PENGARUH NANOKRISTAL JAHE MERAH TERHADAP SITOTOKSISITAS SERTA EKSPRESI GEN *NFKB* DAN *CASP3* PADA LINI SEL MCF-7

SKRIPSI

diajukan untuk memenuhi sebagian dari syarat untuk memperoleh
gelar Sarjana Sains Program Studi Biologi

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PROGRAM STUDI BIOLOGI
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UNIVERSITAS PENDIDIKAN INDONESIA
BANDUNG
2024

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Sebuah Skripsi yang diajukan untuk memenuhi salah satu syarat memperoleh gelar Sarjana Sains pada Program Studi Biologi, Fakultas Pendidikan Matematika dan Ilmu Pengetahuan Alam

Universitas Pendidikan Indonesia
Agustus 2024

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PENGARUH NANOKRISTAL JAHE MERAH TERHADAP SITOTOKSISITAS SERTA EKSPRESI GEN *NFKB* DAN *CASP3* PADA LINI SEL MCF-7

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PERNYATAAN KEASLIAN SKRIPSI

Dengan ini saya menyatakan bahwa skripsi dengan judul "Pengaruh Nanokristal Jahe Merah terhadap Sitotoksisitas serta Ekspresi Gen *NFKB* dan *CASP3* pada Lini Sel MCF-7" ini beserta seluruh isinya adalah benar-benar karya saya sendiri. Saya tidak melakukan penjiplakan atau pengutipan dengan cara-cara yang tidak sesuai dengan etika ilmu yang berlaku dalam masyarakat keilmuan. Atas pernyataan ini, saya siap menanggung sanksi apabila di kemudian hari ditemukan adanya pelanggaran etika keilmuan atau ada klaim dari pihak lain terhadap keaslian karya saya ini.

Bandung, Agustus 2024

Yang membuat pernyataan,

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KATA PENGANTAR

Puji dan syukur penulis panjatkan kehadirat Allah SWT karena berkat rahmat dan ridha-Nya penulis dapat menyelesaikan skripsi yang berjudul "Pengaruh Nanokristal Jahe Merah terhadap Sitotoksisitas serta Ekspresi Gen *NFKB* dan *CASP3* pada Lini Sel MCF-7". Adapun maksud dan tujuan dari penulisan skripsi ini adalah untuk memenuhi salah satu syarat untuk memenuhi salah satu syarat memperoleh gelar Sarjana Sains pada Program Studi Biologi, Fakultas Pendidikan Matematika dan Ilmu Pengetahuan Alam, Universitas Pendidikan Indonesia.

Dalam proses penyusunan skripsi ini, penulis menyadari bahwa masih banyak kekurangan yang perlu ditingkatkan. Oleh karena itu, kritik dan saran yang bersifat membangun sangat diharapkan agar skripsi ini dapat menjadi referensi yang lebih baik di masa mendatang. Akhir kata, semoga skripsi ini dapat memberikan gambaran yang jelas dan bermanfaat, tidak hanya bagi penulis, tetapi juga bagi pembaca yang berkepentingan.

Bandung, Agustus 2024

Penulis

UCAPAN TERIMA KASIH

Penulis menyadari dalam menyelesaikan penulisan skripsi ini, banyak mendapat bantuan, dorongan, dan bimbingan dari berbagai pihak. Oleh karena, itu penulis mengucapkan terima kasih kepada:

1. Bapak Dr. Didik Priyandoko, M.Si. selaku Dosen Pembimbing Skripsi Pertama yang telah meluangkan waktu, tenaga, dan pikiran untuk memberikan bimbingan, saran, serta masukan yang sangat berarti dalam penyusunan skripsi ini.
2. Ibu Dr. Hernawati, S.Pt., M.Si. selaku Dosen Pembimbing Skripsi Kedua yang telah meluangkan waktu, tenaga, dan pikiran untuk memberikan bimbingan, saran, serta masukan yang sangat berarti dalam penyusunan skripsi ini.
3. Ibu Prof. Dr. Wahyu Widowati, M.Si. selaku Pembimbing Skripsi Ketiga yang telah meluangkan waktu, tenaga, dan pikiran untuk memberikan bimbingan, saran, serta masukan yang sangat berarti dalam penyusunan skripsi ini.
4. Bapak Dr. Wahyu Surakusumah, M.T. selaku Ketua Program Studi Biologi FPMIPA UPI yang telah memberikan arahan dan dukungan administratif selama masa studi.
5. Hj. Tina Safaria Nilawati, M.Si., sebagai dosen pembimbing akademik yang telah memberikan bimbingan dan dukungan selama perkuliahan.
6. Seluruh Bapak dan Ibu dosen di Program Studi Biologi FPMIPA UPI atas segala ilmu dan dukungan yang telah diberikan selama perkuliahan.
7. Seluruh staf akademik Program Studi Biologi dan FPMIPA UPI atas bantuan dan dukungannya dalam proses administrasi selama masa studi.
8. Ibu Hanna Sari Widya Kusuma, S.Si. selaku Direktur Utama PT Aretha Medika Utama yang telah memberikan kesempatan dan izin kepada penulis untuk melakukan penelitian di PT. Aretha Medika Utama.
9. Kak Adilah Hafizha Nur Sabrina, S.Si. dan Kak Fadhilah Haifa Zahiroh, S.Si. selaku asisten peneliti di PT. Aretha Medika Utama yang telah memberikan bimbingan, dukungan, dan bantuan selama penyusunan skripsi

ini. Terima kasih atas waktu, pengetahuan, dan kesabaran dalam membimbing serta memberikan masukan yang sangat berharga.

10. Seluruh tim PT. Aretha Medika Utama yang telah memberikan bantuan dan dukungan dalam penyelesaian skripsi ini.
11. Kedua orang tua penulis, yaitu Bapak Dodi Tatang dan Ibu Dedeh Sukaesih, yang senantiasa mendoakan penulis dan memberikan dukungan moral dan materil untuk segala aktivitas yang penulis lakukan selama menyelesaikan masa studi dan skripsi ini.
12. Kakak penulis, yaitu Aprijal Ghiyas Setiawan, yang telah memberikan bantuan, dukungan, dan motivasi selama menyelesaikan masa studi dan skripsi ini.
13. Keluarga besar penulis yang senantiasa mendoakan penulis dan memberikan dukungan selama menyelesaikan perkuliahan ini.
14. Ghaida Nurin Athifah dan Siti Ratu Rahayu Ningrum sebagai teman seperjuangan yang telah bersama-sama melalui proses bimbingan dan penyelesaian skripsi. Terima kasih atas dukungan, kerja sama, dan kebersamaan yang telah menjadi sumber motivasi yang tak ternilai.
15. Teman-teman seperjuangan kelas Biologi C 2020, khususnya Khodijah Khoirun Nisa, Datia Siti Nur Lisa, Zeranita Ageng Nur Anisa, dan Fanny Nuuranisa, yang telah memberikan motivasi, dukungan, dan kebersamaan selama perkuliahan.
16. Semua pihak yang tidak dapat disebutkan satu persatu yang telah memberikan bantuan, dukungan, dan kontribusi dalam penyelesaian skripsi ini.

PENGARUH NANOKRISTAL JAHE MERAH TERHADAP SITOTOKSISITAS SERTA EKSPRESI GEN *NFKB* DAN *CASP3* PADA LINI SEL MCF-7

ABSTRAK

Kanker payudara adalah penyebab utama kematian pada wanita dengan jumlah kasus tinggi di seluruh dunia, termasuk di Indonesia. Aktivasi jalur molekuler, seperti *NFKB* dan *CASP3*, memainkan peran kunci dalam perkembangan kanker ini. Pengobatan konvensional kanker menghadapi tantangan, seperti resistensi obat dan efek samping. Jahe merah (*Zingiber officinale* var. *Rubrum*), khususnya senyawa 6-gingerol dan 6-shogaol, menunjukkan potensi antikanker. Pemanfaatan ekstrak rimpang jahe merah yang diformulasikan dalam bentuk nanokristal diharapkan dapat meningkatkan efektivitas terapi dengan memperbaiki kelarutan dan ketersediaan hayati. Penelitian ini dilakukan untuk mengetahui pengaruh nanokristal jahe merah (NKJM) terhadap sitotoksisitas serta ekspresi gen *NFKB* dan *CASP3* pada sel MCF-7. NKJM dibuat di PT Nanotech Herbal Indonesia dengan metode *top-down* menggunakan *High Energy Milling Machine* (*HEM-Ellipse 3 Dimension*). Sitotoksisitas MCF-7 dianalisis dengan metode WST-8, sedangkan ekspresi gen *NFKB* dan *CASP3* pada sel MCF-7 diukur menggunakan RT-qPCR. Data dianalisis menggunakan secara statistik menggunakan analisis varian (ANOVA) satu arah, kemudian dilanjutkan dengan *Dunnet T3 Post-Hoc Test* dan *Tukey HSD Post Hoc Test* ($P \leq 0,05$). Hasil penelitian menunjukkan bahwa NKJM secara signifikan meningkatkan efek toksik terhadap sel MCF-7 pada konsentrasi 400 µg/mL dengan nilai IC_{50} sebesar 353,34 µg/mL setelah pemberian NKJM selama 24 jam, menurunkan ekspresi gen *NFKB* pada konsentrasi 125 µg/mL, dan meningkatkan ekspresi gen *CASP3* pada konsentrasi 125 µg/mL pada sel MCF-7 dibandingkan dengan kontrol. Selain itu, ekspresi gen *NFKB* memiliki korelasi berbanding terbalik yang sangat kuat dengan ekspresi gen *CASP3* pada sel MCF-7. Dengan demikian, dapat disimpulkan bahwa NKJM berpotensi untuk digunakan sebagai agen terapi kanker payudara.

Kata Kunci: *CASP3*, MCF-7, Nanokristal, *NFKB*, Sitotoksisitas, *Zingiber officinale* var. *Rubrum*

EFFECT OF RED GINGER NANOCRYSTALS ON CYTOTOXICITY AND GENE EXPRESSION OF NFKB AND CASP3 IN MCF-7 CELL LINE

ABSTRACT

Breast cancer is the leading cause of death in women with a high number of cases worldwide, including in Indonesia. Activation of molecular pathways, such as NFKB and CASP3, plays a key role in the development of these cancers. Conventional treatments of cancer face challenges, such as drug resistance and side effects. Red ginger (Zingiber officinale var. Rubrum), particularly the compounds 6-gingerol and 6-shogaol, show anticancer potential. Utilization of red ginger rhizome extract formulated in nanocrystal form is expected to increase therapeutic effectiveness by improving solubility and bioavailability. This study was conducted to determine the effect of red ginger nanocrystals (NKJM) on cytotoxicity and gene expression of NFKB and CASP3 in MCF-7 cells. NKJM was made at PT Nanotech Herbal Indonesia by top-down method using High Energy Milling Machine (HEM-Ellipse 3 Dimension). MCF-7 cytotoxicity was analyzed by WST-8 method, while NFKB and CASP3 gene expression in MCF-7 cells was measured using RT-qPCR. Data were statistically analyzed using one-way analysis of variance (ANOVA), followed by Dunnet T3 Post-Hoc Test and Tukey HSD Post Hoc Test ($P \leq 0.05$). The results showed that NKJM significantly increased the toxic effect on MCF-7 cells at a concentration of 400 µg/mL with an IC_{50} value of 353.34 µg/mL after treatment of NKJM for 24 hours, decreased NFKB gene expression at a concentration of 125 µg/mL, and increased CASP3 gene expression at a concentration of 125 µg/mL in MCF-7 cells compared to the control. In addition, NFKB gene expression has a very strong inverse correlation with CASP3 gene expression in MCF-7 cells. Thus, it can be concluded that NKJM has the potential to be used as a potential therapeutic agent for breast cancer.

Keywords: *CASP3, MCF-7, Nanocrystals, NFKB, Cytotoxicity, Zingiber officinale var. Rubrum*

DAFTAR ISI

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DAFTAR LAMPIRAN

DAFTAR PUSTAKA

Ali, M., Wani, S. U. D., Salahuddin, M., Manjula, S. N., Mruthunjaya, K., Dey, T., ... & Singh, J. (2023). Recent advance of herbal medicines in cancer-a molecular approach. *Heliyon*, *9*(2). doi: https://doi.org/10.1016%2Fj.heliyon.2023.e13684

American Type Culture Collection. (n.d.). HTB-22. Diakses pada 10 Desember 2023, dari https://www.atcc.org/products/htb-22

Arnold, M., Morgan, E., Rumgay, H., Mafra, A., Singh, D., Laversanne, M., ... & Soerjomataram, I. (2022). Current and future burden of breast cancer: Global statistics for 2020 and 2040. *The Breast*, *66*, 15-23. doi: https://doi.org/10.1016/j.breast.2022.08.010

Arzanova, E., & Mayrovitz, H. N. (2022). *The Epidemiology of Breast Cancer*. Brisbane (AU): Exon Publications.

Ataollahi, M. R., Sharifi, J., Paknahad, M. R., & Paknahad, A. (2015). Breast cancer and associated factors: a review. *Journal of medicine and life*, *8*(Spec Iss 4), 6.

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. doi: https://doi.org/10.7150%2Fijms.3635

Bawadood, A. S., Al-Abbasi, F. A., Anwar, F., El-Halawany, A. M., & Al-Abd, A. M. (2020). 6-Shogaol suppresses the growth of breast cancer cells by inducing apoptosis and suppressing autophagy via targeting notch signaling pathway. *Biomedicine & Pharmacotherapy*, *128*, 110302. doi: https://doi.org/10.1016/j.biopha.2020.110302

Bohlouli, S., Jafarmadar Gharehbagh, F., Dalir Abdolahinia, E., Kouhsoltani, M., Ebrahimi, G., Roshangar, L., ... & Maleki Dizaj, S. (2021). Preparation, characterization, and evaluation of rutin nanocrystals as an anticancer agent against head and neck squamous cell carcinoma cell line. *Journal of Nanomaterials*, *2021*, 1-8. doi: https://doi.org/10.1155/2021/9980451

Cai, L., Qin, X., Xu, Z., Song, Y., Jiang, H., Wu, Y., ... & Chen, J. (2019). Comparison of cytotoxicity evaluation of anticancer drugs between real-time cell analysis and CCK-8 method. *ACS omega*, *4*(7), 12036-12042. doi: https://doi.org/10.1021%2Facsomega.9b01142

Camarillo, I. G., Xiao, F., Madhivanan, S., Salameh, T., Nichols, M., Reece, L. M., ... & Sundararajan, R. (2014). Low and high voltage electrochemotherapy for breast cancer: An in vitro model study. *Electroporation-Based Therapies for Cancer*, 55-102. doi: https://doi.org/10.1533/9781908818294.55

Cancer Research UK. (2023). *Choosing between breast conserving surgery (lumpectomy) or mastectomy*. Diakses melalui https://www.cancerresearchuk.org/about-cancer/breast-

cancer/treatment/surgery/lumpectomy-or-mastectomy#:~:text=Advantages%20of%20mastectomy,you%20won't%20need%20mammograms

Chakraborty, D., Bishayee, K., Ghosh, S., Biswas, R., Mandal, S. K., & Khuda-Bukhsh, A. R. (2012). [6]-Gingerol induces caspase 3 dependent apoptosis and autophagy in cancer cells: drug–DNA interaction and expression of certain signal genes in HeLa cells. *European journal of pharmacology*, *694*(1-3), 20-29. doi: https://doi.org/10.1016/j.ejphar.2012.08.001

Cohen, S. Y., Stoll, C. R., Anandarajah, A., Doering, M., & Colditz, G. A. (2023). Modifiable risk factors in women at high risk of breast cancer: a systematic review. *Breast Cancer Research*, *25*(1), 1-20. doi: https://doi.org/10.1186/s13058-023-01636-1

Collins, K. K., Liu, Y., Schootman, M., Aft, R., Yan, Y., Dean, G., ... & Jeffe, D. B. (2011). Effects of breast cancer surgery and surgical side effects on body image over time. *Breast cancer research and treatment*, *126*, 167-176. doi: https://doi.org/10.1007%2Fs10549-010-1077-7

Comșa, Ș., 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.

Debela, D. T., Muzazu, S. G., Heraro, K. D., Ndalama, M. T., Mesele, B. W., Haile, D. C., Kitui, S. K., & Manyazewal, T. (2021). New approaches and procedures for cancer treatment: Current perspectives. *SAGE open medicine*, *9*, 20503121211034366. doi: https://doi.org/10.1177/20503121211034366

Devanaboyina, M., Kaur, J., Whiteley, E., Lin, L., Einloth, K., Morand, S., ... & Nemunaitis, J. (2022). NF-κB signaling in tumor pathways focusing on breast and ovarian cancer. *Oncology reviews*, *16*, 10568. doi: https://doi.org/10.3389/or.2022.10568

Diantari, N. K., & Astuti, K. W. (2023). "Potensi Ekstrak Rimpang Jahe Merah (*Zingiber officinale* Rosc. var *rubrum*) Sebagai Nutraceutical". Dalam *Prosiding Workshop dan Seminar Nasional Farmasi* (Vol. 2, pp. 631-642).

DiDonato, J. A., Mercurio, F., & Karin, M. (2012). NF-κB and the link between inflammation and cancer. *Immunological reviews*, *246*(1), 379-400. doi: https://doi.org/10.1111/j.1600-065x.2012.01099.x

Dieci, M. V., Orvieto, E., Dominici, M., Conte, P., & Guarneri, V. (2014). Rare breast cancer subtypes: histological, molecular, and clinical peculiarities. *The oncologist*, *19*(8), 805-813. doi: https://doi.org/10.1634%2Ftheoncologist.2014-0108

Dou, H., Yu, P. Y., Liu, Y. Q., Zhu, Y., Li, F. C., Wang, Y. Y., ... & Xiao, M. (2023). Recent advances in caspase-3, breast cancer, and traditional Chinese

medicine: a review. *Journal of Chemotherapy*, 1-19. doi: https://doi.org/10.1080/1120009X.2023.2278014

Ekowati, H., Septiyaningsih, S., Harwoko, H., & Trisnowati, T. (2010). Anticancer Activity of Zingiber Officinale and Piper Retrofractum Extract Combination on Hela Cell Line. *Indonesian Journal of Plant Medicine*, *3*(2), 142065.

El-Rahman, A., Atef, A., El-Shafei, S. M. A., Elwan, H. A., & Alimova, F. K. (2017). Ginger essential oil in vitro inhibits cell growth and induces apoptosis in mcf-7 human breast adenocarcinoma cells. *Zagazig Journal of Agricultural Research*, *44*(6), 2673-2683. doi: https://dx.doi.org/10.21608/zjar.2017.51379

Fristiohady, A., & Agustina, I. (2020). Review Artikel: Apoptosis Pada Kanker Payudara. *Media Farmasi*, *16*(2), 130-140. doi: https://doi.org/10.32382/mf.v16i2.1561

Garcia-Molina, P., Garcia-Molina, F., Teruel-Puche, J. A., Rodriguez-Lopez, J. N., Garcia-Canovas, F., & Muñoz-Muñoz, J. L. (2022). The relationship between the IC50 values and the apparent inhibition constant in the study of inhibitors of tyrosinase diphenolase activity helps confirm the mechanism of inhibition. *Molecules*, *27*(10), 3141. doi: https://doi.org/10.3390%2Fmolecules27103141

Gautama, W. (2022). Breast cancer in indonesia in 2022: 30 years of marching in place. *Indonesian Journal of Cancer*, *16*(1), 1-2. doi: http://dx.doi.org/10.33371/ijoc.v16i1.920

Gavas, S., Quazi, S., & Karpiński, T. M. (2021). Nanoparticles for cancer therapy: current progress and challenges. *Nanoscale research letters*, *16*(1), 173. doi: https://doi.org/10.1186/s11671-021-03628-6

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: https://doi.org/10.3390/molecules15064324

Gigliobianco, M. R., Casadidio, C., Censi, R., & Di Martino, P. (2018). Nanocrystals of poorly soluble drugs: drug bioavailability and physicochemical stability. *Pharmaceutics*, *10*(3), 134. doi: https://doi.org/10.3390%2Fpharmaceutics10030134

Girsang, E., Lister, I. N. E., Ginting, C. N., Widowati, W., Arumwardana, S., Marthania, M., & Rizal, R. (2023). Chlorogenic acid in preventing and curing ultraviolet-induced damage in human skin fibroblast as an antiaging cell model. Pharmaciana, 13(2), 159. doi: https://doi.org/10.12928/pharmaciana.v13i2.24459

Goethals, A., & Rose, J. (2022). *Mastectomy*. Treasure Island (FL): StatPearls Publishing.

Goffin, V., Bogorad, R. L., & Touraine, P. (2010). Identification of gain-of-function variants of the human prolactin receptor. *Methods in enzymology* (Vol. 484, pp. 329-355). Academic Press. doi: https://doi.org/10.1016/B978-0-12-381298-8.00017-4

Gote, V., Nookala, A. R., Bolla, P. K., & Pal, D. (2021). Drug resistance in metastatic breast cancer: tumor targeted nanomedicine to the rescue. *International Journal of Molecular Sciences*, *22*(9), 4673. doi: https://doi.org/10.3390/ijms22094673

Guo, M., Qin, S., Wang, S., Sun, M., Yang, H., Wang, X., ... & Jin, Z. (2023). Herbal Medicine Nanocrystals: A Potential Novel Therapeutic Strategy. *Molecules*, *28*(17), 6370. doi: https://doi.org/10.3390%2Fmolecules28176370

Hanna, K., & Mayden, K. (2021). Chemotherapy treatment considerations in metastatic breast cancer. *Journal of the Advanced Practitioner in Oncology*, *12*(Suppl 2), 6. doi: https://doi.org/10.6004%2Fjadpro.2021.12.2.11

Hendra, R. J., Rusdi, R. A., & Misfadhila, S. (2022). Phytochemical and Traditional Uses of Red Ginger: A Review (Zingiber officinale var. rubrum). doi: https://doi.org/10.36349/easjpp.2022.v04i03.002

Herdiana, Y., Wathoni, N., Shamsuddin, S., & Muchtaridi, M. (2022). Cytotoxicity Enhancement in MCF-7 Breast Cancer Cells with Depolymerized Chitosan Delivery of α-Mangostin. *Polymers*, *14*(15), 3139. https://doi.org/10.3390/polym14153139

Herupradoto, E. B. A., Wungu, T. D. K., Wijaya, C. H., Sarassina, R. R. F., Hidayatik, N., Pertiwi, H., & Puspitasari, N. (2022). Differences effect of red and big white ginger extract as anti-inflammatory agents by In vitro. *Ecology, Environment and Conservation*, *28*(Suppl.), 79-84. doi: http://doi.org/10.53550/EEC.2022.v28i02s.013

Ibrahim, A. H., Hasan, H., & Pakaya, M. S. (2021). Skrining Fitokimia dan Uji Daya Hambat Ektrak Daun Jahe Merah (*Zingiber officinale* var. *rubrum*) Terhadap Bakteri *Staphylococcus Epidermidis* dan *Escherichia Coli*. *Indonesian Journal of Pharmaceutical Education*, *1*(2), 107-118. doi: http://dx.doi.org/10.37311/ijpe.v1i2.10547

Indriwati, I., Mariya, S., Andrianto, V., & Iskandriati, D. (2022). Apoptosis of Human Breast Cancer Cells (MCF-7) Induced by Psidium guajava Simplisia Extract. *Indonesian Journal of Primatology*, *1*(01), 33-41. doi: https://doi.org/10.29244/primatology.1.01.33-41

Jaedun, A. (2011). Metodologi penelitian eksperimen. *Fakultas Teknik UNY*, *12*. Diakses melalui https://staffnew.uny.ac.id/upload/131569339/pengabdian/metode-penelitian-eksperimen.pdf

Janssens, S., & Tschopp, J. (2006). Signals from within: the DNA-damage-induced NF-κB response. *Cell Death & Differentiation*, *13*(5), 773-784. doi: https://doi.org/10.1038/sj.cdd.4401843

Jiang, X., Wang, J., Chen, P., He, Z., Xu, J., Chen, Y., ... & Jiang, J. (2021). [6]-Paradol suppresses proliferation and metastases of pancreatic cancer by decreasing EGFR and inactivating PI3K/AKT signaling. *Cancer Cell International*, *21*(1), 420. doi: https://doi.org/10.1186%2Fs12935-021-02118-0

Junghanns, J. U. A., & Müller, R. H. (2008). Nanocrystal technology, drug delivery and clinical applications. *International journal of nanomedicine*, *3*(3), 295-310. doi: https://doi.org/10.2147%2Fijn.s595

Joshi, S. C., Khan, F. A., Pant, I., & Shukla, A. N. (2007). Role of radiotherapy in early breast cancer: an overview. *International journal of health sciences*, *1*(2), 259.

Kaczor-Kamińska, M., Kaszuba, K., Bilska-Wilkosz, A., Iciek, M., Wróbel, M., & Kamiński, K. (2024). Dimethyl Sulfoxide (DMSO) as a Potential Source of Interference in Research Related to Sulfur Metabolism—A Preliminary Study. *Antioxidants*, *13*(5), 582. doi: https://doi.org/10.3390%2Fantiox13050582

Kashyap, D., Pal, D., Sharma, R., Garg, V. K., Goel, N., Koundal, D., ... & Belay, A. (2022). Global increase in breast cancer incidence: risk factors and preventive measures. *BioMed research international*, *2022*. doi: https://doi.org/10.1155/2022/9605439

Khairul, W. M., Hashim, F., Mohammed, M., Shah, N. S., Johari, S. A., Rahamathullah, R., ... & Ma, N. L. (2021). Synthesis, Molecular Docking and Biological Activity Evaluation of Alkoxy Substituted Chalcone Derivatives: Potential Apoptosis Inducing Agent on MCF-7 Cells. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, *21*(13), 1738-1750. doi: http://dx.doi.org/10.3389/conf.fphar.2018.63.00123

Kim, H. W., Oh, D. H., Koh, J. T., & Lim, Y. C. (2015). Apoptotic Effects of 6-Gingerol in Human Breast Cancer Cells. *International Journal of Oral Biology*, *40*(4), 223-228. doi: https://doi.org/10.11620/IJOB.2015.40.4.223

Kumar, S. (2007). Caspase function in programmed cell death. *Cell Death & Differentiation*, *14*(1), 32-43. doi: https://doi.org/10.1038/sj.cdd.4402060

Kumar, M., Shanthi, N., Mahato, A. K., Soni, S., & Rajnikanth, P. S. (2019). Preparation of luliconazole nanocrystals loaded hydrogel for improvement of dissolution and antifungal activity. *Heliyon*, *5*(5). doi: https://doi.org/10.1016/j.heliyon.2019.e01688

Kumar, P., Mangla, B., Javed, S., Ahsan, W., Musyuni, P., Sivadasan, D., ... & Aggarwal, G. (2023). A review of nanomaterials from synthetic and natural

molecules for prospective breast cancer nanotherapy. *Frontiers in Pharmacology*, *14*, 1149554. doi: https://doi.org/10.3389/fphar.2023.1149554

Kusumaningtyas, A., N., Harahap, Y., Mun'im, A., & Supandi Supandi. (2022). Studi Pengaruh Iradiasi Gamma Terhadap Kadar Senyawa Bioaktif dan Aktivitas Antiinflamasi Jahe Merah (Zingiber officinale roscoe). *BIOEDUSCIENCE*, *6*(3), 294–303. https://doi.org/10.22236/jbes/6310688

Kwan, Y. P., Saito, T., Ibrahim, D., Al-Hassan, F. M. S., Ein Oon, C., Chen, Y., ... & Sasidharan, S. (2016). Evaluation of the cytotoxicity, cell-cycle arrest, and apoptotic induction by Euphorbia hirta in MCF-7 breast cancer cells. *Pharmaceutical biology*, *54*(7), 1223-1236. doi: https://doi.org/10.3109/13880209.2015.1064451

Lazaraviciute, G., & Chaturvedi, S. (2017). Mastectomy—A critical review. *Open Journal of Clinical Diagnostics*, *7*(2), 58-66. doi: https://doi.org/10.4236/ojcd.2017.72006

Liambo, I. S., Frisitiohady, A., Malaka, M. H., & Kendari, M. (2022). Review: Patofisiologi, epidemiologi, dan lini sel kanker payudara. *Pharmauho: Jurnal Farmasi, Sains, dan Kesehatan*, *8*(1), 17-22. doi: https://doi.org/10.33772/pharmauho.v8i1.13093

Lim, Y. X., Lim, Z. L., Ho, P. J., & Li, J. (2022). Breast cancer in Asia: incidence, mortality, early detection, mammography programs, and risk-based screening initiatives. *Cancers*, *14*(17), 4218. doi: https://doi.org/10.3390/cancers14174218

Lin, Y., Bai, L., Chen, W., & Xu, S. (2010). The NF-κB activation pathways, emerging molecular targets for cancer prevention and therapy. *Expert opinion on therapeutic targets*, *14*(1), 45-55. doi: https://doi.org/10.1517%2F14728220903431069

Lin, J., & Redies, C. (2012). Histological evidence: housekeeping genes beta-actin and GAPDH are of limited value for normalization of gene expression. *Development genes and evolution*, *222*, 369-376. doi: https://doi.org/10.1007/s00427-012-0420-x

Ling, H., Yang, H., Tan, S. H., Chui, W. K., & Chew, E. H. (2010). 6-Shogaol, an active constituent of ginger, inhibits breast cancer cell invasion by reducing matrix metalloproteinase-9 expression via blockade of nuclear factor-κB activation. *British journal of pharmacology*, *161*(8), 1763-1777. doi: https://doi.org/10.1111/j.1476-5381.2010.00991.x

Liu, T., Zhang, L., Joo, D., & Sun, S. C. (2017). NF-κB signaling in inflammation. *Signal transduction and targeted therapy*, *2*(1), 1-9. doi: https://doi.org/10.1038/sigtrans.2017.23

Liu, C. M., An, L., Wu, Z., Ouyang, A. J., Su, M., Shao, Z., ... & Jiang, Y. (2022). 6-Gingerol suppresses cell viability, migration and invasion via inhibiting

EMT, and inducing autophagy and ferroptosis in LPS-stimulated and LPS-unstimulated prostate cancer cells. *Oncology letters*, *23*(6), 1-11. doi: https://doi.org/10.3892/ol.2022.13307

Łukasiewicz, S., Czeczelewski, M., Forma, A., Baj, J., Sitarz, R., & Stanisławek, A. (2021). Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. *Cancers*, *13*(17), 4287. doi: https://doi.org/10.3390%2Fcancers13174287

Manatunga, D. C., de Silva, R. M., de Silva, K. N., Wijeratne, D. T., Malavige, G. N., & Williams, G. (2018). Fabrication of 6-gingerol, doxorubicin and alginate hydroxyapatite into a bio-compatible formulation: enhanced anti-proliferative effect on breast and liver cancer cells. *Chemistry Central Journal*, *12*, 1-13. doi: https://doi.org/10.1186/s13065-018-0482-6

Mandlekar, S., Yu, R., Tan, T. H., & Kong, A. N. T. (2000). Activation of caspase-3 and c-Jun NH2-terminal kinase-1 signaling pathways in tamoxifen-induced apoptosis of human breast cancer cells. *Cancer Research*, *60*(21), 5995-6000.

Marzanti, A., Aprianti, R. W., Mariya, S., Noviana, R., Rohaeti, E., & Suparto, I. H. (2023). Antioxidant, Cytotoxic, and Insulinotropic Activities of Several Leaves Extracts of Medicinal Plants. *Jurnal Kimia Sains dan Aplikasi*, *26*(1), 34-38. doi: https://doi.org/10.14710/jksa.26.1.34-38

McGrowder, D. A., Miller, F. G., Nwokocha, C. R., Anderson, M. S., Wilson-Clarke, C., Vaz, K., ... & Brown, J. (2020). Medicinal herbs used in traditional management of breast cancer: Mechanisms of action. *Medicines*, *7*(8), 47. doi: https://doi.org/10.3390%2Fmedicines7080047

Mirabelli, P., Coppola, L., & Salvatore, M. (2019). Cancer cell lines are useful model systems for medical research. *Cancers*, *11*(8), 1098. doi: https://doi.org/10.3390/cancers11081098

Mirza, R. M., Ahirrao, S. P., & Kshirsagar, S. J. (2017). A nanocrystal technology: to enhance solubility of poorly water soluble drugs. *Journal of Applied Pharmaceutical Research*, *5*(1), 01-13.

Mohammed, M. S. (2021). The molecular activity of gingerol on inhibits proliferation of breast cancer cell line (MCF7) through caspase activity. *Annals of the Romanian Society for Cell Biology*, 11095-11103. Diakses dari https://www.annalsofrscb.ro/index.php/journal/article/view/3889

Munadi, R. (2020). Analisis Komponen Kimia dan Uji Aktivitas Antioksidan Ekstrak Rimpang Jahe Merah (Zingiber officinale Rosc. Var Rubrum). *Cokroaminoto Journal of Chemical Science*, *2*(1), 1-6.

Negi, C. K., Gadara, D., Kohoutek, J., Bajard, L., Spacil, Z., & Blaha, L. (2023). Replacement flame-retardant 2-ethylhexyldiphenyl phosphate (EHDPP) disrupts hepatic lipidome: evidence from human 3D hepatospheroid cell

culture. *Environmental Science & Technology*, *57*(5), 2006-2018. doi: https://doi.org/10.1021%2Facs.est.2c03998

Nemati, F., & Janitermi, M. (2015). Cytotoxic effect of Zataria multiflora on breast cancer cell line (MCF-7) and normal fibroblast cells. *Cumhuriyet Üniversitesi Fen Edebiyat Fakültesi Fen Bilimleri Dergisi*, *36*(3), 1895-1904.

Nurdyansyah, F., & Widyastuti, D. A. (2022). *JAHE MERAH Senyawa Bioaktif, Manfaat, dan Metode Analisisnya*. Bandung: Penerbit Widina Bhakti Persada Bandung.

Nurhadi, B., Saputra, R. A., & Sukri, N. (2020). The role of encapsulant materials on the stability of bioactive compounds of red ginger (Zingiber officinale Roscoe. var. Rubrum) extract powder during storage. *Food Chemistry*, *333*, 127490. doi: https://doi.org/10.1016/j.foodchem.2020.127490

Nourazarian, A. R., Kangari, P., & Salmaninejad, A. (2014). Roles of oxidative stress in the development and progression of breast cancer. *Asian Pacific Journal of Cancer Prevention*, *15*(12), 4745-4751. doi: http://dx.doi.org/10.7314/APJCP.2014.15.12.4745

Onuki, R., Kawasaki, H., Baba, T., & Taira, K. (2003). Analysis of a mitochondrial apoptotic pathway using Bid-targeted ribozymes in human MCF7 cells in the absence of a caspase-3-dependent pathway. *Antisense and Nucleic Acid Drug Development*, *13*(2), 75-82. doi: https://doi.org/10.1089/108729003321629629

O'Donovan, N., Crown, J., Stunell, H., Hill, A. D., McDermott, E., O'Higgins, N., & Duffy, M. J. (2003). Caspase 3 in breast cancer. *Clinical Cancer Research*, *9*(2), 738-742.

Papageorgiou, S. N. (2022). On correlation coefficients and their interpretation. *Journal of orthodontics*, *49*(3), 359-361. doi: https://doi.org/10.1177%2F14653125221076142

Pavitra, E., Kancharla, J., Gupta, V. K., Prasad, K., Sung, J. Y., Kim, J., ... & Huh, Y. S. (2023). The role of NF-κB in breast cancer initiation, growth, metastasis, and resistance to chemotherapy. *Biomedicine & Pharmacotherapy*, *163*, 114822. doi: https://doi.org/10.1016/j.biopha.2023.114822

Phogat, N., Kohl, M., Uddin, I., & Jahan, A. (2018). Interaction of nanoparticles with biomolecules, protein, enzymes, and its applications. Dalam *Precision Medicine* (pp. 253-276). Academic Press. doi: https://doi.org/10.1016/B978-0-12-805364-5.00011-1

Pires, B. R., Mencalha, A. L., Ferreira, G. M., De Souza, W. F., Morgado-Díaz, J. A., Maia, A. M., ... & Abdelhay, E. S. (2017). NF-kappaB is involved in the regulation of EMT genes in breast cancer cells. *PloS one*, *12*(1), e0169622. doi: https://doi.org/10.1371%2Fjournal.pone.0169622

Polyak, K. (2011). Heterogeneity in breast cancer. *The Journal of clinical investigation*, *121*(10), 3786-3788. doi: https://doi.org/10.1172%2FJCI60534

Poobalan, K., Lim, V., Kamal, N. N. S. N. M., Yusoff, N. A., Khor, K. Z., & Samad, N. A. (2018). Effects of ultrasound assisted sequential extraction (UASE) of Moringa oleifera leaves extract on MCF 7 human breast cell line. *Malaysian Journal of Medicine & Health Sciences*, *14*.

Poortmans, P. (2013). Optimal approach in early breast cancer: radiation therapy. *European Journal of Cancer Supplements*, *11*(2), 27-36. doi: https://doi.org/10.1016/j.ejcsup.2013.07.028

Poyraz, F. S., Colpan, R. D., Derman, S., Mansuroglu, B., & Erdemir, A. (2023). Investigation of cellular and molecular mechanisms of caffeic acid phenethyl ester loaded nanoparticle systems in breast cancer cell lines. *Process Biochemistry*, *134*, 32-43. doi: https://doi.org/10.1016/j.procbio.2023.09.016

Prabandari, Y. S., Hartanti, W., Widiastuti, M., Witaningrum, R., Hutajulu, S. H., & Allsop, M. J. (2022). "Alas… my sickness becomes my family's burden": A nested qualitative study on the experience of advanced breast cancer patients across the disease trajectory in Indonesia. *The Breast*, *63*, 168-176. doi: https://doi.org/10.1016/j.breast.2022.04.001

Prasetyo, A., Sidharta, B. R., Hartini, Y. S., & Mursyanti, E. (2019). Toxicity of bioactive compound from endophytic fungi isolated from red ginger (Zingiber officinale var. rubrum) utilizing brine shrimp lethality assay. *Biogenesis: Jurnal Ilmiah Biologi*, *7*(1), 30-37. doi: https://doi.org/10.24252/bio.v7i1.6000

Pu, X., Storr, S. J., Zhang, Y., Rakha, E. A., Green, A. R., Ellis, I. O., & Martin, S. G. (2017). Caspase-3 and caspase-8 expression in breast cancer: caspase-3 is associated with survival. *Apoptosis*, *22*, 357-368. doi: https://doi.org/10.1007%2Fs10495-016-1323-5

Radhakrishnan, E. K., Bava, S. V., Narayanan, S. S., Nath, L. R., Thulasidasan, A. K. T., Soniya, E. V., & Anto, R. J. (2014). [6]-Gingerol induces caspase-dependent apoptosis and prevents PMA-induced proliferation in colon cancer cells by inhibiting MAPK/AP-1 signaling. *PloS one*, *9*(8), e104401. doi: https://doi.org/10.1371/journal.pone.0104401

Raheem, M. A., Rahim, M. A., Gul, I., Zhong, X., Xiao, C., Zhang, H., ... & Qin, P. (2023). Advances in nanoparticles-based approaches in cancer theranostics. *OpenNano*, 100152. doi: https://doi.org/10.1016/j.onano.2023.100152

Ratriantari, U., Suradi, S., & Probandari, A. (2019). "The Effect of Red Ginger Ethanol Extract on Blood MDA Level of White Male Wistar Strain Rats Induced with Cigarette Smoke". Dalam *Proceedings of the 1st Seminar and Workshop on Research Design, for Education, Social Science, Arts, and*

Humanities, SEWORD FRESSH 2019, April 27 2019, Surakarta, Central Java, Indonesia. doi: https://doi.org/10.4108/eai.27-4-2019.2286933

Riduan, R. J. (2015). Pengaruh pemberian ekstrak jahe merah terhadap gambaran histopatologi pankreas yang diinduksi aloksan. *Jurnal Majority*, *4*(8), 11-16.

Rivenbark, A. G., O'Connor, S. M., & Coleman, W. B. (2013). Molecular and cellular heterogeneity in breast cancer: challenges for personalized medicine. *The American journal of pathology*, *183*(4), 1113-1124. doi: https://doi.org/10.1016/j.ajpath.2013.08.002

Robi, F. S., & Setiowati, F. K. (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.

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

Ruan, W., & Lai, M. (2007). Actin, a reliable marker of internal control?. *Clinica chimica acta*, *385*(1-2), 1-5. doi: https://doi.org/10.1016/j.cca.2007.07.003

Sajedi, N., Homayoun, M., Mohammadi, F., & Soleimani, M. (2020). Myricetin exerts its apoptotic effects on MCF-7 breast cancer cells through evoking the BRCA1-GADD45 pathway. *Asian Pacific Journal of Cancer Prevention: APJCP*, *21*(12), 3461. doi: https://doi.org/10.31557%2FAPJCP.2020.21.12.3461

Sarmoko, S., Solihati, I., Setyono, J., Ekowati, H., & Fadlan, A. (2020). Zingiber Officinale Var. Rubrum extract increases the cytotoxic activity of 5-fluorouracil in colon adenocarcinoma widr cells. *Indonesian Journal of Pharmacy*, 266-272. doi: https://doi.org/10.22146/ijp.859

Schieber, M., & Chandel, N. S. (2014). ROS function in redox signaling and oxidative stress. *Current biology*, *24*(10), R453-R462. doi: https://doi.org/10.1016%2Fj.cub.2014.03.034

Semwal, R. B., Semwal, D. K., Combrinck, S., & Viljoen, A. M. (2015). Gingerols and shogaols: Important nutraceutical principles from ginger. *Phytochemistry*, *117*, 554-568. doi: https://doi.org/10.1016/j.phytochem.2015.07.012

Shang, C., & Xu, D. (2022). Epidemiology of Breast Cancer. *Oncologie (Tech Science Press)*, *24*(4). doi: https://doi.org/10.32604/oncologie.2022.027640

Shanmugam, K. R., Shanmugam, B., Venkatasubbaiah, G., Ravi, S., & Reddy, K. S. (2022). Recent Updates on the Bioactive Compounds of Ginger (Zingiber officinale) on Cancer: A Study with Special Emphasis of Gingerol and Its

Anticancer Potential: Effect of Ginger and Its Compounds in Cancer Subjects. Dalam *Handbook of Oxidative Stress in Cancer: Therapeutic Aspects* (pp. 1-18). Singapore: Springer Nature Singapore. doi: https://doi.org/10.1007/978-981-16-5422-0_188

Sharim, M., & Shamsiah, A. (2021). Detection of changes in growth, yield and genetic variation using RAPD markers among M1V2 and M1V3 generations of irradiated ginger (*Zingiber officinale* Roscoe). *Food Research*, *5*(4), 74-82. doi: https://doi.org/10.26656/fr.2017.5(S4).009

Shostak, K., & Chariot, A. (2011). NF-κB, stem cells and breast cancer: the links get stronger. *Breast Cancer Research*, *13*(4), 1-7. doi: https://doi.org/10.1186/bcr2886

Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. *CA: a cancer journal for clinicians*, *73*(1), 17-48. doi: https://doi.org/10.3322/caac.21763

Smolarz, B., Nowak, A. Z., & Romanowicz, H. (2022). Breast cancer—epidemiology, classification, pathogenesis and treatment (review of literature). *Cancers*, *14*(10), 2569. doi: https://doi.org/10.3390/cancers14102569

Sholikhati, A., Kurnia, S. D., & Farikhah, L. (2023, January). Senyawa Fitokimia dan Aktivitas Farmakologis pada Jahe Merah (*Zingiber officinale* var. *Rubrum*). Dalam *Prosiding University Research Colloquium* (pp. 82-94).

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), 4660. doi: https://doi.org/10.3390%2Fijms22094660

Staudt, L. M. (2010). Oncogenic activation of NF-κB. *Cold Spring Harbor perspectives in biology*, *2*(6), a000109. doi: https://doi.org/10.1101%2Fcshperspect.a000109

Suciyati, S. W., & Adnyana, I. K. (2017). Red ginger (Zingiber officinale roscoe var rubrum): A review. *Pharmacologyonline*, *2*(8), 60-65.

Sun, Y. S., Zhao, Z., Yang, Z. N., Xu, F., Lu, H. J., Zhu, Z. Y., ... & Zhu, H. P. (2017). Risk factors and preventions of breast cancer. *International journal of biological sciences*, *13*(11), 1387. doi: https://doi.org/10.7150%2Fijbs.21635

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 journal for clinicians*, *71*(3), 209-249. doi: https://doi.org/10.3322/caac.21660

Supu, R. D., Diantini, A., & Levita, J. (2018). Red ginger (Zingiber officinale var. rubrum): Its chemical constituents, pharmacological activities and safety. *Fitofarmaka Jurnal Ilmiah Farmasi*, *8*(1), 25-31. doi: https://doi.org/10.33751/jf.v8i1.1168

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.v12i6.18

Sutjiatmo, A. B., Widowati, W., Sumiati, I., Priestu, T., Arumwardana, S., Kusuma, H. S. W., & Azizah, A. M. Antioxidant and Anticancer Potential of Raja Bulu Banana Peel and Heart (Musa acuminata Colla (AAB group)) Ethanol Extracts in MCF-7 Cell Lines. *Majalah Obat Tradisional*, *26*(1), 49-58. doi: https://doi.org/10.22146/mot.55333

Tran, V., Kim, R., Maertens, M., Hartung, T., & Maertens, A. (2021). Similarities and differences in gene expression networks between the breast cancer cell line Michigan cancer foundation-7 and invasive human breast cancer tissues. *Frontiers in artificial intelligence*, *4*, 674370. doi: https://doi.org/10.3389/frai.2021.674370

Turashvili, G., & Brogi, E. (2017). Tumor heterogeneity in breast cancer. *Frontiers in medicine*, *4*, 227. doi: https://doi.org/10.3389%2Ffmed.2017.00227

Vantangoli, M. M., Madnick, S. J., Huse, S. M., Weston, P., & Boekelheide, K. (2015). MCF-7 human breast cancer cells form differentiated microtissues in scaffold-free hydrogels. *PloS one*, *10*(8), e0135426. doi: https://doi.org/10.1371%2Fjournal.pone.0135426

Vickers, P. J., Dickson, R. B., Shoemaker, R., & Cowan, K. H. (1988). A multidrug-resistant MCF-7 human breast cancer cell line which exhibits cross-resistance to antiestrogens and hormone-independent tumor growth in vivo. *Molecular Endocrinology*, *2*(10), 886-892. doi: https://doi.org/10.1210/mend-2-10-886

Viswanathan, P., Muralidaran, Y., & Ragavan, G. (2017). Challenges in oral drug delivery: a nano-based strategy to overcome. *Nanostructures for oral medicine* (pp. 173-201). Elsevier. doi: https://doi.org/10.1016/B978-0-323-47720-8.00008-0

Végran, F., Boidot, R., Oudin, C., Riedinger, J. M., Bonnetain, F., & Lizard-Nacol, S. (2006). Overexpression of caspase-3s splice variant in locally advanced breast carcinoma is associated with poor response to neoadjuvant chemotherapy. *Clinical cancer research*, *12*(19), 5794-5800. doi: https://doi.org/10.1158/1078-0432.ccr-06-0725

Wang, W., Nag, S. A., & Zhang, R. (2015). Targeting the NFκB signaling pathways for breast cancer prevention and therapy. *Current medicinal chemistry*, *22*(2), 264-289. doi: https://doi.org/10.2174%2F0929867321666141106124315

Wennstig, A. K. (2020). *Long-term side effects of radiotherapy in breast cancer: Studies in ischemic heart disease and lung cancer* (Doctoral dissertation, Umeå Universitet). Diakses melalui https://www.diva-portal.org/smash/get/diva2:1390646/FULLTEXT01.pdf

Widowati, W., Jasaputra, D. K., Onggowidjaja, P., Sumitro, S. B., Widodo, M. A., Afifah, E., ... & 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). doi: https://doi.org/10.5614/j.math.fund.sci.2019.51.3.1

Widowati, W., Tjokropranoto, R., Onggowidjaja, P., Kusuma, H. S. W., Wijayanti, C. R., Marthania, M., ... & 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

Xu, Q., Yu, J., Jia, G., Li, Z., & Xiong, H. (2022). Crocin attenuates NF-κB-mediated inflammation and proliferation in breast cancer cells by down-regulating PRKCQ. *Cytokine*, *154*, 155888. doi: https://doi.org/10.1016/j.cyto.2022.155888

Yamashita, K., Tagawa, R., Higami, Y., & Tokunaga, E. (2020). Noninvasive and safe cell viability assay for breast cancer MCF-7 cells using natural food pigment. *Biology*, *9*(8), 227. doi: https://doi.org/10.3390%2Fbiology9080227

Yang, X., Zhu, C., & Gu, Y. (2015). The prognosis of breast cancer patients after mastectomy and immediate breast reconstruction: a meta-analysis. *PLoS One*, *10*(5), e0125655. doi: https://doi.org/10.1371/journal.pone.0125655

Yang, X., Liu, Y., Zhao, Y., Han, M., Guo, Y., Kuang, H., & Wang, X. (2016). A stabilizer-free and organic solvent-free method to prejahe merah 10-hydroxycamptothecin nanocrystals: in vitro and in vivo evaluation. *International Journal of Nanomedicine*, 2979-2994. doi: https://doi.org/10.2147%2FIJN.S102726

Yeap, S. K., Ali, N. M., Akhtar, M. N., Razak, N. A., Chong, Z. X., Ho, W. Y., ... & Alitheen, N. B. (2021). Induction of apoptosis and regulation of microRNA expression by (2 E, 6 E)-2, 6-bis-(4-hydroxy-3-methoxybenzylidene)-cyclohexanone (BHMC) treatment on MCF-7 breast cancer cells. *Molecules*, *26*(5), 1277. doi: https://doi.org/10.3390/molecules26051277

Yenurkar, D., Nayak, M., & Mukherjee, S. (2023). Recent advances of nanocrystals in cancer theranostics. *Nanoscale Advances*. doi: https://doi.org/10.1039%2Fd3na00397c

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*. doi: https://doi.org/10.1155%2F2013%2F302426

Yücel, Ç., Karatoprak, G. Ş., Açıkara, Ö. B., Akkol, E. K., Barak, T. H., Sobarzo-Sánchez, E., ... & Shirooie, S. (2022). Immunomodulatory and anti-inflammatory therapeutic potential of gingerols and their nanoformulations. *Frontiers in pharmacology*, *13*, 902551. doi: https://doi.org/10.3389%2Ffphar.2022.902551

Yudissanta, A., & Ratna, M. (2012). Analisis pemakaian kemoterapi pada kasus kanker payudara dengan menggunakan metode regresi logistik multinomial (studi kasus pasien di rumah sakit "x" surabaya). *Jurnal Sains dan seni its*, *1*(1), D112-D117.

Zhang, M., Zhao, R., Wang, D., Wang, L., Zhang, Q., Wei, S., ... & Wu, C. (2021). Ginger (Zingiber officinale Rosc.) and its bioactive components are potential resources for health beneficial agents. *Phytotherapy Research*, *35*(2), 711-742. doi: https://doi.org/10.1002/ptr.6858

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), 775. doi: https://doi.org/10.3390%2Fmolecules27030775

Zhang, Y., & Jimenez, J. J. (2023). Mild oxidative stress protects against chemotherapy-induced hair loss. *Frontiers in Oncology*, *12*, 1078916. doi: https://doi.org/10.3389/fonc.2022.1078916

Zinatizadeh, M. R., Schock, B., Chalbatani, G. M., Zarandi, P. K., Jalali, S. A., & Miri, S. R. (2021). The Nuclear Factor Kappa B (NF-kB) signaling in cancer development and immune diseases. *Genes & diseases*, *8*(3), 287-297. doi: https://doi.org/10.1016%2Fj.gendis.2020.06.005

Zubair, M., Wang, S., & Ali, N. (2021). Advanced approaches to breast cancer classification and diagnosis. *Frontiers in Pharmacology*, *11*, 632079. doi: https://doi.org/10.3389/fphar.2020.632079