

**PENGARUH EKSTRAK JAHE MERAH TERHADAP SEL *SENESCENCE*
SERTA EKSPRESI GEN *P53* DAN *BCL-2* PADA LINI SEL MCF-7**

SKRIPSI

diajukan untuk Memenuhi Sebagian dari Syarat untuk Memperoleh Gelar Sarjana
Sains Program Studi Biologi



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UNIVERSITAS PENDIDIKAN INDONESIA
BANDUNG
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Skripsi yang diajukan untuk memenuhi sebagian dari syarat memperoleh gelar Sarjana Sains Program Studi Biologi pada Fakultas Pendidikan Matematika dan Ilmu Pengetahuan Alam

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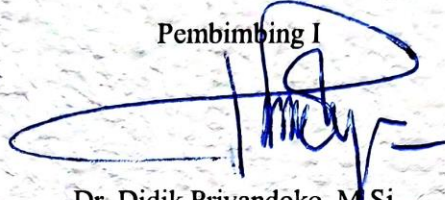
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**PENGARUH EKSTRAK JAHE MERAH TERHADAP SEL *SENESCENCE*
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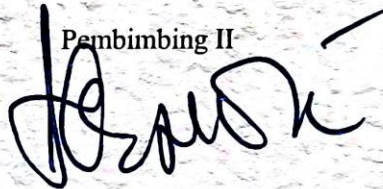
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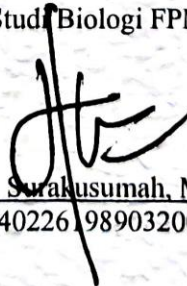
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Dengan ini saya menyatakan bahwa skripsi dengan judul **Pengaruh Ekstrak Jahe Merah Terhadap Sel *Senescence* serta Ekspresi Gen *p53* dan *Bcl-2* pada Lini Sel MCF-7** dan semua isinya benar-benar karya saya sendiri. Saya menyatakan bahwa tidak ada bagian dari skripsi ini yang merupakan hasil plagiasi atau mengambil karya orang lain tanpa memberikan penghargaan yang sesuai. Apabila di kemudian hari terbukti bahwa terdapat pelanggaran terhadap ketentuan akademik terkait orisinalitas karya ilmiah, saya bersedia menerima sanksi yang berlaku sesuai dengan peraturan dan kebijakan yang ditetapkan oleh universitas. Demikian pernyataan ini saya buat dengan sebenar-benarnya tanpa ada paksaan dari pihak manapun.

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Yang membuat pernyataan,

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Penelitian ini dapat diselesaikan dengan baik berkat bimbingan, dukungan, dan bantuan dari berbagai pihak. Penulis menyadari bahwa skripsi ini masih jauh dari sempurna. Oleh karena itu, penulis mengharapkan saran dan kritik yang membangun demi perbaikan di masa mendatang. Semoga skripsi ini dapat memberikan manfaat bagi penulis, pembaca, dan pengembangan ilmu pengetahuan, khususnya dalam bidang penelitian kanker dan terapi alternatif.

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PENGARUH EKSTRAK JAHE MERAH TERHADAP SEL *SENESCENCE* SERTA EKSPRESI GEN *P53* DAN *BCL-2* PADA LINI SEL MCF-7

ABSTRAK

Kanker payudara adalah jenis kanker yang berkembang di jaringan payudara dan penyebab kematian akibat kanker paling tinggi kelima di seluruh dunia. Perkembangan kanker payudara sangat dipengaruhi oleh aktivasi jalur molekuler seperti gen *p53* dan *Bcl-2*. Pengobatan kanker secara konvensional dapat menyebabkan efek samping bagi penderita. Senyawa 6-gingerol dan 6-shogaol yang terkandung pada jahe merah (*Zingiber officinale* Roscoe var. *rubrum*) berpotensi sebagai antikanker. Penelitian ini bertujuan untuk mengetahui pengaruh ekstrak jahe merah (EJM) terhadap sel *senescence* serta ekspresi gen *p53* dan *Bcl-2* pada lini sel kanker payudara (MCF-7). Penelitian ini dilakukan dengan menginduksi EJM pada lini sel kanker payudara (MCF-7). Pewarnaan β -galactosidase digunakan untuk mengamati dan menghitung lini sel kanker payudara (MCF-7) yang mengalami *senescence*, dengan konsentrasi EJM 100 $\mu\text{g/mL}$; 50 $\mu\text{g/mL}$; 25 $\mu\text{g/mL}$. Ekspresi gen *p53* dan *Bcl-2* ditentukan menggunakan qRT-PCR, dengan konsentrasi EJM 175 $\mu\text{g/mL}$; 350 $\mu\text{g/mL}$; 700 $\mu\text{g/mL}$. Data ekspresi gen dianalisis secara statistik menggunakan uji *ANOVA* dan uji *Post Hoc Tukey*, sedangkan data hubungan antara ekspresi gen *p53* dan *Bcl-2* dengan *senescence* pada sel MCF-7 menggunakan uji *Pearson Correlation*. EJM dapat menginduksi *senescence* pada sel MCF-7. EJM meningkatkan ekspresi gen *p53* serta menurunkan ekspresi gen *Bcl-2* pada lini sel kanker payudara (MCF-7). Terdapat hubungan ekspresi gen *p53* dan *Bcl-2* dengan penuaan dini pada lini sel kanker payudara (MCF-7). Ekstrak jahe merah terbukti berpotensi sebagai agen antikanker.

Kata Kunci: *Bcl-2*, Jahe Merah, Kanker Payudara, *p53*, *Senescence*

**THE EFFECT OF RED GINGER EXTRACT ON SENESCENCE CELLS
AND P53 AND BCL-2 GENE EXPRESSION IN MCF-7 CELL LINE**

ABSTRACT

*Breast cancer is a type of cancer that develops in breast tissue and is the fifth highest cause of cancer death worldwide. The development of breast cancer is strongly influenced by the activation of molecular pathways such as the p53 and Bcl-2 genes. Conventional cancer treatment can cause side effects for sufferers. The compounds 6-gingerol and 6-shogaol contained in red ginger (*Zingiber officinale* Roscoe Var. *rubrum*) have potential anticancer properties. This study aims to determine the effect of red ginger extract (EJM) on cell senescence and p53 and Bcl-2 gene expression in breast cancer cell lines (MCF-7). This research was carried out by inducing EJM in a breast cancer cell line (MCF-7). β -galactosidase staining was used to observe and quantify the breast cancer cell line (MCF-7) undergoing senescence, with an EJM concentration of 100 $\mu\text{g}/\text{mL}$; 50 $\mu\text{g}/\text{mL}$; 25 $\mu\text{g}/\text{mL}$. The expression of p53 and Bcl-2 genes was determined using qRT-PCR, with an EJM concentration of 175 $\mu\text{g}/\text{mL}$; 350 $\mu\text{g}/\text{mL}$; 700 $\mu\text{g}/\text{mL}$. Gene expression data was analyzed statistically using the ANOVA test and Tukey's Post Hoc test, while data on the relationship between p53 and Bcl-2 gene expression and senescence in MCF-7 cells used the Pearson Correlation test. EJM can induce senescence in MCF-7 cells. EJM increased p53 gene expression as well as decreased Bcl-2 gene expression in breast cancer cell lines (MCF-7). There is a relationship between p53 and Bcl-2 gene expression with premature aging in breast cancer cell lines (MCF-7). Red ginger extract has been proven to have potential as an anticancer agent.*

Keywords: *Bcl-2, Breast Cancer, p53, Red Ginger, Senescence*

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DAFTAR PUSTAKA

- Aggarwal, B. B., & Shishodia, S. (2006). Molecular Targets of Dietary Agents for Prevention and Therapy of Cancer. *Biochemical pharmacology*, *71*(10), 1397-1421. doi: <https://doi.org/10.1016/j.bcp.2006.02.009>
- Akimoto, M., Iizuka, M., Kanematsu, R., Yoshida, M., & Takenaga, K. (2015). Anticancer Effect of Ginger Extract Against Pancreatic Cancer Cells Mainly Through Reactive Oxygen Species-Mediated Autotic Cell Death. *PloS one*, *10*(5), 1-22. doi: [10.1371/journal.pone.0126605](https://doi.org/10.1371/journal.pone.0126605)
- Ali, M., Wani, S. U. D., Salahuddin, M., Manjula, S. N., Mruthunjaya, K., Dey, T., Zargar, M. I., & Singh, J. (2023). Recent advance of herbal medicines in cancer-a molecular approach. *Heliyon*, *9*(2), 1-23. doi: <https://doi.org/10.1016/j.heliyon.2023.e13684>
- Alsner, J., Yilmaz, M., Guldborg, P., Hansen, L. L., & Overgaard, J. (2000). Heterogeneity in the Clinical Phenotype of TP53 Mutations in Breast Cancer Patients. *Breast Cancer Research*, *2*, 1-1. doi: [10.1186/bcr109](https://doi.org/10.1186/bcr109)
- Amjad, M. T., Chidharla, A., & Kasi, A. (2023). *Cancer Chemotherapy*. Florida: StatPearls Publishing.
- Anand, K., Massaon, H. K., & Prabhakar, P. K. (2024). Herbal Therapies in Cancer Patients: Managing Side Effects and Improving Quality of Life. *Sumatera Medical Journal*, *7*(1), 28-37. doi: <https://doi.org/10.32734/sumej.v7i1.14603>
- Anand, U., Dey, A., Chandel, A. K. S., Sanyal, R., Mishra, A., Pandey, D. K., De Falco, V., Upadhyay, A., Kandimalla, R., Chaudhary, A., Dhanjal, J. K., Dewanjee, S., Vallamkondu, J., & Pérez de la Lastra, J. M. (2022). Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes & diseases*, *10*(4), 1367–1401. <https://doi.org/10.1016/j.gendis.2022.02.007>
- Andersson, J., Larsson, L., Klaar, S., Holmberg, L., Nilsson, J., Inganäs, M., Carlsson, G., Öhd, J., Rudenstam, C.M., Gustavsson, B., & Bergh, J. (2005). Worse Survival for TP53 (p53)-Mutated Breast Cancer Patients Receiving

- Adjuvant CMF. *Annals of oncology*, 16(5), 743-748. doi: <https://doi.org/10.1093/annonc/mdi150>
- Ashkenazi, A. (2015). Targeting the Extrinsic Apoptotic Pathway in Cancer: Lessons Learned and Future Directions. *The Journal of clinical investigation*, 125(2), 487-489. doi: 10.1172/JCI80420
- Aslam, M. S., Naveed, S., Ahmed, A., Abbas, Z., Gull, I., & Athar, M. A. (2014). Side Effects of Chemotherapy in Cancer Patients and Evaluation of Patients Opinion About Starvation Based Differential Chemotherapy. *Journal of Cancer Therapy*, 5(8), 818-822. doi: <http://dx.doi.org/10.4236/jct.2014.58089>
- Baskar, R., Lee, K. A., Yeo, R., & Yeoh, K. W. (2012). Cancer and Radiation Therapy: Current Advances and Future Directions. *International journal of medical sciences*, 9(3), 193-199. doi: 10.7150/ijms.3635
- Barriuso, D., Alvarez-Frutos, L., Gonzalez-Gutierrez, L., Motiño, O., Kroemer, G., Palacios-Ramirez, R., & Senovilla, L. (2023). Involvement of Bcl-2 Family Proteins in Tetraploidization-Related Senescence. *International Journal of Molecular Sciences*, 24(7), 1-20. doi: <https://doi.org/10.3390/ijms24076374>
- Basu, A. (2022). The interplay between apoptosis and cellular senescence: Bcl-2 family proteins as targets for cancer therapy. *Pharmacology & therapeutics*, 230, 1-18. doi: <https://doi.org/10.1016/j.pharmthera.2021.107943>
- Beck, J., Turnquist, C., Horikawa, I., & Harris, C. (2020). Targeting cellular senescence in cancer and aging: Roles of p53 and its isoforms. *Carcinogenesis*, 41(8), 1017-1029. doi: <https://doi.org/10.1093/carcin/bgaa071>
- Bhushan, A., Gonsalves, A., & Menon, J. U. (2021). Current State of Breast Cancer Diagnosis, Treatment, and Theranostics. *Pharmaceutics*, 13(5), 1-24. <https://doi.org/10.3390/pharmaceutics13050723>
- Borrero, L. J. H., & El-Deiry, W. S. (2021). Tumor Suppressor p53: Biology, Signaling Pathways, and Therapeutic Targeting. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, 1876(1), 1-30. doi: <https://doi.org/10.1016/j.bbcan.2021.188556>

- Bousset, L., & Gil, J. (2022). Targeting Senescence as an Anticancer Therapy. *Molecular Oncology*, *16*(21), 3855-3880. doi: <https://doi.org/10.1002/1878-0261.13312>
- Budanov, A.V. (2014). The Role of Tumor Suppressor p53 in the Antioxidant Defense and Metabolism. In: Deb, S., Deb, S. (eds) Mutant p53 and MDM2 in Cancer. *Subcellular Biochemistry*, *85*, 1-22. doi: https://doi.org/10.1007/978-94-017-9211-0_18
- Burn S. F. (2012). Detection of β -galactosidase activity: X-gal staining. *Methods in molecular biology (Clifton, N.J.)*, *886*, 241–250. doi: https://doi.org/10.1007/978-1-61779-851-1_21
- Chatupheeraphat, C., Nantasenamat, C., Deesrisak, K., Roytrakul, S., Anurathapan, U., & Tanyong, D. (2020). Bioinformatics and experimental studies of anti-leukemic activity from 6-gingerol demonstrate its role in p53 mediated apoptosis pathway. *EXCLI journal*, *19*, 582–595. <https://doi.org/10.17179/excli2019-2008>
- Chen, J. H., Hales, C. N., & Ozanne, S. E. (2007). DNA damage, cellular senescence and organismal ageing: causal or correlative?. *Nucleic acids research*, *35*(22), 7417–7428. doi: <https://doi.org/10.1093/nar/gkm681>
- Chen, J. (2016). The Cell-Cycle Arrest and Apoptotic Functions of p53 in Tumor Initiation and Progression. *Cold Spring Harbor perspectives in medicine*, *6*(3). 1-15. doi: 10.1101/cshperspect.a026104.
- Comşa, Ş., Cimpean, A. M., & Raica, M. (2015). The Story of MCF-7 Breast Cancer Cell Line: 40 years of experience in research. *Anticancer research*, *35*(6), 3147-3154. doi: -
- Dai, M. S., Sun, X. X., & Lu, H. (2008). Aberrant Expression of Nucleostemin Activates p53 and Induces Cell Cycle Arrest via Inhibition of MDM2. *Molecular and Cellular Biology*, *28*(13), 4365-4376. doi: 10.1128/MCB.01662-07
- Daran, A. M., Rashid, K., Ibrahim, H., Jalil, M., & Yusof, Y. M. (2017). Toxic Trace Elements in Selected Edible Rhizomes of Medicinal Plants Using INAA and ICP-MS Techniques. *Int J Complement Alt Med*, *6*(4), 1-4. doi: 10.15406/ijcam.2017.06.00195

- Dehghanipour, S., Saadatmand, S., Roodbari, N. H., & Mahdavi, M. (2022). Anti-tumor effect of the ethanolic extract of *Vinca herbacea* on human breast cancer cell line: a mechanism study. *Irianian Red Crescent Medical Journal*, 24(8), 1-7. doi: <https://doi.org/10.32592/ircmj.2022.24.8.1922>
- Dietrich, A., Koi, L., Zöphel, K., Sihver, W., Kotzerke, J., Baumann, M., & Krause, M. (2015). Improving external beam radiotherapy by combination with internal irradiation. *The British journal of radiology*, 88(1051), 1-12. <https://doi.org/10.1259/bjr.20150042>
- Dorcheh, N. S., Rahgozar, S., & Talei, D. (2021). 6-Shogaol induces apoptosis in acute lymphoblastic leukaemia cells by targeting p53 signalling pathway and generation of reactive oxygen species. *Journal of Cellular and Molecular Medicine*, 25(13), 6148-6160. Doi: 10.1111/jcmm.16528
- Duo, J., Ying, G. G., Wang, G. W., & Zhang, L. (2012). Quercetin inhibits human breast cancer cell proliferation and induces apoptosis via Bcl-2 and Bax regulation. *Molecular medicine reports*, 5(6), 1453-1456. doi: <https://doi.org/10.3892/mmr.2012.845>
- Ebrahimi, R., Bahirae, A., Alipour, N. J., Toolabi, K., & Emamgholipour, S. (2018). Evaluation of the Housekeeping Genes; β -Actin, Glyceraldehyde-3-Phosphate-Dehydrogenase, and 18S rRNA for Normalization in Real-Time Polymerase Chain Reaction Analysis of Gene Expression in Human Adipose Tissue. *Archives of Medical Laboratory Sciences*, 4(3), 1-6. doi: <https://doi.org/10.22037/amls.v4i3.26269>
- Ewald, J. A., Desotelle, J. A., Wilding, G., & Jarrard, D. F. (2010). Therapy-induced Senescence in Cancer. *JNCI: Journal of the National Cancer Institute*, 102(20), 1536-1546. doi: 10.1093/jnci/djq364
- Fujita, K. (2019). p53 isoforms in cellular senescence-and ageing-associated biological and physiological functions. *International journal of molecular sciences*, 20(23), 1-19. doi: <https://doi.org/10.3390/ijms20236023>
- Ghasemzadeh, A., Jaafar, H. Z., & Rahmat, A. (2010). Antioxidant Activities, Total Phenolics and Flavonoids Content in Two Varieties of Malaysia Young Ginger (*Zingiber officinale* Roscoe). *Molecules*, 15(6), 4324-4333. doi: 10.3390/molecules15064324

- Gordeev, S. A., Bykova, T. V., Zubova, S. G., Aksenov, N. D., & Pospelova, T. V. (2015). The antiapoptotic gene bcl-2 prevents reactivation of the senescence program induced by the histone deacetylase inhibitor sodium butyrate in rat fibroblasts transformed by the oncogenes E1A and c-Ha-Ras. *Cell and Tissue Biology*, 9, 182-190. doi: <https://doi.org/10.1134/S1990519X15030050>
- Guterres, A. N., & Villanueva, J. (2020). Targeting telomerase for cancer therapy. *Oncogene*, 39(36), 5811-5824. doi: <https://doi.org/10.1038/s41388-020-01405-w>
- Haider, R. (2023). Anatomy of the Breast. *International Journal of Scientific Multidisciplinary Research*, 1(5), 401-422. doi: <https://doi.org/10.55927/ijsmr.v1i5.4394>
- Haldar, S., Negrini, M., Monne, M., Sabbioni, S., & Croce, C. M. (1994). Down-regulation of bcl-2 by p53 in breast cancer cells. *Cancer research*, 54(8), 2095-2097. doi: -
- Han, Y. A., Song, C. W., Koh, W. S., Yon, G. H., Kim, Y. S., Ryu, S. Y., Kwon, H.J., & Lee, K. H. (2013). Anti-inflammatory Effects of the *Zingiber officinale* roscoe Constituent 12-dehydrogingerdione in lipopolysaccharide-stimulated Raw 264.7 cells. *Phytotherapy Research*, 27(8), 1200-1205. doi: [10.1002/ptr.4847](https://doi.org/10.1002/ptr.4847)
- Harmida, Sarno, & Yuni, V. N. (2011). Studi Etnofitomedika di Desa Lawang Agung Kecamatan Mulak Ulu Kabupaten Lahat Sumatera Selatan. *Jurnal Penelitian Sains*. 14(1(D)). 42-46. doi: <https://doi.org/10.56064/jps.v14i1.126>
- Hendra, R. J., Rusdi, R. A., & Misfadhila, S. (2022). Phytochemical and Traditional Uses of Red Ginger: A Review (*Zingiber officinale* var. *rubrum*). *EAS Journal of Pharmacy and Pharmacology*. 4(3), 50-55. doi: [10.36349/easjpp.2022.v04i03.002](https://doi.org/10.36349/easjpp.2022.v04i03.002)
- He, C., Wang, C., Liu, H., & Shan, B. (2022). Kayadiol exerted anticancer effects through p53-mediated ferroptosis in NKTCL cells. *BMC cancer*, 22(1), 2-10. doi: <https://doi.org/10.1186/s12885-022-09825-5>

- Ho, K., Lin, H., Ann, D. K., Chu, P. G., & Yen, Y. (2011). An Overview of the Rare Parotid Gland Cancer. *Head & Neck Oncology*, 3(1), 1-7. doi: 10.1186/1758-3284-3-40.
- Honma, N., Horii, R., Ito, Y., Saji, S., Younes, M., Iwase, T., & Akiyama, F. (2015). Differences in Clinical Importance of Bcl-2 in Breast Cancer According to Hormone Receptors Status or Adjuvant Endocrine Therapy. *BMC cancer*, 15, 1-11. doi: 10.1186/s12885-015-1686-y
- Hsu, Y. L., Hung, J. Y., Tsai, Y. M., Tsai, E. M., Huang, M. S., Hou, M. F., & Kuo, P. L. (2015). 6-shogaol, an active constituent of dietary ginger, impairs cancer development and lung metastasis by inhibiting the secretion of CC-chemokine ligand 2 (CCL2) in tumor-associated dendritic cells. *Journal of agricultural and food chemistry*, 63(6), 1730-1738. doi: <https://doi.org/10.1021/jf504934m>
- Hu, L., Li, H., Zi, M., Li, W., Liu, J., Yang, Y., Zhou, D., Kong, Q. P., Zhang, Y., & He, Y. (2022). Why Senescent Cells Are Resistant to Apoptosis: An Insight for Senolytic Development. *Frontiers in cell and developmental biology*, 10, 1-17. doi: <https://doi.org/10.3389/fcell.2022.822816>
- Huang, L., Jin, K., & Lan, H. (2019). Luteolin inhibits cell cycle progression and induces apoptosis of breast cancer cells through downregulation of human telomerase reverse transcriptase. *Oncology Letters*, 17, 3842-3850. doi: <https://doi.org/10.3892/ol.2019.10052>
- Ibrahim, A. H., Hasan, H., & Pakaya, M. S. (2021). Skrining Fitokimia dan Uji Daya Hambat Ekstrak Daun Jahe Merah (*Zingiber officinale* var *rubrum*) Terhadap Bakteri *Staphylococcus epidermidis* dan *Escherichia coli*. *Indonesian Journal of Pharmaceutical Education*, 1(2), 107-118. doi: <https://doi.org/10.37311/ijpe.v1i2.10547>
- Itahana, K., Itahana, Y., & Dimri, G. P. (2013). Colorimetric detection of senescence-associated β galaktosidase. *Cell Senescence: Methods and Protocols*, 965, 143-156. doi: https://doi.org/10.1007%2F978-1-62703-239-1_8
- Jackson, J. G., Pant, V., Li, Q., Chang, L. L., Quintás-Cardama, A., Garza, D., Tavana, O., Yang, P., Manshouri, T., Li, Y., El-Naggar A.K., & Lozano, G.

- (2012). p53-mediated Senescence Impairs the Apoptotic Response to Chemotherapy and Clinical Outcome in Breast Cancer. *Cancer Cell*, 21(6), 793-806. doi: 10.1016/j.ccr.2012.04.027.
- Kapoor, I., Bodo, J., Hill, B. T., Hsi, E. D., & Almasan, A. (2020). Targeting BCL-2 in B-cell Malignancies and Overcoming Therapeutic Resistance. *Cell Death & Disease*, 11(11), 941. doi: 10.1038/s41419-020-03144-y
- Karimi-Busheri, F., Rasouli-Nia, A., Mackey, J. R., & Weinfield, M. (2010). Senescence evasion by MCF-7 human breast tumor-initiating cells. *Breast Cancer Research*, 12, 1-16. doi: <https://doi.org/10.1186%2Fbcr2583>
- Kementrian Kesehatan RI. (2022). *Kanker Payudara Paling Banyak di Indonesia, Kemenkes Targetkan Pemerataan Layanan Kesehatan*. Diakses dari: <https://sehatnegeriku.kemkes.go.id/baca/umum/20220202/1639254/kanker-payudara-paling-banyak-di-indonesia-kemenkes-targetkan-pemerataan-layanan-kesehatan/#:~:text=Kanker%20payudara%20menempati%20urutan%20pertama,kasus%20baru%20kanker%20di%20Indonesia.>
- Kim, Y. Y., Um, J. H., Yoon, J. H., Lee, D. Y., Lee, Y. J., Kim, D. H., Park, J. I., & Yun, J. (2020). p53 regulates mitochondrial dynamics by inhibiting Drp1 translocation into mitochondria during cellular senescence. *The FASEB Journal*, 34(2), 2451-2464. doi: <https://doi.org/10.1096/fj.201901747RR>
- Kooti, W., Servatyari, K., Behzadifar, M., Asadi-Samani, M., Sadeghi, F., Nouri, B., & Zare, M. H. (2017). Effective medicinal plant in cancer treatment, part 2: review study. *Journal of evidence-based complementary & alternative medicine*, 22(4), 982-995. doi: <https://doi.org/10.1177%2F2156587217696927>
- Kumari, R., & Jat, P. (2021). Mechanisms of cellular senescence: cell cycle arrest and senescence associated secretory phenotype. *Frontiers in cell and developmental biology*, 9, 1-24. doi: <https://doi.org/10.3389/fcell.2021.645593>
- Levenson, A. S., & Jordan, V. C. (1997). MCF-7: The First Hormone-Responsive Breast Cancer Cell Line. *Cancer research*, 57(15), 3071-3078. doi: -

- Li, X., Li, B., Ni, Z., Zhou, P., Wang, B., He, J., Xiong, H., Yang, F., Wu, Y., Lyu, X., Zhang, Y., Zeng, Y., Lian, J., & He, F. (2017). Metformin synergizes with BCL-XL/BCL-2 inhibitor ABT-263 to induce apoptosis specifically in p53-defective cancer cells. *Molecular Cancer Therapeutics*, *16*(9), 1806-1818. doi: <https://doi.org/10.1158/1535-7163.MCT-16-0763>
- Liang, H., Li, Y., Wang, F., Zhao, J., Yang, X., Wu, D., Zhang, C., Liu, Y., Huang, J., Su, M., He, Z., Liu, Y., Wang, J., & Tang, D. (2022). Combining network pharmacology and experimental validation to study the action and mechanism of water extract of Asparagus against colorectal cancer. *Frontiers in Pharmacology*, *13*, 1-17. doi: <https://doi.org/10.3389/fphar.2022.862966>
- Liau, S. L., Connell, P. P., & Weichselbaum, R. R. (2013). New Paradigms and Future Challenges in Radiation Oncology: An Update of Biological Targets and Technology. *Science Translational Medicine*, *5*(173), 173sr2-173sr2. doi: [10.1126/scitranslmed.3005148](https://doi.org/10.1126/scitranslmed.3005148).
- Liu, Q., Peng, Y. B., Zhou, P., Qi, L. W., Zhang, M., Gao, N., Liu, E. H., & Li, P. (2013). 6-Shogaol induces apoptosis in human leukemia cells through a process involving caspase-mediated cleavage of eIF2 α . *Molecular cancer*, *12*(1), 135. doi: <https://doi.org/10.1186/1476-4598-12-135>
- Liu, H., Specht, C. D., Zhao, T., & Liao, J. (2020a). Morphological Anatomy of Leaf and Rhizome in *Zingiber officinale* Roscoe, with Emphasis on Secretory Structures. *HortScience*, *55*(2), 204-207. doi: <https://doi.org/10.21273/HORTSCI14555-19>
- Liu, Y., Yang, S., Wang, K., Lu, J., Bao, X., Wang, R., Qiu, Y., Wang, T., & Yu, H. (2020b). Cellular Senescence and Cancer: Focusing on Traditional Chinese Medicine and Natural Products. *Cell Proliferation*, *53*(10), e12894. doi: [10.1111/cpr.12894](https://doi.org/10.1111/cpr.12894).
- Liu, C., Zeng, Y., Wen, Y., Huang, X., & Liu, Y. (2022a). Natural products modulate cell apoptosis: A promising way for the treatment of ulcerative colitis. *Frontiers in pharmacology*, *13*, 1-16. doi: <https://doi.org/10.3389/fphar.2022.806148>
- Liu, J., Li, B., Li, W., Pan, T., Diao, Y., & Wang, F. (2022b). 6-Shogaol inhibits oxidative stress-induced rat vascular smooth muscle cell apoptosis by

- regulating OXR1-p53 axis. *Frontiers in Molecular Biosciences*, 9, 1-12. doi: <https://doi.org/10.3389/fmolb.2022.808162>
- Lowe, S. W., Bodis, S., McClatchey, A., Remington, L., Ruley, H. E., Fisher, D. E., Housman, D.E., & Jacks, T. (1994). p53 Status and the Efficacy of Cancer Therapy In vivo. *Science*, 266(5186), 807-810. doi: 10.1126/science.7973635.
- Lu H. F., Chie Y. J., Yang M. S., Lee C. S., Fu J. J., Yang J. S., Tan T. W., Wu S. H., Ma Y. S., & Ip S. W. Apigenin induces caspase-dependent apoptosis in human lung cancer A549 cells through BAX-and Bcl-2-triggered mitochondrial pathway. *International journal of oncology*. 36(6), 1477–1484. doi: https://doi.org/10.3892/ijo_00000634
- Majeed, H., & Gupta, V. (2023). *Adverse Effects of Radiation Therapy*. Florida: StatPearls Publishing.
- Makki, J. (2015). Diversity of Breast Carcinoma: Histological Subtypes and Clinical Relevance. *Clinical Medicine Insights: Pathology*, 8, 23-31. doi: 10.4137/CPath.S31563.
- Mao, Q. Q., Xu, X. Y., Cao, S. Y., Gan, R. Y., Corke, H., Beta, T., & Li, H. B. (2019). Bioactive Compounds and Bioactivities of Ginger (*Zingiber officinale* Roscoe). *Foods*, 8(6), 1-21. doi: 10.3390/foods8060185
- Marchetti, C., De Felice, F., Musella, A., Palaia, I., Monti, M., Musio, D., Muzii, L., Tombolini, V., & Panici, P. B. (2016). Weekly versus three weeks chemotherapy for advanced ovarian cancer: a meta-analysis. *Oncotarget*, 7(36), 58709. doi: <https://doi.org/10.18632/oncotarget.11094>
- Mariadoss, A. V., Kathiresan, S., Muthusamy, R., & Kathiresan, S. (2013). Protective effects of [6]-paradol on histological lesions and immunohistochemical gene expression in DMBA induced hamster buccal pouch carcinogenesis. *Asian Pacific Journal of Cancer Prevention*, 14(5), 3123-3129. doi: <https://doi.org/10.7314/apjcp.2013.14.5.3123>
- Marvalim, C., Datta, A., & Lee, S. C. (2023). Role of p53 in breast cancer progression: An insight into p53 targeted therapy. *Theranostics*, 13(4), 1421. doi: <https://doi.org/10.7150/thno.81847>

- Mavrogiannis, A. V., Kokkinopoulou, I., Kontos, C. K., & Sideris, D. C. (2018). Effect of vinca alkaloids on the expression levels of microRNAs targeting apoptosis-related genes in breast cancer cell lines. *Current Pharmaceutical Biotechnology*, *19*(13), 1076-1086. doi: <https://doi.org/10.2174/1389201019666181112103204>
- Mehrgou, A., & Akouchekian, M. (2016). The importance of BRCA1 and BRCA2 genes mutations in breast cancer development. *Medical journal of the Islamic Republic of Iran*, *30*. 1-12. doi: -
- Merrill, A. Y., White, A., & Howard-McNatt, M. (2017). Paget's disease of the breast: an institutional review and surgical management. *The American Surgeon*, *83*(3), 96-98. doi: <https://doi.org/10.1177/000313481708300312>
- Mijit, M., Caracciolo, V., Melillo, A., Amicarelli, F., & Giordano, A. (2020). Role of p53 in the regulation of cellular senescence. *Biomolecules*, *10*(3), 1-16. doi: <https://doi.org/10.3390/biom10030420>
- Mirabelli, P., Coppola, L., & Salvatore, M. (2019). Cancer Cell Lines are Useful Model Systems for Medical Research. *Cancers*, *11*(8), 1-18. doi: [10.3390/cancers11081098](https://doi.org/10.3390/cancers11081098).
- Miyoshi, N., Nakamura, Y., Ueda, Y., Abe, M., Ozawa, Y., Uchida, K., & Osawa, T. (2003). Dietary Ginger Constituents, Galanals A and B, are Potent Apoptosis Inducers in Human T Lymphoma Jurkat Cells. *Cancer Letters*, *199*(2), 113-119. doi: [10.1016/s0304-3835\(03\)00381-1](https://doi.org/10.1016/s0304-3835(03)00381-1).
- Moaddel, R., Rossi, M., Rodriguez, S., Munk, R., Khadeer, M., Abdelmohsen, K., Gorospe, M., & Ferrucci, L. (2022). Identification of gingerenone A as a novel senolytic compound. *PLoS one*, *17*(3), e0266135. doi: <https://doi.org/10.1371/journal.pone.0266135>
- Mollaei, M., Hassan, Z. M., Khorshidi, F., & Langroudi, L. (2021). Chemotherapeutic drugs: Cell death- and resistance-related signaling pathways. Are they really as smart as the tumor cells?. *Translational oncology*, *14*(5), 1-26. <https://doi.org/10.1016/j.tranon.2021.101056>
- Nakopoulou, L. L., Alexiadou, A., Theodoropoulos, G. E., Lazaris, A. C., Tzonou, A., & Keramopoulos, A. (1996). Prognostic Significance of the Co-expression of p53 and c-erbB-2 Proteins in Breast Cancer. *The Journal of*

- pathology*, 179(1), 31-38. doi: [https://doi.org/10.1002/\(sici\)1096-9896\(199605\)179:1<31::aid-path523>3.0.co;2-o](https://doi.org/10.1002/(sici)1096-9896(199605)179:1<31::aid-path523>3.0.co;2-o)
- Nazim, U. M., & Park, S. Y. (2019). Attenuation of autophagy flux by 6-shogaol sensitizes human liver cancer cells to TRAIL-induced apoptosis via p53 and ROS. *International Journal of Molecular Medicine*, 43(2), 701-708. doi: <https://doi.org/10.3892/ijmm.2018.3994>
- Orth, M., Lauber, K., Niyazi, M., Friedl, A. A., Li, M., Maihöfer, C., Schüttrumpf, L., Ernst, A., Niemöller, O. M., & Belka, C. (2014). Current Concepts in Clinical Radiation Oncology. *Radiation and Environmental Biophysics*, 53, 1-29. doi: 10.1007/s00411-013-0497-2
- Oyenihi, O. R., Oyenihi, A. B., Erhabor, J. O., Matsabisa, M. G., & Oguntibeju, O. O. (2021). Unravelling the Anticancer Mechanisms of Traditional Herbal Medicines with Metabolomics. *Molecules*, 26(21), 1-24. doi: 10.3390/molecules26216541
- Ozaki, T., & Nakagawara, A. (2011). Role of p53 in cell death and human cancers. *Cancers*, 3(1), 1-20. doi: <https://doi.org/10.3390/cancers3010994>
- Prasanna, P. G., Citrin, D. E., Hildesheim, J., Ahmed, M. M., Venkatachalam, S., Riscuta, G., Xi, D., Zheng, G., Deursen, J. V., Goronzy, J., Kron, S. J., Anscher, M. S., Sharpless, N. E., Campisi, J., Brown, S. L., Niedernhofer, L. J., O'Longhlen, A., Georgakilas, A. G., Paris, F., Gius, D., Gewirtz, D. A., Schmitt, C. A., Abazeed, M. E., Kirkland, J. L., Richmond, A., Romesser, P. B., Lowe, S. W., Gil, J., Mendonca, M. S., Burma, S., Zhou, D., & Coleman, C. N. Therapy-induced senescence: opportunities to improve anticancer therapy. *JNCI: Journal of the National Cancer Institute*, 10 (2021), 1285-1298. doi: <https://doi.org/10.1093/jnci/djab064>
- Prasad, S., & Tyagi, A. K. (2015). Ginger and its Constituents: Role in Prevention and Treatment of Gastrointestinal Cancer. *Gastroenterology research and practice*, 2015, 1-11. doi: <https://doi.org/10.1155/2015/142979>
- Qian, S., Wei, Z., Yang, W., Huang, J., Yang, Y., & Wang, J. (2022). The Role of BCL-2 Family Proteins in Regulating Apoptosis and Cancer Therapy. *Frontiers in Oncology*, 12, 1-16. doi: 10.3389/fonc.2022.985363

- Rahminiwati, M., Saadah, S., & Unang, P. (2010). Bioprospeksi Ekstrak Jahe Gajah sebagai Anti-CRD: Kajian Aktivitas Antibakteri Terhadap *Mycoplasma galliseptikum* dan *E. coli* in vitro. *Jurnal Ilmu Pertanian Indonesia*, 15(1), 7-13. doi: -
- Ramani, K. V., Ramani, H., Alurkar, S., Ajaikumar, B. S., & Trivedi, R. G. (2017). *Breast cancer: Medical treatment, side effects, and complementary therapies*. Momentum Press.
- Ray, A., Vasudevan, S., & Sengupta, S. (2015). 6-Shogaol inhibits breast cancer cells and stem cell-like spheroids by modulation of Notch signaling pathway and induction of autophagic cell death. *PloS one*, 10(9), 1-22. doi: 10.1371/journal.pone.0137614
- Reinhardt, H. C., & Schumacher, B. (2012). The p53 network: cellular and systemic DNA damage responses in aging and cancer. *Trends in Genetics*, 28(3), 128-136. doi: <https://doi.org/10.1016/j.tig.2011.12.002>
- Riaz, M., Khalid, R., Afzal, M., Anjum, F., Fatima, H., Zia, S., Rasool G, Egbuna, C, Mtewa, AG, Uche, CZ., & Aslam, M. A. (2023). Phytobioactive Compounds as Therapeutic Agents for Human Diseases: A review. *Food Science & Nutrition*. 11(6), 2500-2529. doi: 10.1002/fsn3.3308.
- Robi, F. S., Setiowati, F. K., & Balqis (2023). Potency of Bioactive Compounds 6-gingerol, Morin, Cinnamic, Gallic, and Kaemferol in Red Ginger (*Zingiber officinale* Var. Rubrum Rhizoma) as Oral Cavity Anticancer Drugs against Galectin-1 Protein: Study In silico. *Biomolecular and Health Science Journal*, 6(1), 13-19. doi: 10.4103/bhsj.bhsj_2_23
- Rochaniawan, A. (2021). Herbal Medicines as Cancer Treatment: A Narrative Literature Review. *Open Access Indonesian Journal of Medical Reviews*, 1(5), 79-82. doi: <https://doi.org/10.37275/oaijmr.v1i5.49>
- Rolland, P., Spendlove, I., Madjid, Z., Rakha, E. A., Patel, P., Ellis, I. O., & Durrant, L. (2007). The p53 Positive Bcl-2 Negative Phenotype is an Independent Marker of Prognosis in Breast Cancer. *International Journal of Cancer*, 120(6), 1311-1317. doi: 10.1002/ijc.22430.
- Salari, Z., Khosravi, A., Pourkhandani, E., Molaakbari, E., Salarkia, E., Keyhani, A., Sahrifi, I., Tavakkoli, H., Sohbati, S., Dabiri. S., Ren, G., & Shafie'ei, M.

- (2023). The inhibitory effect of 6-gingerol and cisplatin on ovarian cancer and antitumor activity: In silico, in vitro, and in vivo. *Frontiers in Oncology*, *13*, 1-17. doi: <https://doi.org/10.3389/fonc.2023.1098429>
- Samuels, N., Morag, O., & Maimon, Y. (2015). Use of herbal medicine for cancer treatment-related toxicities. *Harefuah*, *154*(1), 43-6. doi: -
- Schadich, E., Hlaváč, J., Volná, T., Varanasi, L., Hajdúch, M., & Džubák, P. (2016). Effects of Ginger Phenylpropanoids and Quercetin on Nrf2-ARE Pathway in Human BJ Fibroblasts and HaCaT Keratinocytes. *BioMed research international*, *2016*, 1-6. doi: [10.1155/2016/2173275](https://doi.org/10.1155/2016/2173275)
- Schober, P., Boer, C., & Schwarte, L. A. (2018). Correlation coefficients: appropriate use and interpretation. *Anesthesia & analgesia*, *126*(5), 1763-1768. doi: [10.1213/ANE.0000000000002864](https://doi.org/10.1213/ANE.0000000000002864)
- Seong, M. K., Lee, J. Y., Byeon, J., Sohn, Y. J., Seol, H., Lee, J. K., Kim, E.K., Kim, H.A., & Noh, W. C. (2015). Bcl-2 is a Highly Significant Prognostic Marker of Hormone-receptor-positive, Human Epidermal Growth Factor Receptor-2-Negative Breast Cancer. *Breast Cancer Research and Treatment*, *150*, 141-148. doi: [10.1007/s10549-015-3305-7](https://doi.org/10.1007/s10549-015-3305-7).
- Shang, C., & Xu, D. (2022). Epidemiology of Breast Cancer. *Oncologie*, *24*(4), 649-663. doi: <https://doi.org/10.32604/oncologie.2022.027640>
- Shim, H. Y., Park, J. H., Paik, H. D., Nah, S. Y., Kim, D. S., & Han, Y. S. (2007). Acacetin-induced apoptosis of human breast cancer MCF-7 cells involves caspase cascade, mitochondria-mediated death signaling and SAPK/JNK1/2-c-Jun activation. *Molecules and cells*, *24*(1), 95-104. doi: [https://doi.org/10.1016/S1016-8478\(23\)10760-6](https://doi.org/10.1016/S1016-8478(23)10760-6)
- Shrihastini, V., Muthuramalingam, P., Adarshan, S., Sujitha, M., Chen, J. T., Shin, H., & Ramesh, M. (2021). Plant Derived Bioactive Compounds, Their Anti-Cancer Effects and In silico Approaches as an Alternative Target Treatment Strategy for Breast Cancer: An Updated Overview. *Cancers*, *13*(24), 1-21. doi: [10.3390/cancers13246222](https://doi.org/10.3390/cancers13246222)
- Shukla, Y., & Singh, M. (2007). Cancer Preventive Properties of Ginger: A Brief Review. *Food and Chemical Toxicology*, *45*(5), 683-690. doi: [10.1016/j.fct.2006.11.002](https://doi.org/10.1016/j.fct.2006.11.002).

- Soule, H. D., Vazquez, J., Long, A., Albert, S., & Brennan, M. (1973). A Human Cell Line from a Pleural Effusion Derived from A Breast Carcinoma. *Journal of the National Cancer Institute*, 51(5), 1409-1416. doi: 10.1093/jnci/51.5.1409.
- Schmitt, C. A., Wang, B., & Demaria, M. (2022). Senescence and cancer—role and therapeutic opportunities. *Nature reviews Clinical oncology*, 19(10), 619-636. doi: <https://doi.org/10.1038/s41571-022-00668-4>
- Stoner, G. D. (2013). Ginger: Is It Ready for Prime Time?. *Cancer Prevention Research*, 6(4), 257-262. doi: 10.1158/1940-6207.CAPR-13-0055.
- Sp, N., Kang, D. Y., Lee, J. M., Bae, S. W., & Jang, K. J. (2021). Potential Antitumor Effects of 6-gingerol in p53-dependent Mitochondrial Apoptosis and Inhibition of Tumor Sphere Formation in Breast Cancer Cells. *International Journal of Molecular Sciences*, 22(9), 1-21. doi: 10.3390/ijms22094660
- Su, P., Veeraraghavan, V. P., Krishna Mohan, S., & Lu, W. (2019). A ginger derivative, zingerone—a phenolic compound—induces ROS-mediated apoptosis in colon cancer cells (HCT-116). *Journal of biochemical and molecular toxicology*, 33(12), 1-8. doi: <https://doi.org/10.1002/jbt.22403>
- Susanty, S., & Yulendra, L. (2018). Panduan Proses Pengolahan Jahe Menjadi Jahe Serbuk Instan. *Media Bina Ilmiah*, 1(1), 85-92. doi: <https://doi.org/10.33758/mbi.v1i2i6.18>
- Sweeney, E. E., McDaniel, R. E., Maximov, P. Y., Fan, P., & Jordan, V. C. (2012). Models and Mechanisms of Acquired Antihormone Resistance in Breast Cancer: Significant Clinical Progress Despite Limitations. *Hormone Molecular Biology and Clinical Investigation*, 9(2), 143-163. doi: 10.1515/hmbci-2011-0004.
- Syaputri, E. R., Selaras, G. H., & Farma, S. A. (2021). Manfaat Tanaman Jahe (*Zingiber officinale*) sebagai Obat-obatan Tradisional (Traditional Medicine). *Prosiding Seminar Nasional Biologi*. 1(1), 579-586. doi: <https://doi.org/10.24036/prosemnasbio/vol1/71>
- Tilahun, S., Alemu, M., Tsegaw, M., & Berhane, N. (2022). Morphological and Molecular Diversity of Ginger (*Zingiber officinale* Roscoe) Pathogenic Fungi

- in Chilga District, North Gondar, Ethiopia. *Frontiers in Fungal Biology*, 2, 1-11. doi: 10.3389/ffunb.2021.765737
- Tonnessen-Murray, C. A., Frey, W. D., Rao, S. G., Shahbandi, A., Ungerleider, N. A., Olayiwola, J. O., Murray, L. B., Vinson, B. T., Chrisey, D. B., Lord, C. J., & Jackson, J. G. (2019). Chemotherapy-Induced Senescent Cancer Cells Engulf Other Cells to Enhance Their Survival. *Journal of Cell Biology*, 218(11), 3827-3844. doi: <https://doi.org/10.1083/jcb.201904051>
- Ueno, T. (2020). Biomarkers of Neoadjuvant/Adjuvant Endocrine Therapy for ER-Positive/HER2-Negative Breast Cancer. *Chin Clin Oncol*, 9(3), 1-7. doi: <http://dx.doi.org/10.21037/cco-20>
- Varesi, A., Chirumbolo, S., Campagnoli, L. I. M., Pierella, E., Piccini, G. B., Carrara, A., Ricevuti, G., Scassellati, C., Bonvicini, C., & Pascale, A. (2022). The role of antioxidants in the interplay between oxidative stress and senescence. *Antioxidants*, 11(7), 1-42. doi: <https://doi.org/10.3390/antiox11071224>
- Wala, K., Szlasa, W., Sauer, N., Kasperkiewicz-Wasilewska, P., Szewczyk, A., Saczko, J., Rembialkowska, N., Kulbacka, J., & Baczyńska, D. (2022). Anticancer efficacy of 6-gingerol with paclitaxel against wild type of human breast adenocarcinoma. *Molecules*, 27(9), 2693. doi: <https://doi.org/10.3390/molecules27092693>
- Wang, L., Lankhorst, L., & Bernards, R. (2022). Exploiting Senescence for the Treatment of Cancer. *Nature Reviews Cancer*, 22(6), 340-355. doi: 10.1038/s41568-022-00450-9.
- Wang, W., Wang, D., & Li, H. (2014). Initiation of premature senescence by Bcl-2 in hypoxic condition. *International journal of clinical and experimental pathology*, 7(5), 2446–2453. doi: -
- Wang, H., Guo, M., Wei, H., & Chen, Y. (2023). Targeting p53 pathways: mechanisms, structures, and advances in therapy. *Signal transduction and targeted therapy*, 8(1), 1-35. doi: <https://doi.org/10.1038/s41392-023-01347-1>
- Wang, W., Guo, Q., You, Q., Zhang, K., Yang, Y., Yu, J., Wei, L., Li, Z., Hongyan, G., Yang, H., Zi, T., & Wang, X. (2006). Involvement of BAX/bcl-2 in

- wogonin-induced apoptosis of human hepatoma cell line SMMC-7721. *Anti-Cancer Drugs*, 17(7), 797-805. doi: 10.1097/01.cad.0000217431.64118.3f
- Warren, C. F., Wong-Brown, M. W., & Bowden, N. A. (2019). BCL-2 Family Isoforms in Apoptosis and Cancer. *Cell Death & Disease*, 10(3), 1-12. doi: <https://doi.org/10.1038/s41419-019-1407-6>
- Warin, R. F., Chen, H., Soroka, D. N., Zhu, Y., & Sang, S. (2014). Induction of Lung Cancer Cell Apoptosis Through A p53 Pathway by [6]-shogaol and its Cysteine-Conjugated Metabolite M2. *Journal of Agricultural and Food Chemistry*, 62(6), 1352-1362. doi: <https://doi.org/10.1021/jf405573e>
- Widowati, W., Jasaputra, D. K., Sumitro, S. B., Widodo, M. A., Afifah, E., Rizal, R., Rihibiha, D. D., Kusuma, H. S. W., Murti, H., Bachtiar, I., & Faried, A. (2018). Direct and indirect effect of TNF α and IFN γ toward apoptosis in breast cancer cells. *Molecular and Cellular Biomedical Sciences*, 2(2), 60-9. doi: 10.21705/mcbs.v2i2.21
- Widowati, W., Jasaputra, D. K., Onggowidjaja, P., Sumitro, S. B., Widodo, M. A., Afifah, E., Rihibiha, D. D., Kusuma, H. S. W., Murti, H., Bachtiar, I., & Bachtiar, I. (2019). Effects of Conditioned Medium of Co-Culture IL-2 Induced NK Cells and Human Wharton's Jelly Mesenchymal Stem Cells (hWJMSCs) on Apoptotic Gene Expression in a Breast Cancer Cell Line (MCF-7). *Journal of Mathematical & Fundamental Sciences*, 51(3), 60-69. doi: 10.21705/mcbs.v2i2.21
- Widowati, W., Tjokropranoto, R., Onggowidjaja, P., Kusuma, H. S. W., Wijayanti, C. R., Marthania, M., Yati, A., & Rizal, R. (2023). Protective Effect of Yacon Leaves Extract (*Smallanthus sonchifolius* (Poepp.) H. Rob) Through Antifibrosis, Anti-inflammatory, and Antioxidant Mechanisms Toward Diabetic Nephropathy. *Research in Pharmaceutical Sciences*, 18(3), 336-345. doi: <https://doi.org/10.4103%2F1735-5362.371589>
- Williams, A. B., & Schumacher, B. (2016). p53 in the DNA-Damage-Repair Process. *Cold Spring Harbor perspectives in medicine*, 6(5), 1-15. <https://doi.org/10.1101/cshperspect.a026070>

- Windarsih, G., Utami, D. W., & Yuriah, S. (2021). Morphological Characteristics of Zingiberaceae in Serang District, Banten, Indonesia. *Biodiversitas Journal of Biological Diversity*, 22(12), 336-345. doi: 10.4103/1735-5362.371589
- World Health Organization. (2023). *Breast Cancer*. Diakses dari: <https://www.who.int/news-room/fact-sheets/detail/breast-cancer#:~:text=Breast%20cancer%20is%20a%20disease,producing%20lobules%20of%20the%20breast>.
- Wu, Y. Y., Xu, Y. M., & Lau, A. T. (2023). Epigenetic effects of herbal medicine. *Clinical Epigenetics*, 15(1), 1-21. doi: <https://doi.org/10.1186/s13148-023-01481-1>
- Wu, H., Huang, M., Liu, Y., Shu, Y., & Liu, P. (2015). Luteolin induces apoptosis by up-regulating miR-34a in human gastric cancer cells. *Technology in Cancer Research & Treatment*, 14(6), 747-755. doi: <https://doi.org/10.7785/tcrt.2012.500434>
- Yamashita, H., Toyama, T., Nishio, M., Ando, Y., Hamaguchi, M., Zhang, Z., Kobayashi, S., Fujii, Y., & Iwase, H. (2006). p53 Protein Accumulation Predicts Resistance to Endocrine Therapy and Decreased Post-relapse Survival in Metastatic Breast Cancer. *Breast Cancer Research*, 8, 1-8. doi: 10.1186/bcr1536
- Yeh, H. Y., Chuang, C. H., Chen, H. C., Wan, C. J., Chen, T. L., & Lin, L. Y. (2014). Bioactive Components Analysis of Two Various Gingers (*Zingiber officinale* Roscoe) and Antioxidant Effect of Ginger Extracts. *LWT-Food Science and Technology*, 55(1), 329-334. doi: 10.1016/j.lwt.2013.08.003
- Yin, S. Y., Wei, W. C., Jian, F. Y., & Yang, N. S. (2013). Therapeutic applications of herbal medicines for cancer patients. *Evidence-based complementary and alternative medicine*, 2013, 1-15. doi: <https://doi.org/10.1155/2013/302426>
- Zahra, H., Haridas, R. B., Gholam, G. M., & Setiawan, A. G. (2022). Aktivitas Antiulseratif Berbagai Tanaman Herbal dan Prospek Masa Depan Sebagai Tanaman Budidaya: Anti-ulceritis Activity of Various Herbal Plants and Future Prospects as Cultivated Plants. *Jurnal Sains dan Kesehatan*, 4(3), 343-353. doi: <https://doi.org/10.25026/jsk.v4i3.1046>

- Zhang, S., Kou, X., Zhao, H., Mak, K. K., Balijepalli, M. K., & Pichika, M. R. (2022). *Zingiber officinale* var. *rubrum*: Red Ginger's Medicinal Uses. *Molecules*, 27(3), 1-31. doi: <https://doi.org/10.3390/molecules27030775>
- Zhou, Q. M., Wang, S., Zhang, H., Lu, Y. Y., Wang, X. F., Motoo, Y., & Su, S. B. (2009). The combination of baicalin and baicalein enhances apoptosis via the ERK/p38 MAPK pathway in human breast cancer cells. *Acta Pharmacologica Sinica*, 30(12), 1648-1658. doi: <https://doi.org/10.1038/aps.2009.166>
- Zhuang, H., Zhao, X., Zhao, L., Chang, J. Y., & Wang, P. (2014). Progress of Clinical Research on Targeted Therapy Combined with Thoracic Radiotherapy for Non-small-cell Lung Cancer. *Drug design, development, and therapy*, 8,667-675. doi: 10.2147/DDDT.S61977