, C.H., 2017. Protein Bioinformatics Databases and Resources, in: Wu, C.H., Arighi, C.N., Ross, K.E. (Eds.), *Protein Bioinformatics, Methods in Molecular Biology*. Springer New York, New York, NY, pp. 3–39. [https://doi.org/10.1007/978-1-4939-6783-4\\_1](https://doi.org/10.1007/978-1-4939-6783-4_1)
- Chen, J., Mathews, C.E., 2014. Use of Chemical Probes to Detect Mitochondrial ROS by Flow Cytometry and Spectrofluorometry, in: *Methods in Enzymology*. Elsevier, pp. 223–241. <https://doi.org/10.1016/B978-0-12-416618-9.00012-1>
- Childs, B.G., Durik, M., Baker, D.J., van Deursen, J.M., 2015. Cellular senescence in aging and age-related disease: from mechanisms to therapy. *Nat. Med.* 21, 1424–1435. <https://doi.org/10.1038/nm.4000>
- Chou, T.-C., Talalay, P., 1984. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv. Enzyme Regul.* 22, 27–55. [https://doi.org/10.1016/0065-2571\(84\)90007-4](https://doi.org/10.1016/0065-2571(84)90007-4)
- Choudhuri, S., 2014. Chapter 4 - The Beginning of Bioinformatics\*\*The opinions expressed in this chapter are the author's own and they do not necessarily reflect the opinions of the FDA, the DHHS, or the Federal Government., in: Choudhuri, S. (Ed.), *Bioinformatics for Beginners*. Academic Press, Oxford, pp. 73–76. <https://doi.org/10.1016/B978-0-12-410471-6.00004-9>
- d'Adda di Fagagna, F., 2008. Living on a break: cellular senescence as a DNA-damage response. *Nat. Rev. Cancer* 8, 512–522. <https://doi.org/10.1038/nrc2440>
- Da'i, M., Jenie, U.A., Am, S., Kawaichi, M., Meiyanto, E., 2007. T47D cells arrested at G2M and Hyperploidy Formation Induced by a Curcumin's Analogue PGV- 8.
- Da'i, M., Suhendi, A., Meiyanto, E., Jenie, U.A., Kawaichi, M., 2017. APOPTOSIS INDUCTION EFFECT OF CURCUMIN AND ITS ANALOGS PENTAGAMAVUNON-0 AND PENTAGAMAVUNON-1 ON CANCER CELL LINES. *Asian J. Pharm. Clin. Res.* 10, 373. <https://doi.org/10.22159/ajpcr.2017.v10i3.16311>
- Daina, A., Michielin, O., Zoete, V., 2019. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. *Nucleic Acids Res.* 47, W357–W364. <https://doi.org/10.1093/nar/gkz382>
- Damaghi, M., Wojtkowiak, J.W., Gillies, R.J., 2013. pH sensing and regulation in cancer. *Front. Physiol.* 4. <https://doi.org/10.3389/fphys.2013.00370>
- Davalli, P., Mitic, T., Caporali, A., Lauriola, A., D'Arca, D., 2016. ROS, Cell Senescence, and Novel Molecular Mechanisms in Aging and Age-Related

Diseases. Oxid. Med. Cell. Longev. 2016, 1–18.  
<https://doi.org/10.1155/2016/3565127>

Davis, T., van Niekerk, G., Peres, J., Prince, S., Loos, B., Engelbrecht, A.-M., 2018. Doxorubicin resistance in breast cancer: A novel role for the human protein AHNAK. Biochem. Pharmacol. 148, 174–183.  
<https://doi.org/10.1016/j.bcp.2018.01.012>

De Angelis, P.M., Svendsrud, D.H., Kravik, K.L., Stokke, T., 2006. Cellular response to 5-fluorouracil (5-FU) in 5-FU-resistant colon cancer cell lines during treatment and recovery. Mol. Cancer 5, 20. <https://doi.org/10.1186/1476-4598-5-20>

Debacq-Chainiaux, F., Erusalimsky, J.D., Campisi, J., Toussaint, O., 2009. Protocols to detect senescence-associated beta-galactosidase (SA-βgal) activity, a biomarker of senescent cells in culture and in vivo. Nat. Protoc. 4, 1798–1806.  
<https://doi.org/10.1038/nprot.2009.191>

Denard, B., Lee, C., Ye, J., 2012. Doxorubicin blocks proliferation of cancer cells through proteolytic activation of CREB3L1. eLife 1, e00090.  
<https://doi.org/10.7554/eLife.00090>

Du, G., He, S., Zhang, L., Sun, C., Mi, L., Sun, Z., 2018. Hesperidin exhibits in vitro and in vivo antitumor effects in human osteosarcoma MG-63 cells and xenograft mice models via inhibition of cell migration and invasion, cell cycle arrest and induction of mitochondrial-mediated apoptosis. Oncol. Lett.  
<https://doi.org/10.3892/ol.2018.9439>

Du, G.-Y., He, S.-W., Zhang, L., Sun, C.-X., Mi, L.-D., Sun, Z.-G., 2018. Hesperidin exhibits antitumor effects in human osteosarcoma MG-63 cells and xenograft mice models via inhibition of cell migration and invasion, cell cycle arrest and induction of mitochondrial-mediated apoptosis. Oncol. Lett. 16, 6299–6306.  
<https://doi.org/10.3892/ol.2018.9439>

Elmore, S., 2007. Apoptosis: A Review of Programmed Cell Death. Toxicol. Pathol. 35, 495–516. <https://doi.org/10.1080/01926230701320337>

Endah, E., Wulandari, F., Putri, Y.M., Jenie, R.I., Meiyanto, E., 2022. Piperine Increases Pentagamavunone-1 Anti-cancer Activity on 4T1 Breast Cancer through Mitotic Catastrophe Mechanism and Senescence with Sharing Targeting on Mitotic Regulatory Proteins. Iran. J. Pharm. Res. 21, 1–15.  
<https://doi.org/10.22037/ijpr.2021.115723.15488>

Febriansah, R., Dyaningtyas, D.P.P., Sarmoko, Nurulita, N.A., Meiyanto, E., Nugroho, A.E., 2014. Hesperidin as a preventive resistance agent in MCF-7 breast cancer cells line resistance to doxorubicin. Asian Pac. J. Trop. Biomed. 4, 228–233.  
[https://doi.org/10.1016/S2221-1691\(14\)60236-7](https://doi.org/10.1016/S2221-1691(14)60236-7)

Feng, Y., Spezia, M., Huang, S., Yuan, C., Zeng, Z., Zhang, L., Ji, X., Liu, W., Huang, B., Luo, W., Liu, B., Lei, Y., Du, S., Vuppalapati, A., Luu, H.H., Haydon, R.C., He, T.-C., Ren, G., 2018. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes Dis.* 5, 77–106. <https://doi.org/10.1016/j.gendis.2018.05.001>

Ferreira de Oliveira, J.M.P., Santos, C., Fernandes, E., 2020. Therapeutic potential of hesperidin and its aglycone hesperetin: Cell cycle regulation and apoptosis induction in cancer models. *Phytomedicine* 73, 152887. <https://doi.org/10.1016/j.phymed.2019.152887>

Fu, Z., Jiao, Y., Li, Y., Ji, B., Jia, B., Liu, B., 2019. TYMS presents a novel biomarker for diagnosis and prognosis in patients with pancreatic cancer. *Medicine (Baltimore)* 98, e18487. <https://doi.org/10.1097/MD.00000000000018487>

Fujita, K., 2019. p53 Isoforms in Cellular Senescence- and Ageing-Associated Biological and Physiological Functions. *Int. J. Mol. Sci.* 20, 6023. <https://doi.org/10.3390/ijms20236023>

Geng, Y.-Q., Guan, J.-T., Xu, X.-H., Fu, Y.-C., 2010. Senescence-associated beta-galactosidase activity expression in aging hippocampal neurons. *Biochem. Biophys. Res. Commun.* 396, 866–869. <https://doi.org/10.1016/j.bbrc.2010.05.011>

Ghorbani, A., Nazari, M., Jeddi-Tehrani, M., Zand, H., 2012. The citrus flavonoid hesperidin induces p53 and inhibits NF- $\kappa$ B activation in order to trigger apoptosis in NALM-6 cells: involvement of PPAR $\gamma$ -dependent mechanism. *Eur. J. Nutr.* 51, 39–46. <https://doi.org/10.1007/s00394-011-0187-2>

Gil, J., Peters, G., 2006. Regulation of the INK4b–ARF–INK4a tumour suppressor locus: all for one or one for all. *Nat. Rev. Mol. Cell Biol.* 7, 667–677. <https://doi.org/10.1038/nrm1987>

Gilang, Y., Hermawan, A., Fitriasari, A., Jenie, R.I., 2012. Hesperidin Increases Cytotoxic Effect of 5-Fluorouracil on WiDr Cells. *Indones. J. Cancer Chemoprevention* 3, 404. <https://doi.org/10.14499/indonesianjcanchemoprev3iss2pp404-409>

Hadi, I., Jenie, R.I., Meiyanto, E., 2020. Pentagamavunon-0 (PGV-0) Enhance Cytotoxic Effect of Doxorubicin through Increasing of Apoptosis, Senescence and ROS Level on Triple Negative Breast Cancer 4T1. *Indones. J. Cancer Chemoprevention* 11, 7. <https://doi.org/10.14499/indonesianjcanchemoprev11iss1pp7-15>

Hasbiyani, N.A.F., Wulandari, F., Nugroho, E.P., Hermawan, A., Meiyanto, E., 2021. Bioinformatics Analysis Confirms the Target Protein Underlying Mitotic Catastrophe of 4T1 Cells under Combinatorial Treatment of PGV-1 and Galangin. *Sci. Pharm.* 89, 38. <https://doi.org/10.3390/scipharm89030038>

Hassanpour, S.H., Dehghani, M., 2017. Review of cancer from perspective of molecular. J. Cancer Res. Pract. 4, 127–129. <https://doi.org/10.1016/j.jcrpr.2017.07.001>

Heberle, H., Meirelles, G.V., da Silva, F.R., Telles, G.P., Minghim, R., 2015. InteractiVenn: a web-based tool for the analysis of sets through Venn diagrams. BMC Bioinformatics 16, 169. <https://doi.org/10.1186/s12859-015-0611-3>

Hermawan, A., 2011. PGV-0 and PGV-1 Increased Apoptosis Induction of Doxorubicin on MCF-7 Breast Cancer Cells. Pharm. J. Indones. Vol 12.

Hermawan, A., Meiyanto, E., 2010. Hesperidin meningkatkan efek sitotoksik doxorubicin pada sel MCF-7 11.

Hernández, J.L., Padilla, L., Dakhel, S., Coll, T., Hervas, R., Adan, J., Masa, M., Mitjans, F., Martinez, J.M., Coma, S., Rodríguez, L., Noé, V., Ciudad, C.J., Blasco, F., Messeguer, R., 2013. Therapeutic Targeting of Tumor Growth and Angiogenesis with a Novel Anti-S100A4 Monoclonal Antibody. PLoS ONE 8, e72480. <https://doi.org/10.1371/journal.pone.0072480>

Hsu, P.-H., Chen, W.-H., Juan-Lu, C., Hsieh, S.-C., Lin, S.-C., Mai, R.-T., Chen, S.-Y., 2021. Hesperidin and Chlorogenic Acid Synergistically Inhibit the Growth of Breast Cancer Cells via Estrogen Receptor/Mitochondrial Pathway. Life 11, 950. <https://doi.org/10.3390/life11090950>

Ikawati, M., Armandari, I., Khumaira, A., Ertanto, Y., 2020. Effects of Peel Extract from Citrus reticulata and Hesperidin, A Citrus Flavonoid, on Macrophage Cell Line. Indones. J. Pharm. 30, 260. <https://doi.org/10.14499/indonesianjpharm30iss4pp260>

Ikawati, M., Septisetyani, E.P., 2018. Pentagamavunone-0 (PGV-0), a Curcumin Analog, Enhances Cytotoxicity of 5-Fluorouracil and Modulates Cell Cycle in WiDr Colon Cancer Cells. Indones. J. Cancer Chemoprevention 9, 23. <https://doi.org/10.14499/indonesianjcanchemoprev9iss1pp23-31>

Iriondo, O., Mecnas, D., Li, Y., Chin, C.R., Thomas, A., Amzaleg, Y., Ortiz, V., MacKay, M., Dickerson, A., Lee, G., Harotoonian, S., Benayoun, B.A., Smith, A., Mason, C., Roussos Torres, E.T., Yu, M., 2022. Hypoxic memory of tumor intrinsic type I interferon suppression promotes breast cancer metastasis (preprint). Cancer Biology. <https://doi.org/10.1101/2022.05.12.491632>

Itahana, K., Campisi, J., Dimri, G.P., 2007. Methods to Detect Biomarkers of Cellular Senescence, in: Tollefsbol, T.O. (Ed.), Biological Aging, Methods in Molecular Biology. Humana Press, Totowa, NJ, pp. 21–31. [https://doi.org/10.1007/978-1-59745-361-5\\_3](https://doi.org/10.1007/978-1-59745-361-5_3)

Izadi, S., Nikkhoo, A., Hojjat-Farsangi, M., Namdar, A., Azizi, G., Mohammadi, H., Yousefi, M., Jadidi-Niaragh, F., 2020. CDK1 in Breast Cancer: Implications for



Theranostic Potential. *Former. Curr. Med. Chem. - Anti-Cancer Agents* 20, 758–767. <https://doi.org/10.2174/1871520620666200203125712>

Jain, M., Zhang, L., He, M., Zhang, Y.-Q., Shen, M., Kebebew, E., 2013. TOP2A is overexpressed and is a therapeutic target for adrenocortical carcinoma. *Endocr. Relat. Cancer* 20, 361–370. <https://doi.org/10.1530/ERC-12-0403>

Junedi, S., Hermawan, A., Setiawati, A., Fitriyasari, A., Susidarti, R.A., Meiyanto, E., 2021. The Doxorubicin-Induced G2/M Arrest in Breast Cancer Cells Modulated by Natural Compounds Naringenin and Hesperidin 7.

Kaminska, K., Akrap, N., Staaf, J., Alves, C.L., Ehinger, A., Ebbesson, A., Hedenfalk, I., Beumers, L., Veerla, S., Harbst, K., Ehmsen, S., Borgquist, S., Borg, Å., Pérez-Fidalgo, A., Ditzel, H.J., Bosch, A., Honeth, G., 2021. Distinct mechanisms of resistance to fulvestrant treatment dictate level of ER independence and selective response to CDK inhibitors in metastatic breast cancer. *Breast Cancer Res.* 23, 26. <https://doi.org/10.1186/s13058-021-01402-1>

Kang, J., Sergio, C.M., Sutherland, R.L., Musgrove, E.A., 2014. Targeting cyclin-dependent kinase 1 (CDK1) but not CDK4/6 or CDK2 is selectively lethal to MYC-dependent human breast cancer cells. *BMC Cancer* 14, 32. <https://doi.org/10.1186/1471-2407-14-32>

Khamis, A.A.A., Ali, E.M.M., El-Moneim, M.A.A., Abd-Alhaseeb, M.M., El-Magd, M.A., Salim, E.I., 2018. Hesperidin, piperine and bee venom synergistically potentiate the anticancer effect of tamoxifen against breast cancer cells. *Biomed. Pharmacother.* 105, 1335–1343. <https://doi.org/10.1016/j.biopha.2018.06.105>

Kim, G.D., 2015. Hesperidin Inhibits Vascular Formation by Blocking the AKT/mTOR Signaling Pathways. *Prev. Nutr. Food Sci.* 20, 221–229. <https://doi.org/10.3746/pnf.2015.20.4.221>

Kongtawelert, P., Wudtiwai, B., Shwe, T.H., Pothacharoen, P., Phitak, T., 2020. Inhibitory Effect of Hesperidin on the Expression of Programmed Death Ligand (PD-L1) in Breast Cancer. *Molecules* 25, 252. <https://doi.org/10.3390/molecules25020252>

Kopecka, J., Campia, I., Jacobs, A., Frei, A.P., Ghigo, D., Wollscheid, B., Riganti, C., 2015. Carbonic anhydrase XII is a new therapeutic target to overcome chemoresistance in cancer cells. *Oncotarget* 6, 6776–6793. <https://doi.org/10.18632/oncotarget.2882>

Korah, R., Boots, M., Wieder, R., 2004. Integrin  $\alpha_5\beta_1$  Promotes Survival of Growth-Arrested Breast Cancer Cells: An in Vitro Paradigm for Breast Cancer Dormancy in Bone Marrow 9.

Kumar, B., Koul, S., Khandrika, L., Meacham, R.B., Koul, H.K., 2008. Oxidative Stress Is Inherent in Prostate Cancer Cells and Is Required for Aggressive

Phenotype. *Cancer Res.* 68, 1777–1785. <https://doi.org/10.1158/0008-5472.CAN-07-5259>

Kurz, D.J., Decary, S., Hong, Y., Erusalimsky, J.D., 2000. Senescence-associated  $\beta$ -galactosidase reflects an increase in lysosomal mass during replicative ageing of human endothelial cells 10.

Kusharyanti, I., Larasati, L., Susidarti, R.A., Meiyanto, E., 2011. Hesperidin Increase Cytotoxic Activity of Doxorubicin on Hela Cell Line Through Cell Cycle Modulation and Apoptosis Induction. *Indones. J. Cancer Chemoprevention* 2, 267. <https://doi.org/10.14499/indonesianjcanchemoprev2iss2pp267-273>

Leal-Esteban, L.C., Fajas, L., 2020. Cell cycle regulators in cancer cell metabolism. *Biochim. Biophys. Acta BBA - Mol. Basis Dis.* 1866, 165715. <https://doi.org/10.1016/j.bbadis.2020.165715>

Lee, J.-A., Lee, M.-Y., Seo, C.-S., Jung, D.Y., Lee, N.-H., Kim, J.-H., Ha, H., Shin, H.K., 2010. Anti-asthmatic effects of an *Amomum compactum* extract on an ovalbumin (OVA)-induced murine asthma model. *Biosci. Biotechnol. Biochem.* 74, 1814–1818. <https://doi.org/10.1271/bbb.100177>

Lee, K.-A., Lee, S.-H., Lee, Y.-J., Baeg, S.-M., Shim, J.-H., 2012. Hesperidin Induces Apoptosis by Inhibiting Sp1 and Its Regulatory Protein in MSTO-211H Cells. *Biomol. Ther.* 20, 273–279. <https://doi.org/10.4062/biomolther.2012.20.3.273>

Lestari, B., Nakamae, I., Yoneda-Kato, N., Morimoto, T., Kanaya, S., Yokoyama, T., Shionyu, M., Shirai, T., Meiyanto, E., Kato, J., 2019a. Pentagamavunon-1 (PGV-1) inhibits ROS metabolic enzymes and suppresses tumor cell growth by inducing M phase (prometaphase) arrest and cell senescence. *Sci. Rep.* 9, 14867. <https://doi.org/10.1038/s41598-019-51244-3>

Li, Y., Lei, B., Zou, J., Wang, W., Chen, A., Zhang, J., Fu, Y., Li, Z., 2019. High expression of carbonic anhydrase 12 (CA12) is associated with good prognosis in breast cancer. *Neoplasma* 66, 420–426. [https://doi.org/10.4149/neo\\_2018\\_180819N624](https://doi.org/10.4149/neo_2018_180819N624)

Lim, S., Kaldis, P., 2013. Cdks, cyclins and CKIs: roles beyond cell cycle regulation. *Development* 140, 3079–3093. <https://doi.org/10.1242/dev.091744>

Liou, G.-Y., Storz, P., 2010. Reactive oxygen species in cancer. *Free Radic. Res.* 44, 479–496. <https://doi.org/10.3109/10715761003667554>

Liu, T., Zhang, H., Yi, S., Gu, L., Zhou, M., 2019. Mutual regulation of MDM4 and TOP2A in cancer cell proliferation. *Mol. Oncol.* 13, 1047–1058. <https://doi.org/10.1002/1878-0261.12457>

Liu, X., Zhou, H., Cai, L., Zhang, W., Ma, J., Tao, X., Yu, J., 2014. NADPH oxidase-dependent formation of reactive oxygen species contributes to



transforming growth factor  $\beta$ 1-induced epithelial-mesenchymal transition in rat peritoneal mesothelial cells, and the role of astragalus intervention. *Chin. J. Integr. Med.* 20, 667–674. <https://doi.org/10.1007/s11655-012-1176-x>

Lobert, S., Correia, J.J., 2000. Energetics of vinca alkaloid interactions with tubulin, in: *Methods in Enzymology*. Elsevier, pp. 77–103. [https://doi.org/10.1016/S0076-6879\(00\)23362-4](https://doi.org/10.1016/S0076-6879(00)23362-4)

Malumbres, M., Barbacid, M., 2001. To cycle or not to cycle: a critical decision in cancer. *Nat. Rev. Cancer* 1, 222–231. <https://doi.org/10.1038/35106065>

Martins, C.P., Brown-Swigart, L., Evan, G.I., 2006. Modeling the Therapeutic Efficacy of p53 Restoration in Tumors. *Cell* 127, 1323–1334. <https://doi.org/10.1016/j.cell.2006.12.007>

Meiyanto, E., Hermawan, A., Anindyajati, A., 2012. Natural Products for Cancer-Targeted Therapy: Citrus Flavonoids as Potent Chemopreventive Agents. *Asian Pac. J. Cancer Prev.* 13, 427–436. <https://doi.org/10.7314/APJCP.2012.13.2.427>

Meiyanto, E., Husnaa, U., Kastian, R.F., Putri, H., Larasati, Y.A., Khumaira, A., Pamungkas, D.D.P., Jenie, R.I., Kawaichi, M., Lestari, B., Yokoyama, T., Kato, J., 2020. The Target Differences of Anti-Tumorigenesis Potential of Curcumin and its Analogues Against HER-2 Positive and Triple-Negative Breast Cancer Cells. *Adv. Pharm. Bull.* 11, 188–196. <https://doi.org/10.34172/apb.2021.020>

Meiyanto, E., Larasati, Y.A., 2019. The Chemopreventive Activity of Indonesia Medicinal Plants Targeting on Hallmarks of Cancer. *Adv. Pharm. Bull.* 9, 219–230. <https://doi.org/10.15171/apb.2019.025>

Meiyanto, E., Melannisa, R., Da'i, M., 2006. PGV-1 menurunkan ekspresi faktor angiogenesis (VEGF dan COX-2) pada sel T47D terinduksi estrogen 6.

Meiyanto, E., Nugraheni, N., Ahlina, F.N., Salsabila, I.A., Haryanti, S., 2021. Anti-senescence Activity of Indonesian Black Pepper Essential Oil (*Piper nigrum* L.) on ovarian CHO-K1 and fibroblast NIH-3T3 Cells:(TJPS-2020-0224.R1). *Thai J. Pharm. Sci. TJPS* 45.

Meiyanto, E., Putri, D.D.P., Susidarti, R.A., Murwanti, R., Sardjiman, S., Fitriasisari, A., Husnaa, U., Purnomo, H., Kawaichi, M., 2014. Curcumin and its Analogues (PGV-0 and PGV-1) Enhance Sensitivity of Resistant MCF-7 Cells to Doxorubicin through Inhibition of HER2 and NF- $\kappa$ B Activation. *Asian Pac. J. Cancer Prev.* 15, 179–184. <https://doi.org/10.7314/APJCP.2014.15.1.179>

Meiyanto, E., Putri, H., Arum Larasati, Y., Yudi Utomo, R., Istighfari Jenie, R., Ikawati, M., Lestari, B., Yoneda-Kato, N., Nakamae, I., Kawaichi, M., Kato, J.-Y., 2019a. Anti-proliferative and Anti-metastatic Potential of Curcumin Analogue, Pentagamavunon-1 (PGV-1), Toward Highly Metastatic Breast Cancer Cells in

Correlation with ROS Generation. *Adv. Pharm. Bull.* 9, 445–452.  
<https://doi.org/10.15171/apb.2019.053>

Meiyanto, E., Septisetyani, E.P., Larasati, Y.A., Kawaichi, M., 2018a. Curcumin Analog Pentagamavunon-1 (PGV-1) Sensitizes Widr Cells to 5-Fluorouracil through Inhibition of NF- $\kappa$ B Activation. *Asian Pac. J. Cancer Prev. APJCP* 19, 49–56. <https://doi.org/10.22034/APJCP.2018.19.1.49>

Meneguzzo, F., Ciriminna, R., Zabini, F., Pagliaro, M., 2020. Review of Evidence Available on Hesperidin-Rich Products as Potential Tools against COVID-19 and Hydrodynamic Cavitation-Based Extraction as a Method of Increasing Their Production. *Processes* 8, 549. <https://doi.org/10.3390/pr8050549>

Menon, V., Ghaffari, S., 2018. Transcription factors FOXO in the regulation of homeostatic hematopoiesis: *Curr. Opin. Hematol.* 25, 290–298. <https://doi.org/10.1097/MOH.0000000000000441>

Moreira, H., Szyjka, A., Paliszkievicz, K., Barg, E., 2019. Prooxidative Activity of Celastrol Induces Apoptosis, DNA Damage, and Cell Cycle Arrest in Drug-Resistant Human Colon Cancer Cells. *Oxid. Med. Cell. Longev.* 2019, 1–12. <https://doi.org/10.1155/2019/6793957>

Mori, J., Kawabata, A., Tang, H., Tadagaki, K., Mizuguchi, H., Kuroda, K., Mori, Y., 2015. Human Herpesvirus-6 U14 Induces Cell-Cycle Arrest in G2/M Phase by Associating with a Cellular Protein, EDD. *PLOS ONE* 10, e0137420. <https://doi.org/10.1371/journal.pone.0137420>

Mori, K., Uchida, T., Yoshie, T., Mizote, Y., Ishikawa, F., Katsuyama, M., Shibamura, M., 2019. A mitochondrial ROS pathway controls matrix metalloproteinase 9 levels and invasive properties in RAS -activated cancer cells. *FEBS J.* 286, 459–478. <https://doi.org/10.1111/febs.14671>

Mumcuoglu, M., Bagislar, S., Yuzugullu, H., Alotaibi, H., Senturk, S., Telkoparan, P., Gur-Dedeoglu, B., Cingoz Insal, B., Bozkurt, B., Tazebay, U., Yulug, I., Akcali, K., Ozturk, M., 2010. The Ability to Generate Senescent Progeny as a Mechanism Underlying Breast Cancer Cell Heterogeneity. *PloS One* 5, e11288. <https://doi.org/10.1371/journal.pone.0011288>

Murphy, M.P., 2009. How mitochondria produce reactive oxygen species. *Biochem. J.* 417, 1–13. <https://doi.org/10.1042/BJ20081386>

Musyayyadah, H., Wulandari, F., Nangimi, A.F., Anggraeni, A., Ikawati, M., Meiyanto, E., 2021. The Growth Suppression Activity of Diosmin and PGV-1 Co-Treatment on 4T1 Breast Cancer Targets Mitotic Regulatory Proteins. *Asian Pac. J. Cancer Prev.* 22, 2929–2938. <https://doi.org/10.31557/APJCP.2021.22.9.2929>

Nielsen, C.F., Zhang, T., Barisic, M., Kalitsis, P., Hudson, D.F., 2020. Topoisomerase II $\alpha$  is essential for maintenance of mitotic chromosome structure.

Proc. Natl. Acad. Sci. 117, 12131–12142.  
<https://doi.org/10.1073/pnas.2001760117>

Palit, S., Kar, S., Sharma, G., Das, P.K., 2015. Hesperetin Induces Apoptosis in Breast Carcinoma by Triggering Accumulation of ROS and Activation of ASK1/JNK Pathway: BREAST CANCER CELL APOPTOSIS BY HESPERETIN. *J. Cell. Physiol.* 230, 1729–1739. <https://doi.org/10.1002/jcp.24818>

Pandey, P., Sayyed, U., Tiwari, R.K., Siddiqui, M.H., Pathak, N., Bajpai, P., 2019. Hesperidin Induces ROS-Mediated Apoptosis along with Cell Cycle Arrest at G2/M Phase in Human Gall Bladder Carcinoma. *Nutr. Cancer* 71, 676–687. <https://doi.org/10.1080/01635581.2018.1508732>

Panvichian, R., Tantiwettrueangdet, A., Angkathunyakul, N., Leelaudomlapi, S., 2015. TOP2A Amplification and Overexpression in Hepatocellular Carcinoma Tissues. *BioMed Res. Int.* 2015, 1–8. <https://doi.org/10.1155/2015/381602>

Paterni, I., Granchi, C., Katzenellenbogen, J.A., Minutolo, F., 2014. Estrogen receptors alpha (ER $\alpha$ ) and beta (ER $\beta$ ): Subtype-selective ligands and clinical potential. *Steroids* 90, 13–29. <https://doi.org/10.1016/j.steroids.2014.06.012>

Patterson, J.C., Joughin, B.A., van de Kooij, B., Lim, D.C., Lauffenburger, D.A., Yaffe, M.B., 2019. ROS and Oxidative Stress Are Elevated in Mitosis during Asynchronous Cell Cycle Progression and Are Exacerbated by Mitotic Arrest. *Cell Syst.* 8, 163–167.e2. <https://doi.org/10.1016/j.cels.2019.01.005>

Pei, Y., Li, G., Ran, J., Wei, F., 2017. Kinesin family member 11 contributes to the progression and prognosis of human breast cancer. *Oncol. Lett.* <https://doi.org/10.3892/ol.2017.7053>

Provan, K.G., Leischow, S.J., Keagy, J., Nodora, J., 2010. Research collaboration in the discovery, development, and delivery networks of a statewide cancer coalition. *Eval. Program Plann.* 33, 349–355. <https://doi.org/10.1016/j.evalproplan.2009.12.005>

Reynisd, I., 1995. Kip/Cip and Ink4 Cdk inhibitors cooperate to induce cell cycle arrest in response to TGF- $\beta$  16.

Saiprasad, G., Chitra, P., Manikandan, R., Sudhandiran, G., 2014. Hesperidin induces apoptosis and triggers autophagic markers through inhibition of Aurora-A mediated phosphoinositide-3-kinase/Akt/mammalian target of rapamycin and glycogen synthase kinase-3 beta signalling cascades in experimental colon carcinogenesis. *Eur. J. Cancer* 50, 2489–2507. <https://doi.org/10.1016/j.ejca.2014.06.013>

Schuler, M., Green, D.R., 2001. Mechanisms of p53-dependent apoptosis 5.

Septisetyani, E.P., Ikawati, M., Widaryanti, B., 2008. Apoptosis Mediated Cytotoxicity of Curcumin Analogues PGV-0 and PGV-1 in WiDr Cell Line 9.

- Septisetyani, E.P., Meiyanto, E., Kawaichi, M., Ikawati, M., 2010. PGV-1 Inhibits G2M Phase Progression in WiDr Colon Cancer Cells.
- Shah, M.A., Schwartz, G.K., 2001. Cell Cycle-mediated Drug Resistance: An Emerging Concept in Cancer Therapy 14.
- Sharma, K., Iyer, A., Sengupta, K., Chakrapani, H., 2013. INDQ/NO, a Bioeductively Activated Nitric Oxide Prodrug. *Org. Lett.* 15, 2636–2639. <https://doi.org/10.1021/ol400884v>
- Sikora, E., Arendt, T., Bennett, M., Narita, M., 2011. Impact of cellular senescence signature on ageing research. *Cell Motil. Ageing* 10, 146–152. <https://doi.org/10.1016/j.arr.2010.10.002>
- Silagi, E.S., Schipani, E., M. Shapiro, I., V. Risbud, M., 2021. The role of HIF proteins in maintaining the metabolic health of the intervertebral disc 14.
- Spoerri, L., Oo, Z.Y., Larsen, J.E., Haass, N.K., Gabrielli, B., Pavey, S., 2015. Cell Cycle Checkpoint and DNA Damage Response Defects as Anticancer Targets: From Molecular Mechanisms to Therapeutic Opportunities, in: Wondrak, G.T. (Ed.), *Stress Response Pathways in Cancer*. Springer Netherlands, Dordrecht, pp. 29–49. [https://doi.org/10.1007/978-94-017-9421-3\\_3](https://doi.org/10.1007/978-94-017-9421-3_3)
- Strober, W., 2015. Trypan Blue Exclusion Test of Cell Viability. *Curr. Protoc. Immunol.* 111. <https://doi.org/10.1002/0471142735.ima03bs111>
- Sugrue, M.M., Shin, D.Y., Lee, S.W., Aaronson, S.A., 1997. Wild-type p53 triggers a rapid senescence program in human tumor cells lacking functional p53. *Proc. Natl. Acad. Sci.* 94, 9648–9653. <https://doi.org/10.1073/pnas.94.18.9648>
- Sun, Y., Zhao, C., Ye, Y., Wang, Z., He, Y., Li, Y., Mao, H., 2019. High expression of fibronectin 1 indicates poor prognosis in gastric cancer. *Oncol. Lett.* <https://doi.org/10.3892/ol.2019.11088>
- Swift, L.P., Rephaeli, A., Nudelman, A., Phillips, D.R., Cutts, S.M., 2006. Doxorubicin-DNA Adducts Induce a Non-Topoisomerase II-Mediated Form of Cell Death. *Cancer Res.* 66, 4863–4871. <https://doi.org/10.1158/0008-5472.CAN-05-3410>
- Szkarczyk, D., Gable, A.L., Nastou, K.C., Lyon, D., Kirsch, R., Pyysalo, S., Doncheva, N.T., Legeay, M., Fang, T., Bork, P., Jensen, L.J., von Mering, C., 2021. The STRING database in 2021: customizable protein–protein networks, and functional characterization of user-uploaded gene/measurement sets. *Nucleic Acids Res.* 49, D605–D612. <https://doi.org/10.1093/nar/gkaa1074>
- Sznarkowska, A., Kostecka, A., Meller, K., Bielawski, K.P., 2017. Inhibition of cancer antioxidant defense by natural compounds. *Oncotarget* 8, 15996–16016. <https://doi.org/10.18632/oncotarget.13723>

T-47D | ATCC [WWW Document], 2022. URL <https://www.atcc.org/products/htb-133> (accessed 6.24.22).

Tacar, O., Sriamornsak, P., Dass, C.R., 2012. Doxorubicin: an update on anticancer molecular action, toxicity and novel drug delivery systems. *J. Pharm. Pharmacol.* 65, 157–170. <https://doi.org/10.1111/j.2042-7158.2012.01567.x>

Terranova, R., Agherbi, H., Boned, A., Meresse, S., Djabali, M., 2006. Histone and DNA methylation defects at Hox genes in mice expressing a SET domain-truncated form of Mll. *Proc. Natl. Acad. Sci.* 103, 6629–6634. <https://doi.org/10.1073/pnas.0507425103>

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

Trachootham, D., Lu, W., Ogasawara, M.A., Valle, N.R.-D., Huang, P., 2008. Redox Regulation of Cell Survival. *Antioxid. Redox Signal.* 10, 1343–1374. <https://doi.org/10.1089/ars.2007.1957>

Tsakamoto, M., Kuroda, K., Ramamoorthy, A., Yasuhara, K., 2014. Modulation of raft domains in a lipid bilayer by boundary-active curcumin. *Chem. Commun.* 50, 3427. <https://doi.org/10.1039/c3cc47738j>

Utomo, R.Y., Wulandari, F., Novitasari, D., Lestari, B., Susidarti, R.A., Jenie, R.I., Kato, J., Sardjiman, S., Meiyanto, E., 2022. Preparation and Cytotoxic Evaluation of PGV-1 Derivative, CCA-1.1, as a New Curcumin Analog with Improved-Physicochemical and Pharmacological Properties. *Adv Pharm Bull* 12, 603–612. <https://doi.org/10.34172/apb.2022.063>

Venere, M., Horbinski, C., Crish, J.F., Jin, X., Vasanji, A., Major, J., Burrows, A.C., Chang, C., Prokop, J., Wu, Q., Sims, P.A., Canoll, P., Summers, M.K., Rosenfeld, S.S., Rich, J.N., 2015. The mitotic kinesin KIF11 is a driver of invasion, proliferation, and self-renewal in glioblastoma. *Sci. Transl. Med.* 7. <https://doi.org/10.1126/scitranslmed.aac6762>

Wang, B., Shen, Y., Zou, Y., Qi, Z., Huang, G., Xia, S., Gao, R., Li, F., Huang, Z., 2020. TOP2A Promotes Cell Migration, Invasion and Epithelial–Mesenchymal Transition in Cervical Cancer via Activating the PI3K/AKT Signaling. *Cancer Manag. Res.* Volume 12, 3807–3814. <https://doi.org/10.2147/CMAR.S240577>

Wang, Q., Su, L., Liu, N., Zhang, L., Xu, W., Fang, H., 2011. Cyclin Dependent Kinase 1 Inhibitors: A Review of Recent Progress. *Curr. Med. Chem.* 18, 2025–2043. <https://doi.org/10.2174/092986711795590110>

Wang, W., Nag, S.A., Zhang, R., 2015. Targeting the NFκB signaling pathways for breast cancer prevention and therapy. *Curr. Med. Chem.* 22, 264–289. <https://doi.org/10.2174/0929867321666141106124315>



Weinberg, R.A., 2007. Is metastasis predetermined? *Mol. Oncol.* 1, 263–264. <https://doi.org/10.1016/j.molonc.2007.07.001>

Whitcomb, S.J., Basu, A., Allis, C.D., Bernstein, E., 2007. Polycomb Group proteins: an evolutionary perspective. *Trends Genet.* 23, 494–502. <https://doi.org/10.1016/j.tig.2007.08.006>

Wooller, S.K., Benstead-Hume, G., Chen, X., Ali, Y., Pearl, F.M.G., 2017. Bioinformatics in translational drug discovery. *Biosci. Rep.* 37, BSR20160180. <https://doi.org/10.1042/BSR20160180>

Wu, D., Zhang, J., Wang, J., Li, J., Liao, F., Dong, W., 2016. Hesperetin induces apoptosis of esophageal cancer cells via mitochondrial pathway mediated by the increased intracellular reactive oxygen species. *Tumor Biol.* 37, 3451–3459. <https://doi.org/10.1007/s13277-015-4176-6>

Wulandari, F., Ikawati, M., Kirihaata, M., Kato, J.-Y., Meiyanto, E., 2021. A new curcumin analog, CCA-1.1, induces cell death and cell cycle arrest in WiDr colon cancer cells via ROS generation. *J. Appl. Pharm. Sci.* <https://doi.org/10.7324/JAPS.2021.1101014>

Xia, R., Sheng, X., Xu, X., Yu, C., Lu, H., 2017. Hesperidin induces apoptosis and G0/G1 arrest in human non-small cell lung cancer A549 cells. *Int. J. Mol. Med.* <https://doi.org/10.3892/ijmm.2017.3250>

Xia, R., Xu, G., Huang, Y., Sheng, X., Xu, X., Lu, H., 2018. Hesperidin suppresses the migration and invasion of non-small cell lung cancer cells by inhibiting the SDF-1/CXCR-4 pathway. *Life Sci.* 201, 111–120. <https://doi.org/10.1016/j.lfs.2018.03.046>

Yao, H., He, G., Yan, S., Chen, C., Song, L., Rosol, T.J., Deng, X., 2017. Triple-negative breast cancer: is there a treatment on the horizon? *Oncotarget* 8, 1913–1924. <https://doi.org/10.18632/oncotarget.12284>

Yap, K.M., Sekar, M., Wu, Y.S., Gan, S.H., Rani, N.N.I.M., Seow, L.J., Subramaniyan, V., Fuloria, N.K., Fuloria, S., Lum, P.T., 2021. Hesperidin and its aglycone hesperetin in breast cancer therapy: A review of recent developments and future prospects. *Saudi J. Biol. Sci.* 28, 6730–6747. <https://doi.org/10.1016/j.sjbs.2021.07.046>

Ye, M., He, Z., Dai, W., Li, Z., Chen, X., Liu, J., 2018. A TOP2A-derived cancer panel drives cancer progression in papillary renal cell carcinoma. *Oncol. Lett.* <https://doi.org/10.3892/ol.2018.9179>

Yeh, M.-H., Kao, S.-T., Hung, C.-M., Liu, C.-J., Lee, K.-H., Yeh, C.-C., 2009. Hesperidin inhibited acetaldehyde-induced matrix metalloproteinase-9 gene expression in human hepatocellular carcinoma cells. *Toxicol. Lett.* 184, 204–210. <https://doi.org/10.1016/j.toxlet.2008.11.018>



Yersal, O., 2014. Biological subtypes of breast cancer: Prognostic and therapeutic implications. *World J. Clin. Oncol.* 5, 412. <https://doi.org/10.5306/wjco.v5.i3.412>

Zhang, J., Wu, D., Vikash, Song, J., Wang, J., Yi, J., Dong, W., 2015. Hesperetin Induces the Apoptosis of Gastric Cancer Cells via Activating Mitochondrial Pathway by Increasing Reactive Oxygen Species. *Dig. Dis. Sci.* 60, 2985–2995. <https://doi.org/10.1007/s10620-015-3696-7>

Zhao, J., Li, Y., Gao, J., De, Y., 2017. Hesperidin inhibits ovarian cancer cell viability through endoplasmic reticulum stress signaling pathways. *Oncol. Lett.* <https://doi.org/10.3892/ol.2017.6873>

Zhou, T., Wang, Y., Qian, D., Liang, Q., Wang, B., 2018. Over-expression of TOP2A as a prognostic biomarker in patients with glioma 10.

Zitka, O., Skalickova, S., Gumulec, J., Masarik, M., Adam, V., Hubalek, J., Trnkova, L., Kruseova, J., Eckschlager, T., Kizek, R., 2012. Redox status expressed as GSH:GSSG ratio as a marker for oxidative stress in paediatric tumour patients. *Oncol. Lett.* 4, 1247–1253. <https://doi.org/10.3892/ol.2012.931>