UNIVERSITAS
GADJAH MADA
**Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts**
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

DAFTAR PUSTAKA

Aalaa, M., Malazy, O. T., Sanjari, M., Peimani, M., & Mohajeri-Tehrani, M. (2012). Nurses' role in diabetic foot prevention and care: A review. *Journal of Diabetes & Metabolic Disorders*, *11*(1), 24. https://doi.org/10.1186/2251-6581-11-24

Akkol, E. K., Süntar, I., Keleş, H., Sezik, E., & Gürler, G. (2015). Bioassay-guided isolation and characterization of wound healer compounds from morus nigra l. (moraceae). *Records of Natural Products*, *9*(4), 484–495.

Alavi, A., Sibbald, R. G., Mayer, D., Goodman, L., Botros, M., Armstrong, D. G., Woo, K., Boeni, T., Ayello, E. A., & Kirsner, R. S. (2014). Diabetic foot ulcers: Part I. Pathophysiology and prevention. In *Journal of the American Academy of Dermatology* (Vol. 70, Issue 1). https://doi.org/10.1016/j.jaad.2013.06.055

Alexandru, V., Gaspar, A., Toma, A., & Tatia, R. (2015). Phenolic content, antioxidant activity and effect on collagen synthesis of a traditional wound healing polyherbal formula. *Studia Universitatis "Vasile Goldis" Seria Stiintele Vietii*, *25*(September), 41–46. https://www.researchgate.net/profile/Valentina_Alexandru/publication/281645225_Phenolic_content_antioxidant_activity_and_effect_on_collagen_synthesis_of_a_traditional_wound_healing_polyherbal_formula/links/55f2979d08ae0af8ee1f8f8e/Phenolic-content-antioxi

Alshammari, M., Duff, J., & Guilhermino, M. (2019). Barriers to nurse-patient communication in Saudi Arabia: An integrative review. *BMC Nursing*, *18*(1), 1–10. https://doi.org/10.1186/s12912-019-0385-4

Anastasi, J. K., Chang, M., & Capili, B. (2011). Herbal supplements: Talking with your patients. *Journal for Nurse Practitioners*, *7*(1), 29–35. https://doi.org/10.1016/j.nurpra.2010.06.004

Anugrahwati, M., Purwaningsih, T., Rustina, Manggalarini, J. A., Alnavis, N. B., Wulandari, D. N., & Pranowo, H. D. (2016). Extraction of ethanolic extract of red betel leaves and its cytotoxicity test on HeLa cells. *Procedia Engineering*, *148*, 1402–1407. https://doi.org/10.1016/j.proeng.2016.06.569

Arfian, N., Ananda, W., Setyaningsih, W., Romi, M. M., Cahyani, D., & Sari, R. (2019). Heparanase upregulation from adipocyte associates with inflammation and endothelial injury in diabetic condition. *BMC Proceedings*, *13*(Suppl 11), 1–8. https://doi.org/10.1186/s12919-019-0181-x

Astuti, P., Wahyono, & Nababan, O. A. (2014). Antimicrobial and cytotoxic activities of endophytic fungi isolated from Piper crocatum Ruiz & Pav. *Asian Pacific Journal of Tropical Biomedicine*, *4*(Suppl 2), S592–S596. https://doi.org/10.12980/APJTB.4.2014APJTB-2014-0073

Ayuk, S. M., Abrahamse, H., & Houreld, N. N. (2016). The role of matrix metalloproteinases in diabetic wound healing in relation to photobiomodulation. In *Journal of Diabetes Research* (Vol. 2016). https://doi.org/10.1155/2016/2897656

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Backer, C. H and Brink, V. B. (1965). Flora of Java. In *Wolters Mood Hoff N. V* (2nd ed.). Groningen, Netherlands. https://doi.org/10.1017/CBO9781107415324.004

Bainbridge, P. (2013). Wound healing and the role of fibroblasts. *Journal of Wound Care*, *22*(8), 407–412. https://doi.org/10.12968/jowc.2013.22.8.407

Baltzis, D., Eleftheriadou, I., & Veves, A. (2014a). Pathogenesis and treatment of impaired wound healing in Diabetes Mellitus: New insights. In *Advances in Therapy* (Vol. 31, Issue 8, pp. 817–836). https://doi.org/10.1007/s12325-014-0140-x

Baltzis, D., Eleftheriadou, L., & Veves, A. (2014b). Pathogenesis and treatment of impaired wound healing in Diabetes Mellitus: New insights. *Advances in Therapy*, *31*(2014), pages817–836. https://link.springer.com/article/10.1007/s12325-014-0140-x

Barabutis, N., Schally, A. V., & Siejka, A. (2018). P53, GHRH, inflammation and cancer. *EBioMedicine*, *37*, 557–562. https://doi.org/10.1016/j.ebiom.2018.10.034

Berlanga-acosta, J., Schultz, G. S., López-mola, E., Guillen-nieto, G., García-siverio, M., & Herrera-martínez, L. (2013). Glucose toxic effects on granulation tissue productive cells: The diabetics' impaired healing. *BioMed Research International*, *2013*. https://doi.org/10.1155/2013/256043

Beyeler, J., Schnyder, I., Katsaros, C., & Chiquet, M. (2014). Accelerated wound closure in vitro by fibroblasts from a subgroup of cleft lip/palate patients: Role of transforming growth factor-α. *PLoS ONE*, *9*(10), 1–15. https://doi.org/10.1371/journal.pone.0111752

Bhan, S., Mitra, R., Arya, A. K., Pandey, H. P., & Tripathi, K. (2013). A study on evaluation of apoptosis and expression of Bcl-2-related marker in wound healing of streptozotocin-induced diabetic rats. *ISRN Dermatology*, *2013*, 1–6. https://doi.org/10.1155/2013/739054

Blackburn, J., Ousey, K., & Stephenson, J. (2019). Nurses' education, confidence, and competence in appropriate dressing choice. *Advances in Skin and Wound Care*, *32*(10), 470–476. https://doi.org/10.1097/01.ASW.0000577132.81124.88

Botusan, I. R., Sunkari, V. G., Savu, O., Catrina, A. I., Grünler, J., Lindberg, S., Pereira, T., Ylä-Herttuala, S., Poellinger, L., Brismar, K., & Catrina, S.-B. (2008). Stabilization of HIF-1alpha is critical to improve wound healing in diabetic mice. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(49), 19426–19431. https://doi.org/10.1073/pnas.0805230105

Brem, H., & Tomic-Canic, M. (2007). Cellular and molecular basis of wound healing in diabetes. *The Journal of Clinical Investigation*, *117*(5), 1219–1222. https://doi.org/10.1172/JCI32169

Bryer-Ash, M. (2009). *100 questions & answers diabetes*. Jones and Bartlett Publishers.

Buranasin, P., Mizutani, K., Iwasaki, K., Na, C. P., Kido, D., Takeda, K., & Izumi, Y. (2018). High glucose-induced oxidative stress impairs proliferation and migration of human gingival fibroblasts. *PLoS ONE*, *25862043*, 1–19. https://doi.org/10.1371/journal.pone.0201855 August

Caley, M. P., Martins, V. L. C., & O'Toole, E. A. (2015). Metalloproteinases and wound healing. *Advances in Wound Care*, *4*(4), 225–234.

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

https://doi.org/10.1089/wound.2014.0581

Casqueiro, J., Casqueiro, J., & Alves, C. (2012). Infections in patients with diabetes mellitus: A review of pathogenesis. *Indian Journal of Endocrinology and Metabolism*, *16*, S27-36. https://doi.org/10.4103/2230-8210.94253

Cavanagh, P., Attinger, C., Abbas, Z., Bal, A., Rojas, N., & Xu, Z.-R. (2012). Cost of treating diabetic foot ulcers in five different countries. *Diabetes/Metabolism Research and Reviews*, *28*(Suppl 1), 107–111. https://doi.org/10.1002/dmrr

Chan, S. M., Khoo, K. S., & Sit, N. W. (2015). Interactions between plant extracts and cell viability indicators during cytotoxicity testing: implications for ethnopharmacological studies. *Tropical Journal of Pharmaceutical Research*, *14*(November), 1991–1998. https://doi.org/10.4314/tjpr.v14i11.6

Chang, C.-D., Phillips, P., Lipson, K. E., Crisfalos, V. J., & Baserga, R. (1991). Senescent human fibroblasts have a post-transcriptional block in the expression of the proliferating cell nuclear antigen gene. *The Journal of Biological Chemistry*, *266*(40), 8663–8666.

Chatterjee, S., & Davies, M. J. (2015). Current management of diabetes mellitus and future directions in care. *Postgraduate Medical Journal*, *91*(1081), 612–621. https://doi.org/10.1136/postgradmedj-2014-133200

Chaurasia, S. S., Kaur, H., de Medeiros, F. W., Smith, S. D., & Wilson, S. E. (2009). Dynamics of the expression of intermediate filaments vimentin and desmin during myofibroblast differentiation after corneal injury. *Experimental Eye Research*, *89*(2), 133–139. https://doi.org/10.1016/j.exer.2009.02.022

Chawla, A., Chawla, R., & Jaggi, S. (2016). Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian Journal of Endocrinology and Metabolism*, *20*(4), 546. https://doi.org/10.4103/2230-8210.183480

Chen, C., Yang, S., Zhang, M., Zhang, Z., Zhang, B., Han, D., Ma, J., Wang, X., Hong, J., Guo, Y., & Zhang, L. (2013). In vitro Sirius Red collagen assay measures the pattern shift from soluble to deposited collagen. *XXXIVOxgen Transport to Tissue*, 47–53. https://link.springer.com/chapter/10.1007/978-1-4614-4989-8_7

Chen, K. C., Peng, C. C., Peng, C. H., Hsieh, C. L., & Peng, R. Y. (2011). The aqueous soluble polyphenolic fraction of Psidium guajava leaves exhibits potent anti-angiogenesis and anti-migration actions on DU145 cells. *Evidence-Based Complementary and Alternative Medicine*, *2011*. https://doi.org/10.1093/ecam/neq005

Chen, L., Tuo, B., & Dong, H. (2016). Regulation of intestinal glucose absorption by ion channels and transporters. In *Nutrients* (Vol. 8, Issue 1). https://doi.org/10.3390/nu8010043

Cheng, K., Lin, Z., Cheng, Y., Chiu, H., Yeh, N.-L., Wu, T.-K., & Wu, J.-S. (2018). Wound healing in streptozotocin- induced diabetic rats using atmospheric-pressure argon plasma jet. *Scientific Reports*, *8*(July), 1–15. https://doi.org/10.1038/s41598-018-30597-1

Churgin, S. S., Callaghan, M., Galiano, R., Blechman, K., Ceradini, D., & Gurtner, G. (2005). Therapeutic administration of superoxide healing in diabetic mice. *Journal of the American College of Surgeons*, *201*(3).

UNIVERSITAS GADJAH MADA
Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Clayton, W., & Elasy, T. A. (2009). A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients. *Clinical Diabetes*, *27*(2), 52–58. https://doi.org/10.2337/diaclin.27.2.52

Cohen, D. J., Gloerich, M., & Nelson, W. J. (2016). Epithelial self-healing is recapitulated by a 3D biomimetic E-cadherin junction. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(51), 14698–14703. https://doi.org/10.1073/pnas.1612208113

Corbett, L. Q., & Ennis, W. J. (2014). What do patients want? patient preference in wound care. *Advances in Wound Care*, *3*(8), 537–543. https://doi.org/10.1089/wound.2013.0458

Cotran, R., Kumar, V., Robbins, S., Abbas, A. K., Aster, J. C., & Aster, J. C. (2015). Robbins and Cotran pathologic basis of disease. In *Philadelphia, PA: Saunders, Ipswich, MA* (9th ed.). Elsevier Ltd.

Crawford, M., & Dagnino, L. (2018). Cadherins as central modulators of wound repair. *Wound Healing: Stem Cells Repair and Restorations, Basic and Clinical Aspects*, 15–30. https://doi.org/10.1002/9781119282518.ch2

Damir, A. (2011). Why diabetic foot ulcers do not heal? *Journal International Medical Sciences Academy*, *24*(4), 205–206.

Darby, I. A., Laverdet, B., Bonté, F., & Desmoulière, A. (2014). Fibroblasts and myofibroblasts in wound healing. *Clinical, Cosmetic and Investigational Dermatology*, *7*, 301–311. https://doi.org/10.2147/CCID.S50046

Demaria, M., Ohtani, N., Youssef, S. A., Rodier, F., Toussaint, W., Mitchell, J. R., Laberge, R. M., Vijg, J., VanSteeg, H., Dollé, M. E. T., Hoeijmakers, J. H. J., deBruin, A., Hara, E., & Campisi, J. (2014). An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. In *Developmental Cell* (Vol. 31, Issue 6, pp. 722–733). https://doi.org/10.1016/j.devcel.2014.11.012

Deng, L., Du, C., Song, P., Chen, T., Rui, S., Armstrong, D. G., & Deng, W. (2021). Molecular mechanisms of dietary bioactive compounds in redox balance and metabolic disorders. *Oxidative Medicine and Cellular Longevity*, *2021*(Figure 1), 1–11.

Deursen, J. M. Van, & van Deursen, J. M. (2014). The role of senescent cells in aging. *Nature*, *509*(7501), 439–446. https://doi.org/10.1038/nature13193

Dewi, D., Chairinnisa, E., Sujuti, H., Lirawati, D., & Hernowati, T. (2018). αSMA expression increased over cell passages and decreased by exogenous TGF-β1, in vitro studies on myofibroblast derived from orbital socket contracture. *Journal of Tropical Life Science*, *8*(2), 200–205. https://doi.org/10.11594/jtls.08.02.15

Dewi, Y. F., Anthara, M. S., & Dharmayudha, A. A. G. O. (2014). Effectiveness of red betel leaf extracts (Piper on blood glucose level decreased white male rats (Rattus novergicus) induced alloxan. *Buletin Veteriner Udayana*, *6*(2). https://ocs.unud.ac.id/index.php/buletinvet/article/view/8899/6693

Dhawan, D., & Gupta, J. (2016). Comparison of different solvents for phytochemical extraction potential from Datura metel plant leaves. *International Journal of Biological Chemistry*, *11*(1), 17–22. https://doi.org/10.3923/ijbc.2017.17.22

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Doughty, D. B. (2008). Levin and O'Neal's the diabetic foot. In *Levin and O'Neal's The Diabetic Foot*. https://doi.org/10.1016/B978-0-323-04145-4.50034-X

Duarte, S., Kato, H., Ho, M., Busuttil, R., & Coito, A. (2013). *TIMP-1 deficiency promotes p53 pathway and impairs hepatocyte proliferation in liver ischemi*. American Transplant Congress. https://atcmeetingabstracts.com/abstract/timp-1-deficiency-promotes-p53-pathway-and-impairs-hepatocyte-proliferation-in-liver-ischemia-reperfusion-injury/

Dunnill, C., Patton, T., Brennan, J., Barrett, J., Dryden, M., Cooke, J., Leaper, D., & Georgopoulos, N. T. (2017). Reactive oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. *International Wound Journal*, *14*(1), 89–96. https://doi.org/10.1111/iwj.12557

Eming, S. A., Martin, P., & Tomic-Canic, M. (2014). Wound repair and regeneration: Mechanisms, signaling, and translation. In *Science Translational Medicine* (Vol. 6, Issue 265). https://doi.org/10.1126/scitranslmed.3009337

Emrizal, Fernando, A., Yuliandari, R., Rullah, K., Indrayani, N. R., Susanty, A., Yerti, R., Ahmad, F., Sirat, H. M., & Arbain, D. (2014). Cytotoxic activities of fractions and two isolated compounds from sirih merah (Indonesian red betel), Piper crocatum Ruiz & Pav. *Procedia Chemistry*, *13*, 79–84. https://doi.org/10.1016/j.proche.2014.12.009

Enriquez-Ochoa, D., Robles-Ovalle, P., Mayolo-Deloisa, K., & Brunck, M. E. G. (2020). Immobilization of growth factors for cell therapy manufacturing. *Frontiers in Bioengineering and Biotechnology*, *8*(June), 1–20. https://doi.org/10.3389/fbioe.2020.00620

Eruygur, N., Yilmaz, G., Kutsal, O., Yücel, G., & Üstün, O. (2016). Bioassay-guided isolation of wound healing active compounds from Echium species growing in Turkey. *Journal of Ethnopharmacology*, *185*, 370–376. https://doi.org/10.1016/j.jep.2016.02.045

Fatmawaty, Anggreni, N. G. M., Fadhil, N., & Prasasty, V. D. (2019). Potential in vitro and in vivo antioxidant activities from Piper crocatum and Persea americana leaf extracts. *Biomedical and Pharmacology Journal*, *12*(2), 661–667. https://doi.org/10.13005/bpj/1686

Fithriyah, N., Arifin, S., & Santi, E. (2013). Lumatan daun sirih merah (Piper crocatum) terhadap lama penyembuhan luka bakar derajat II pada kulit kelinci (Cavia cobaya). *DK*, *01*(01), 24–31. https://ppjp.ulm.ac.id/journal/index.php/JDK/article/view/1650

Fitriyani, A., Winarti, L., Muslichah, S., & Nuri, N. (2011). Anti-inflammatory activity of Piper crocatum Ruiz & Pav. leaves methanolic extract in rats. *Traditional Medicine Journal*, *16*(1), 34–42. https://doi.org/10.22146/tradmedj.8020

Flores, I., & Blasco, M. A. (2009). A p53-dependent response limits epidermal stem cell functionality and organismal size in mice with short telomeres. *PLoS ONE*, *4*(3). https://doi.org/10.1371/journal.pone.0004934

Foresman, E. L., & Miller, F. J. (2013). Extracellular but not cytosolic superoxide dismutase protects against oxidant-mediated endothelial dysfunction. *Redox Biology*, *1*(1), 292–296. https://doi.org/10.1016/j.redox.2013.04.003

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Foster, D. S., Jones, R. E., Ransom, R. C., Longaker, M. T., & Norton, J. A. (2018). The evolving relationship of wound healing and tumor stroma. *JCI Insight*, *3*(18), 1–17. https://doi.org/10.1172/jci.insight.99911

Frykberg, R. G., & Banks, J. (2015). Challenges in the treatment of chronic wounds. *Advances in Wound Care*, *4*(9), 560–582. https://doi.org/10.1089/wound.2015.0635

Fujiwara, T., Duscher, D., Rustad, K. C., Kosajaru, R., Rodrigues, M., Whittam, A. J., Januszyk, M., Maan, Z. N., & Gurtner, G. C. (2016). Extracellular superoxide dismutase deficiency impairs wound healing in advanced age by reducing neovascularization and fibroblast function. *Exp Dermatol*, *25*(3), 206–211. https://doi.org/10.1111/exd.12909.Extracellular

Galkowska, H., Olszewski, W. L., Wojewodzka, U., Mijal, J., & Filipiuk, E. (2003). Expression of apoptosis-and cell cycle-related proteins in epidermis of venous leg and diabetic foot ulcers. *Surgery*, *134*(2), 213–220. https://doi.org/10.1067/msy.2003.223

Gaol, Y. E. L., Erly, E., & Sy, E. (2017). Pola resistensi bakteri aerob pada ulkus diabetik terhadap beberapa antibiotika di laboratorium mikrobiologi RSUP Dr. M. Djamil Padang tahun 2011 - 2013. *Jurnal Kesehatan Andalas*, *6*(1), 164. https://doi.org/10.25077/jka.v6i1.664

Gasca-lozano, L. E., Lucano-landeros, S., Ruiz-mercado, H., Salazar-montes, A., Sandoval-rodríguez, A., Garcia-bañuelos, J., Santos-garcia, A., Davila-rodriguez, J. R., Navarro-partida, J., Bojórquez-sepúlveda, H., Castañeda-gomez, J., Domínguez-rosales, J., Ruiz-arcos, M. A., Sánchez-parada, M. G., & Armendariz-borunda, J. (2017). Pirfenidone accelerates wound healing in chronic diabetic foot ulcers: a randomized, double-blind controlled trial. *Journal of Diabetes Research*, *2017*. https://doi.org/10.1155/2017/3159798

Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. In *Circulation Research* (Vol. 107, Issue 9, pp. 1058–1070). https://doi.org/10.1161/CIRCRESAHA.110.223545

Gill, S. E., & Parks, W. C. (2008). Metalloproteinases and their inhibitors: Regulators of wound healing. In *International Journal of Biochemistry and Cell Biology* (Vol. 40, Issues 6–7, pp. 1334–1347). https://doi.org/10.1016/j.biocel.2007.10.024

Ginting, C. N., Lister, I. N. E., Girsang, E., Widowati, W., Yusepany, D. T., Azizah, A. M., & Kusuma, H. S. W. (2021). Hepatotoxicity prevention in Acetaminophen-induced HepG2 cells by red betel (Piper crocatum Ruiz and Pav) extract from Indonesia via antioxidant, anti-inflammatory, and anti-necrotic. *Heliyon*, *7*(1). https://doi.org/10.1016/j.heliyon.2020.e05620

Gould, L., & Li, W. W. (2019). Defining complete wound closure: closing the gap in clinical trials and practice. *Wound Repair and Regeneration*, *27*(3), 201–224. https://doi.org/10.1111/wrr.12707

Goulding, V. (2015). The effects of diabetes on collagen within wound healing. *The Diabetic Foot Journal*, *18*(2), 75–80.

Gu, Y., Mohammad, I. S., & Liu, Z. (2020). Overview of the STAT-3 signaling pathway in cancer and the development of specific inhibitors (Review). *Oncology Letters*, *19*(4),

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

2585–2594. https://doi.org/10.3892/ol.2020.11394

Gumel, A. M., Razaif-Mazinah, M. R. M., Anis, S. N. S., & Annuar, M. S. M. (2015). Poly (3-hydroxyalkanoates)-co-(6-hydroxyhexanoate) hydrogel promotes angiogenesis and collagen deposition during cutaneous wound healing in rats. *Biomedical Materials*, *10*(4). https://iopscience.iop.org/article/10.1088/1748-6041/10/4/045001/meta

Guo, S., & Dipietro, L. A. (2010). Factors affecting wound healing. *Journal of Dental Research*, *89*(3), 219–229. https://doi.org/10.1177/0022034509359125

Han, Y. P., Tuan, T. L., Wu, H., Hughes, M., & Garner, W. L. (2001). TNF-alpha stimulates activation of pro-MMP2 in human skin through NF-(kappa)B mediated induction of MT1-MMP. *Journal of Cell Science*, *114*(Pt 1), 131–139. https://doi.org/10.1016/j.bbi.2008.05.010

Harding, K. G., Moore, K., & Phillips, T. J. (2005). Wound chronicity and fibroblast senescence--implications for treatment. *International Wound Journal*, *2*(4), 364–368. https://doi.org/10.1111/j.1742-4801.2005.00149.x

Hartini, Y. S., Widyarini, S., & Nugroho, L. H. (2018). The comparison of two neolignans isolated from red betel leaf and its extract against macrophage phagocytic activity, the level of AST, and histopathological features of the liver in mice. *Oriental Pharmacy and Experimental Medicine*, *18*(4), 325–333. https://doi.org/10.1007/s13596-018-0326-x

Helgason, C. D., Miller, C. L., & Helgason, C. D. (2005). *Basil cell culture protocols* (3rd ed., Vol. 290). Humana Press.

Hendryani, R., Lutfi, M., & Hawa, L. C. (2015). Antioxidant extraction from dried red Betel Leaf (Piper crotatum) using Ultrasonic Assisted Extraction as pre-treatment (study comparative of solvent and extraction time). *Jurnal Bioproses Komoditas Tropis*, *3*(2), 33–38. https://www.jbkt.ub.ac.id/index.php/jbkt/article/view/178/162

Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. W. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. *The New England Journal of Medicine*, *359*(15), 1577–1589. https://doi.org/10.1056/NEJMoa0806470

Holt, T., & Kumar, S. (2010). *ABC of diabetes* (6th ed.). Wiley-Publishing.

Houreld, N. N., Ayuk, S. M., & Abrahamse, H. (2018). Cell adhesion molecules are mediated by photobiomodulation at 660 nm in diabetic wounded fibroblast cells. *Cells*, *7*(13), 1–17. https://doi.org/10.3390/cells7040030

Huang, X., Meng, B., Iqbal, J., Ding, B. B., Perry, A. M., Cao, W., Smith, L. M., Bi, C., Jiang, C., Greiner, T. C., Weisenburger, D. D., Rimsza, L., Rosenwald, A., Ott, G., Delabie, J., Campo, E., Braziel, R. M., Gascoyne, R. D., Cook, J. R., … Fu, K. (2013). Activation of the STAT3 signaling pathway is associated with poor survival in diffuse large B-cell lymphoma treated with R-CHOP. *Journal of Clinical Oncology*, *31*(36). https://doi.org/10.1200/JCO.2012.45.6004

Huma, K., Mehboob, K., Rashid, A., & Majeed, A. (2021). A comparative analysis of superoxide dismutase 1 level in diabetics with and without neuropathy. *Journal of the College of Physicians and Surgeons Pakistan 2021*, *31*(07), 765–769.

Hunter, M. V., Lee, D. M., Harris, T. J. C., & Fernandez-Gonzalez, R. (2015). Polarized E-

UNIVERSITAS GADJAH MADA
Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

cadherin endocytosis directs actomyosin remodeling during embryonic wound repair. *Journal of Cell Biology*, *210*(5), 801–816. https://doi.org/10.1083/jcb.201501076

International Best Practice. (2014). Best practice guidelines: Wound management. *Wounds International*, *5*(2), 27.

Iraj, B., Khorvash, F., Ebneshahidi, A., & Askari, G. (2013). Prevention of diabetic foot ulcer. *International Journal of Preventive Medicine*, *4*(3), 373–376.

Jelinek, H. F., Osman, W. M., Khandoker, A. H., Khalaf, K., Lee, S., Almahmeed, W., & Alsafar, H. S. (2017). Clinical profiles, comorbidities and complications of type 2 diabetes mellitus in patients from United Arab Emirates. *BMJ Open Diabetes Research & Care*, *5*(1), e000427. https://doi.org/10.1136/bmjdrc-2017-000427

Jeon, B. J., Choi, H. J., Kang, J. S., Tak, M. S., & Park, E. S. (2017). Comparison of five systems of classification of diabetic foot ulcers and predictive factors for amputation. *International Wound Journal*, *14*(3), 537–545. https://doi.org/10.1111/iwj.12642

Jiang, D., de Vries, J. C., Muschhammer, J., Schatz, S., Ye, H., Hein, T., Fidan, M., Romanov, V. S., Rinkevich, Y., & Scharffetter-Kochanek, K. (2020). Local and transient inhibition of p21 expression ameliorates age-related delayed wound healing. *Wound Repair and Regeneration*, *28*(1), 49–60. https://doi.org/10.1111/wrr.12763

Jiang, Y., Zhang, G., Yan, D., Yang, H., Ye, Z., & Ma, T. (2017). Bioactivity-guided fractionation of the traditional Chinese medicine Resina draconis reveals loureirin B as a PAI-1 inhibitor. *Evidence-Based Complementary and Alternative Medicine*, *2017*, 1–8. https://doi.org/10.1155/2017/9425963

Joshi, M. S., Williams, D., Horlock, D., Samarasinghe, T., Andrews, K. L., Jefferis, A.-M., Berger, P. J., Chin-Dusting, J. P., & Kaye, D. M. (2015). Role of mitochondrial dysfunction in hyperglycaemia-induced coronary microvascular dysfunction: Protective role of resveratrol. *Diabetes and Vascular Disease Research*, 1–9. https://doi.org/10.1177/1479164114565629

Juliantina, F., Citra, D. A., Nirwani, B., Nurmasitoh, T., Bowo, E. T., & Gnhjk. (2008). Bakteri gram positif dan gram negatif. *Jurnal Kedokteran Dan Kesehatan Indonesia*, *10*, 10.

Junker, J. P. E., Kamel, R. A., Caterson, E. J., & Eriksson, E. (2013). Clinical impact upon wound healing and inflammation in moist, wet, and dry environments. *Advances in Wound Care*, *2*(7), 348–356. https://doi.org/10.1089/wound.2012.0412

Kakudo, N., Minakata, T., Mitsui, T., Kushida, S., Notodihardjo, F. Z., & Kusumoto, K. (2008). Proliferation-promoting effect of platelet-rich plasma on human adipose-derived stem cells and human dermal fibroblasts. *Plastic and Reconstructive Surgery*, *122*(5), 1352–1360. https://doi.org/10.1097/PRS.0b013e3181882046

Kaur, S., Pandhi, P., & Dutta, P. (2011). Painful diabetic neuropathy: An update. *Annals of Neurosciences*, *18*(4), 168–175. https://doi.org/10.5214/ans.0972.7531.1118409

Kavitha, K. V. (2014). Choice of wound care in diabetic foot ulcer: A practical approach. *World Journal of Diabetes*, *5*(4), 546. https://doi.org/10.4239/wjd.v5.i4.546

Kelly, A. (2020). *Endocrinology and metabolism clinics of North America*. Elsevier. https://doi.org/10.1016/S0889-8529(20)30051-7

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Kendran, A. A. S., Gelgel, K. T. P., Pertiwi, N. W. L., Anthara, M. S., Dharmayuda, A. A. G. O., & Anggreni, L. D. (2013). Toxicity of red betel extract in diabetic white red. *Jurnal Veteriner*, *14*(4), 527–533.

Keshri, G. K., Gupta, A., Yadav, A., Sharma, S. K., & Singh, S. B. (2016). Photobiomodulation with pulsed and continuous wave near-infrared laser (810 nm, Al-Ga-As) augments dermal wound healing in immunosuppressed rats. *PLoS ONE*, *11*(11), 1–21. https://doi.org/10.1371/journal.pone.0166705

Khanna, S., Biswas, S., Shang, Y., Collard, E., Azad, A., Kauh, C., Bhasker, V., Gordillo, G. M., Sen, C. K., & Roy, S. (2010). Macrophage dysfunction impairs resolution of inflammation in the wounds of diabetic mice. *PLoS ONE*, *5*(3). https://doi.org/10.1371/journal.pone.0009539

Kim, H., Anggradita, L. D., Lee, S. J., Hur, S. S., Bae, J., Hwang, N. S. Y., Nam, S. M., & Hwang, Y. (2021). Ameliorating fibrotic phenotypes of keloid dermal fibroblasts through an epidermal growth factor-mediated extracellular matrix remodeling. *International Journal of Molecular Sciences*, *22*(4), 1–17. https://doi.org/10.3390/ijms22042198

Kim, I. Y., Yong, H. Y., Kang, K. W., & Moon, A. (2009). Overexpression of ErbB2 induces invasion of MCF10A human breast epithelial cells via MMP-9. *Cancer Letters*, *275*(2), 227–233. https://doi.org/10.1016/j.canlet.2008.10.013

Ko, K. S., Arora, P. D., Bhide, V., Chen, A., & McCulloch, C. A. G. (2001). Cell-cell adhesion in human fibroblasts requires calcium signaling. *Journal of Cell Science*, *114*(6), 1155–1167. https://doi.org/10.1242/jcs.114.6.1155

Kumar, S., & Pandey, A. K. (2013). Chemistry and biological activities of flavonoids: an overview. *The Scientific World Journal*, *2013*, 1–16. https://doi.org/10.1155/2013/162750

Kurahashi, T., & Fujii, J. (2015). Roles of antioxidative enzymes in wound healing. *Journal of Developmental Biology*, *3*, 57–70. https://doi.org/10.3390/jdb3020057

Kusuma, S., Mita, S., & Mutiara, A. (2017). Antimicrobial lotion containing red Piper betle leaf (Piper crocatum Ruiz and Pav) ethanolic extract for topical application. *National Journal of Physiology, Pharmacy and Pharmacology*, *8*(1), 1. https://doi.org/10.5455/njppp.2018.8.1042115112017

Kuwahara, M., Hatoko, M., Tada, H., & Tanaka, A. (2001). E-cadherin expression in wound healing of mouse skin. *Journal of Cutaneous Pathology*, *28*, 191–199. https://doi.org/10.1034/j.1600-0560.2001.028004191.x

Laksmitawati, D. R., Widyastuti, A., Karami, N., Afifah, E., Rihibiha, D. D., Nufus, H. H., & Widowati, W. (2017). Anti-inflammatory effects of Anredera cordifolia and piper crocatum extracts on lipopolysaccharide-stimulated macrophage cell line. *Bangladesh Journal of Pharmacology*, *12*(1), 35–40. https://doi.org/10.3329/bjp.v12i1.28714

Landén, N. X., Li, D., & Ståhle, M. (2016). Transition from inflammation to proliferation: a critical step during wound healing. In *Cellular and Molecular Life Sciences* (Vol. 73, Issue 20, pp. 3861–3885). https://doi.org/10.1007/s00018-016-2268-0

Lee, Y. J., Cho, H. N., Soh, J. W., Jhon, G. J., Cho, C. K., Chung, H. Y., Bae, S., Lee, S. J., & Lee, Y. S. (2003). Oxidative stress-induced apoptosis is mediated by ERK1/2

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

phosphorylation. *Experimental Cell Research*, *291*(1), 251–266. https://doi.org/10.1016/S0014-4827(03)00391-4

Li, H. X., Widowati, W., Azis, R., Yangg, S. Y., Kim, Y. H., & Li, W. (2019). Chemical constituents of the Piper crocatum leaves and their chemotaxonomic significance. *Biochemical Systematics and Ecology*, *86*(March), 103905. https://doi.org/10.1016/j.bse.2019.05.013

Li, J., Chou, H., Li, L., Li, H., & Cui, Z. (2020). Wound healing activity of neferine in experimental diabetic rats through the inhibition of inflammatory cytokines and nrf-2 pathway. *Artificial Cells, Nanomedicine, and Biotechnology*, *48*(1), 96–106. https://doi.org/10.1080/21691401.2019.1699814

Li, M. O., Wan, Y. Y., Sanjabi, S., Robertson, A.-K. L., & Flavell, R. a. (2006). Transforming growth factor-beta regulation of immune responses. *Annual Review of Immunology*, *24*, 99–146. https://doi.org/10.1146/annurev.immunol.24.021605.090737

Li, Z., Guo, S., Yao, F., Zhang, Y., & Li, T. (2013). Increased ratio of serum matrix metalloproteinase-9 against TIMP-1 predicts poor wound healing in diabetic foot ulcers. *Journal of Diabetes and Its Complications*, *27*(4), 380–382. https://doi.org/10.1016/j.jdiacomp.2012.12.007

Liang, G., Ding, M., Lu, H., Cao, N., Niu, Y., Gao, Y., & Lu, J. (2015). Metformin upregulates E-cadherin and inhibits B16F10 cell motility, invasion and migration. *Oncology Letters*, *10*(3), 1527–1532. https://doi.org/10.3892/ol.2015.3475

Lister, I. N. E., Ginting, C. N., Girsang, E., Nataya, E. D., Azizah, A. M., & Widowati, W. (2020). Hepatoprotective properties of red betel (Piper crocatum Ruiz and Pav) leaves extract towards H2O2-induced HepG2 cells via anti-inflammatory, antinecrotic, antioxidant potency. *Saudi Pharmaceutical Journal*, *28*(10), 1182–1189. https://doi.org/10.1016/j.jsps.2020.08.007

Lodhi, S., & Singhai, A. K. (2013). Wound healing effect of flavonoid rich fraction and luteolin isolated from Martynia annua Linn. on streptozotocin induced diabetic rats. *Asian Pacific Journal of Tropical Medicine*, *6*(4), 253–259. https://doi.org/10.1016/S1995-7645(13)60053-X

Lodovici, M., Bigagli, E., Luceri, C., Mannucci, E., Rotella, C. M., & Raimondi, L. (2015). Gender-related drug effect on several markers of oxidation stress in diabetes patients with and without complications. *European Journal of Pharmacology*, *766*(2015), 86–90. https://doi.org/10.1016/j.ejphar.2015.09.041

Luis Herrera, Y. M.-M. (2013). Histological and transcriptional expression differences between diabetic foot and pressure ulcers. *Journal of Diabetes & Metabolism*, *04*(8). https://doi.org/10.4172/2155-6156.1000296

Maître, J. L., & Heisenberg, C. P. (2013). Three functions of cadherins in cell adhesion. *Current Biology*, *23*(14), 626–633. https://doi.org/10.1016/j.cub.2013.06.019

Malini, D. M., Madinah, M., Kamilawati, F., Ratningsih, N., Alipin, K., & Iskandar, J. (2017). Topical treatment of ointment containing ethanol extract of Archidendron pauciflorum fruit peel on the wound healing in streptozotocin-induced diabetic mice. *Nusantara Bioscience*, *9*(3), 306–311. https://doi.org/10.13057/nusbiosci/n090311

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Malviya, N., Col-, S., & Malviya, S. (2017). Bioassay guided fractionation-an emerging technique influence the isolation, identification and characterization of lead phytomolecules. *International Journal of Hospital Pharmacy (IJHP) Review IJHP*, *11*(15), 1–6.

Martinelli-Kläy, C. P., Lunardi, L. O., Martinelli, C. R., Lombardi, T., Soares, E. G., & Martinelli, C. (2014). Modulation of MCP-1, TGF-B1, and A-SMA expressions in granulation tissue of cutaneous wounds treated with local vitamin B complex: An experimental study. *Dermatopathology*, *1*(2), 98–107. https://doi.org/10.1159/000369163

Matsuyoshi, N., & Imamura, S. (1997). Multiple cadherins are expressed in human fibroblasts. *Biochemical and Biophysical Research Communications*, *235*(2), 355–358. https://doi.org/10.1006/bbrc.1997.6707

Matthijs Blankesteijn, W. (2015). Has the search for a marker of activated fibroblasts finally come to an end? *Journal of Molecular and Cellular Cardiology*, *88*, 120–123. https://doi.org/10.1016/j.yjmcc.2015.10.005

McCaffrey, R., & Reinoso, H. (2016). Transformational leadership. *Jouyrnal of Holistic Nursing*, *XX*(X), 1–8. https://doi.org/10.1177/0898010116685242

McCormack, J. P., Allan, G. M., & Virani, A. S. (2011). Is bigger better? An argument for very low starting doses. *Cmaj*, *183*(1), 65–69. https://doi.org/10.1503/cmaj.091481

McCulloch, David, M. (2015). Clinical presentation and diagnosis of diabetes mellitus in adults. *UptoDate*, 1–14.

Mensah, A. Y., Sampson, J., Houghton, P. J., Hylands, P. J., Westbrook, J., Dunn, M., Hughes, M. A., & Cherry, G. W. (2001). Effects of Buddleja globosa leaf and its constituents relevant to wound healing. *Journal of Ethnopharmacology*. https://doi.org/10.1016/S0378-8741(01)00297-5

Mercut, R., Clurea, M., Mărgăritescu, C., Popescu, S., Crăitoiu, M., Cotoi, O., & Voinescu, D. (2014). Expression of p53, D2-40 and α-smooth muscle actin in different histological subtypes of facial basal cell carcinoma. *Romanian Journal of Morphology and Embryology = Revue Roumaine de Morphologie et Embryologie.*, *55*(2), 263-272. http://europepmc.org/article/med/24969973

Mirza, R., & Koh, T. J. (2011). Dysregulation of monocyte/macrophage phenotype in wounds of diabetic mice. *Cytokine*, *56*(2), 256–264. https://doi.org/10.1016/j.cyto.2011.06.016

Mohammed, S. I., Mikhael, E. M., Ahmed, F. T., Al-Tukmagi, H. F., & Jasim, A. L. (2016). Risk factors for occurrence and recurrence of diabetic foot ulcers among Iraqi diabetic patients. *Diabetic Foot and Ankle*, *7*(May 2017). https://doi.org/10.3402/dfa.v7.29605

Muhammad, A. A., Pauzi, N. A. S., Arulselvan, P., Abas, F., & Fakurazi, S. (2013). In vitro wound healing potential and identification of bioactive compounds from Moringa oleifera Lam. *BioMed Research International*. https://doi.org/10.1155/2013/974580

Mulia, K., Hasan, A. E. Z., & Suryani. (2016). Total phenolic , anticancer and antioxidant activity of ethanol extract of Piper retrofractum Vahl from Pamekasan and Karang Asem. *Current Biochemistry*, *3*(2), 80–90. https://jurnal.ipb.ac.id/index.php/cbj/article/view/18239

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Muralidhar, A., & Babu, K. (2013). Wound healing activity of flavonoid fraction isolated from the stem bark of Butea monosperma (Lam) in albino wistar rats. In *European Journal of Experimental Biology* (Vol. 3, Issue 6, pp. 1–6).

Murini, T., Wahyuningsih, M. S. H., Satoto, T. B. T., Fudholi, A., & Hanafi, M. (2018). Isolation and identification of naturally occurring larvicidal compound isolated from zingiber zerumbet (L).J.E. smith. *Asian Journal of Pharmaceutical and Clinical Research*, *11*(2), 189–193. https://doi.org/10.22159/ajpcr.2018.v11i2.21703

Murphy, P. S., & Evans, G. R. D. (2012). Advances in wound healing: A review of current wound healing products. *Plastic Surgery International*, *2012*, 1–8. https://doi.org/10.1155/2012/190436

Nagori, B. P., & Solanki, R. (2011). Role of medicinal plants in wound healing. In *Research Journal of Medicinal Plant* (Vol. 5, Issue 4, pp. 392–405). https://doi.org/10.3923/rjmp.2011.392.405

Naibaho, O. H., Yamlean, P. V. Y., & Wiyono, W. (2013). Pengaruh basis salep terhadap formulasi sediaan salep ekstrak daun kemangi (Ocimum sanctum L.) pada kulit punggung kelinci yang dibuat infeksi Staphylococcus aureus. *Jurnal Ilmiah Farmasi-UNSRAT*, *2*(02), 27–34.

Narauskaitė, D., Vydmantaitė, G., Rusteikaitė, J., Sampath, R., Rudaitytė, A., Stašytė, G., Aparicio Calvente, M. I., & Jekabsone, A. (2021). Extracellular vesicles in skin wound healing. *Pharmaceuticals*, *14*(8), 811. https://doi.org/10.3390/ph14080811

Nasi, L. S., Kairupan, C. F., & Lintong, P. M. (2015). Efek daun sirih merah (Piper Crocatum) terhadap kadar gula darah dan gambaran morfologi endokrin pankreas tikus wistar (Rattus Novergicus). *Jurnal E-Biomedik (EBm)*, *3*(3), 821–826. https://ejournal.unsrat.ac.id/index.php/ebiomedik/article/view/10151/9737

Nathan, D. M., Cleary, P. A., Backlund, J.-Y. C., Genuth, S. M., Lachin, J. M., Orchard, T. J., Raskin, P., & Zinman, B. (2005). Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *The New England Journal of Medicine*, *353*(25), 2643–2653. https://doi.org/10.1056/NEJMoa052187

Nathan, D. M., & Wolfsdorf, J. I. (2016). Classification of diabetes mellitus and genetic diabetic syndromes. *UpToDate*, *2*, 24. https://doi.org/http://www.uptodate.com/contents/classification-of-diabetes-mellitus-and-genetic-diabetic-syndromes

Nguyen, P. D., Tutela, J. P., Thanik, V. D., Knobel, D., Allen, R. J., Chang, C. C., Levine, J. P., Warren, S. M., & Saadeh, P. B. (2010). Improved diabetic wound healing through topical silencing of p53 is associated with augmented vasculogenic mediators. *Wound Repair and Regeneration*, *18*(6), 553–559. https://doi.org/10.1111/j.1524-475X.2010.00638.x

Noor, S., Zubair, M., & Ahmad, J. (2015). Diabetic foot ulcer - A review on pathophysiology, classification and microbial etiology. In *Diabetes and Metabolic Syndrome: Clinical Research and Reviews* (Vol. 9, Issue 3, pp. 192–199). https://doi.org/10.1016/j.dsx.2015.04.007

Olczyk, P., Mencner, Ł., & Komosinska-Vassev, K. (2014). The role of the extracellular matrix

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

components in cutaneous wound healing. In *BioMed Research International* (Vol. 2014). https://doi.org/10.1155/2014/747584

Orasanu, G., & Plutzky, J. (2009). The pathologic continuum of diabetic vascular disease. In *Journal of the American College of Cardiology* (Vol. 53, Issue 5 SUPPL.). https://doi.org/10.1016/j.jacc.2008.09.055

Ozaki, T., & Nakagawara, A. (2011). Role of p53 in cell death and human cancers. *Cancers*, *3*(1), 994–1013. https://doi.org/10.3390/cancers3010994

Ozougwu, J., Obimba, K., Belonwu, C., & Unakalamba, C. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *Journal of Physiology and Pathophysiology*, *4*(4), 46–57. https://doi.org/10.5897/JPAP2013.0001

Palmer, A. K., Tchkonia, T., LeBrasseur, N. K., Chini, E. N., Xu, M., & Kirkland, J. L. (2015). Cellular senescence in type 2 diabetes: A therapeutic opportunity. *Diabetes*, *64*(7), 2289–2298. https://doi.org/10.2337/db14-1820

Paloma, E., Ovidio, C., Jessica, R., Francisca, S. A., Isabel, M., & Maravillas, G. (2014). Phytotherapy management: a new intervention for Nursing Intervention Classification. *Holistic Nursing Practice*, *28*(6), 381–385. https://doi.org/10.1097/HNP.0000000000000053

Pan, S. C., Li, C. Y., Kuo, C. Y., Kuo, Y. Z., Fang, W. Y., Huang, Y. H., Hsieh, T. C., Kao, H. Y., Kuo, Y., Kang, Y. R., Tsai, W. C., Tsai, S. T., & Wu, L. W. (2018). The p53-S100A2 positive feedback loop negatively regulates epithelialization in cutaneous wound healing. *Scientific Reports*, *8*(1), 1–12. https://doi.org/10.1038/s41598-018-23697-5

Pang, L., Wang, Y., Zheng, M., Wang, Q., Lin, H., Zhang, L., & Wu, L. (2016). Transcriptomic study of high-glucose effects on human skin fibroblast cells. *Molecular Medicine Reports*, *2016*, 2627–2634. https://doi.org/10.3892/mmr.2016.4822

Pang, Y., Wang, D., Hu, X., Wang, H., Fu, W., Fan, Z., Chen, X., & Yu, F. (2014). Effect of volatile oil from Blumea Balsamifera (L.) DC. leaves on wound healing in mice. *Journal of Traditional Chinese Medicine*, *34*(6), 716–724.

Papathanasiou, I. V, & Kourkouta, L. (2013). Holistic nursing care: theories and perspectives. *American Journal of Nursing Science*, *2*(1), 1. https://doi.org/10.11648/j.ajns.20130201.11

Park, J. H., Elpers, C., Reunert, J., McCormick, M. L., Mohr, J., Biskup, S., Schwartz, O., Rust, S., Grüneberg, M., Seelhöfer, A., Schara, U., Boltshauser, E., Spitz, D. R., & Marquardt, T. (2019). SOD1 deficiency: A novel syndrome distinct from amyotrophic lateral sclerosis. *Brain*, *142*(8), 2230–2237. https://doi.org/10.1093/brain/awz182

Patrick E Simon. (2014). *Skin Wound Healing: Overview, Hemostasis, Inflammatory Phase* (pp. 1–8).

Permadi, T., Widjiastuti, I., & Setyabudi. (2016). Biocompatibility of Red Betel Leaf extract (Piper crocatum) and 0,2 Chlorhexidine Gluconat toward BHK-21 fibroblast. *Conservative Dentistry Journal*, *4*(1), 6–11. https://www.researchgate.net/profile/Ira_Widjiastuti3/publication/311843495_Biocompatibility_of_Red_Betel_Leaf_extract_Piper_crocatum_and_02_Chlorhexidine_Gluconat_

UNIVERSITAS GADJAH MADA
**Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts**
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

toward_BHK-21_Fibroblast_Cell/links/585cc56908aebf17d386b558/Biocompatibility-of-Red-Betel-

Peteva, R. (2016). A cross section of nursing research: Journal articles for discussion and evaluation. In *A Cross Section of Nursing Research: Journal Articles for Discussion and Evaluation* (6th ed.). Roudledge. https://doi.org/10.4324/9781315266862

Pradhan, L., Cai, X., Wu, S., Andersen, N. D., Martin, M., Malek, J., Guthrie, P., Veves, A., & Logerfo, F. W. (2011). Gene expression of pro-inflammatory cytokines and neuropeptides in diabetic wound healing. *Journal of Surgical Research*, *167*(2), 336–342. https://doi.org/10.1016/j.jss.2009.09.012

Prayitno, S. A., Kusnadi, J. K., & Murtini, E. S. (2018). Karakteristik (total flavonoid, total fenol, aktivitas antioksidan) ekstrak serbuk daun sirih merah (Piper crocatum Ruiz & Pav.). *Foodscitech*, *1*(2), 26. https://doi.org/10.25139/fst.v1i2.1355

Puspita, P. J., Safithri, M., & Sugiharti, N. P. (2019). Antibacterial activities of sirih merah (Piper crocatum) leaf extracts. *Current Biochemistry*, *5*(3), 1–10. http://biokimia.ipb.ac.id

Putra, A., Alif, I., Hamra, N., Santosa, O., Kustiyah, A., Muhar, A., & Lukman, K. (2020). MSC-released TGF-β regulate αSMA expression of myofibroblast during wound healing. *Journal Stem Cells and Regenerative Medicine*, *16*(2), 73–79. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7772809/pdf/jsrm_16_73.pdf

Qu, J., Cheng, T., Shi, C., Lin, Y., & Ran, X. (2004). A study on the activity of fibroblast cells in connection with tissue recovery in the wounds of skin injury after whole-body irradiation. *J Radiat Res (Tokyo)*, *45*(2), 341–344. https://doi.org/JST.JSTAGE/jrr/45.341 [pii]

Rafehi, H., El-Osta, A., & Karagiannis, T. C. (2012). Epigenetic mechanisms in the pathogenesis of diabetic foot ulcers. *Journal of Diabetes and Its Complications*, *26*(6), 554–561. https://doi.org/10.1016/j.jdiacomp.2012.05.015

Reinke, J. M., & Sorg, H. (2012). Wound repair and regeneration. *European Surgical Research*, *49*(1), 35–43. https://doi.org/10.1159/000339613

Rinanda, T., Zulfitri, & Alga, D. M. (2012). Antibacterial activity of red betel (Piper crocatum) leaf methanolic extracts aginst methicillin resistant Staphylococcus aureus. In Z. A. Muchlisin, Darmawi, & Supardan (Eds.), *Proceedings of The 2nd Annual International Conference Syiah Kuala University 2012 & The 8th IMT-GT Uninet Biosciences Conference* (Vol. 2, Issue 1, pp. 22–24). Universitas Syah Kuala. http://www.jurnal.unsyiah.ac.id/AICS-SciEng/article/view/1781/1678

Rizzi, E. S., Dourado, D. M., Matias, R., Muller, J. A. I., Guilhermino, J. F., Guerrero, A. T. G., Moreira, D. L., Silva, B. A. K., & Barbosa-Ferreira, M. (2017). Potencial cicatrizante da pomada de Sebastiania hispida (mart.) pax (euphorbiaceae) comparado ao laser de baixa potência. *Brazilian Journal of Biology*, *77*(3), 480–489. https://doi.org/10.1590/1519-6984.16115

Rodrigues, M., Kosaric, N., Bonham, C. A., & Gurtner, G. C. (2019). Wound healing: A cellular perspective. *Physiological Reviews*, *99*(1), 665–706. https://doi.org/10.1152/physrev.00067.2017

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Sa, Y., Li, C., Li, H., & Guo, H. (2015). TIMP-1 induces α-smooth muscle actin in fibroblasts to promote urethral scar formation. *Cellular Physiology and Biochemistry*, *35*(6), 2233–2243. https://doi.org/10.1159/000374028

Safithri, M., & Fahma, F. (2008). Potency of Piper crocatum decoction as an antihiperglycemia in rat strain Sprague dawley. *Institut Pertanian Bogor*, *15*(1), 45–48. https://doi.org/10.4308/hjb.15.1.45

Sahoo, N., Manchikanti, P., & Dey, S. (2010). Herbal drugs: Standards and regulation. In *Fitoterapia* (Vol. 81, Issue 6, pp. 462–471). https://doi.org/10.1016/j.fitote.2010.02.001

Santos, C. G., Nascimento, M. F., Oliveira, C. R., Melo, G. C., Cardoso, J. C., Padilha, F. F., Lima, S. O., & Albuquerque-Junior, R. L. (2013). Bioassay-guided evaluation of wound healing effect of fatty acids-incorporated collagen-based films. *Acta Cir Bras*, *28*(5), 346–352. https://doi.org/10.1590/S0102-86502013000500005

Saputra, M. R., Yuniarti, E., & Sumarmin, R. (2018a). Pengaruh ekstrak daun sirih merah (Piper crocatum Ruiz & Pav.) terhadap glukosa darah mencit (Mus musculus L.) jantan yang diinduksi sukrosa. *EKSAKTA*, *19*(1). https://ocs.unud.ac.id/index.php/buletinvet/article/view/8899/6693

Saputra, M. R., Yuniarti, E., & Sumarmin, R. (2018b). Pengaruh ekstrak daun sirih merah (Piper Crocatum Ruiz & Pav.) terhadap glukosa darah mencit (Mus Musculus L.) jantan yang diinduksi sukrosa. *EKSAKTA*, *19*(1), 43–55. http://eksakta.ppj.unp.ac.id/index.php/eksakta/article/view/124

Scanlon, V. M., Teixeira, A. M., Tyagi, T., Zou, S., Zhang, P. X., Booth, C. J., Kowalska, M. A., Bao, J., Hwa, J., Hayes, V., Marks, M. S., Poncz, M., & Krause, D. S. (2019). Epithelial (E)-cadherin is a novel mediator of platelet aggregation and clot stability. *Thrombosis and Haemostasis*, *119*(5), 744–757. https://doi.org/10.1055/s-0039-1679908

Schreml, S., Szeimies, R.-M., Prantl, L., Landthaler, M., & Babilas, P. (2010). Wound healing in the 21st century. *Journal of the American Academy of Dermatology*, *63*(5), 866–881. https://doi.org/10.1016/j.jaad.2009.10.048

Serra, R., Grande, R., Buffone, G., Molinari, V., Perri, P., Perri, A., Amato, B., Colosimo, M., & de Franciscis, S. (2016). Extracellular matrix assessment of infected chronic venous leg ulcers: Role of metalloproteinases and inflammatory cytokines. *International Wound Journal*, *13*(1), 53–58. https://doi.org/10.1111/iwj.12225

Setyowati, E. N. U. R. (2009). *Studi komparatif komponen kimia penyusun minyak atsiri daun sirih merah, sirih hijau, lada dan kemukus*. Universitas Sebelas Maret.

Sharififar, F., Dehghn-nudeh, G., & Mirtajaldini, M. (2009). Major flavonoids with antioxidant activity from Teucrium polium L . *Food Chesmistry*, *112*, 885–888. https://doi.org/10.1016/j.foodchem.2008.06.064

Sharma, Yoges, Jeyabalan, G., & Singh, R. (2013). Potential wound healing agents from medicinal plants: A review. *Pharmacologia*, *4*(5), 349358. https://doi.org/10.5567/pharmacologia.2013.349.358

Sharma, Yogesh, Jeyabalan, G., & Singh, R. (2013). Potential wound healing agents from medicinal plants: A review. In *Pharmacologia* (Vol. 4, Issue 5, pp. 349–358).

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

https://doi.org/10.5567/pharmacologia.2013.349.358

Shavandi, A., Bekhit, A. E. D. A., Saeedi, P., Izadifar, Z., Bekhit, A. A., & Khademhosseini, A. (2018). Polyphenol uses in biomaterials engineering. *Biomaterials*, *167*, 91–106. https://doi.org/10.1016/j.biomaterials.2018.03.018

Sherma, J., & Waksmundzka-Hajnos, M. (2010). High performance liquid chromatography in phytochemical analysis. In *Chromatographic Science Series* (Vol. 8).

Shinde, A. V, Humeres, C., & Frangogiannis, N. G. (2017). The role of α-smooth muscle actin in fibroblast-mediated matrix contraction and remodeling Arti. *Biochim Biophys Acta*, *1863*(1), 298–309. https://doi.org/10.1016/j.bbadis.2016.11.006.

Shinta, D. Y., & Sudyanto. (2016). Pemberian air rebusan daun sirih merah (Piper crocatum Ruiz & Pav) terhadap kadar glukosa dan kolesterol. *Journal of Sainstek*, *8*(2), 180–185. http://ecampus.iainbatusangkar.ac.id/ojs/index.php/sainstek/article/view/480/485

Siagian, N. A., Wahyuni, E. S., Ariani, P., & Manalu', A. B. (2020). The effect of giving red betel leaves (Piper crocatum) on healing of perineum woes in postpartum women in Desa Tanjung Jati Kecamatan Binjai Kabupaten Langkat. *Journal of Community Health*, *6*(3), 255–259.

Singh, A., Singh, P. K., & Singh, R. K. (2014). Antidiabetic and wound healing activity of Catharanthus roseus L. in streptozotocin-induced diabetic mice. *American Journal of Phytomedicine and Clinical Therapeutics*, *2*(6). www.ajpct.org

Singh, S., Young, A., & McNaught, C. E. (2017). The physiology of wound healing. In *Surgery (United Kingdom)* (Vol. 35, Issue 9, pp. 473–477). https://doi.org/10.1016/j.mpsur.2017.06.004

Singh, Y., Salker, M. S., & Lang, F. (2021). Green tea polyphenol-sensitive calcium signaling in immune T cell function. *Frontiers in Nutrition*, *7*(January), 1–10. https://doi.org/10.3389/fnut.2020.616934

Smith, R. G. (2003). Validation of Wagner's classification: a literature review. *Ostomy/Wound Management*, *49*(1), 54–62.

Snyder, R. J., Driver, V., Fife, C. E., Lantis, J., Peirce, B., Serena, T., & Weir, D. (2011). Using a diagnostic tool to identify elevated protease activity levels in chronic and stalled wounds: a consensus panel discussion. *Ostomy/Wound Management*, *57*(12), 36–46.

Soni, H., & Singhai, A. K. (2012). A recent update of botanicals for wound healing activity. *International Research Journal of Pharmacy*, *3*(7), 1–7.

Sood, S., Mohd. Yussof, S., Omar, E., & Pai, D. (2012). Cellular events and biomarkers of wound healing. *Indian Journal of Plastic Surgery*, *45*(2), 220. https://doi.org/10.4103/0970-0358.101282

Sorg, H., Tilkorn, D. J., Hager, S., Hauser, J., & Mirastschijski, U. (2017). Skin wound healing: An update on the current knowledge and concepts. *European Surgical Research*, *58*(1–2), 81–94. https://doi.org/10.1159/000454919

Spange, S., Wagner, T., Heinzel, T., & Krämer, O. H. (2009). Acetylation of non-histone proteins modulates cellular signalling at multiple levels. In *International Journal of*

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Biochemistry and Cell Biology (Vol. 41, Issue 1, pp. 185–198). https://doi.org/10.1016/j.biocel.2008.08.027

Spichler, A., Hurwitz, B. L., Armstrong, D. G., & Lipsky, B. A. (2015). Microbiology of diabetic foot infections: From Louis Pasteur to "crime scene investigation." *BMC Medicine*, *13*(1). https://doi.org/10.1186/s12916-014-0232-0

Stahura, F., & Bajorath, J. (2005). Partitioning methods for the identification of active molecules. *Current Medicinal Chemistry*, *10*(8), 707–715. https://doi.org/10.2174/0929867033457881

Stipcevic, T., Piljac, J., & Berghe, D. Vanden. (2006). Effect of different flavonoids on collagen synthesis in human fibroblasts. *Plant Foods for Human Nutrition*, *61*(1), 29–34. https://doi.org/10.1007/s11130-006-0006-8

Stojadinovic, O., Pastar, I., Gordon, K. A., & Tomic-Canik, M. (2012). *The diabetic foot: medical and surgical management* (G. J. Veves A (ed.); 3rd ed.). Humana Press.

Sukmana, M., Nopriyanto, D., & Alhawaris. (2020). Irrigation of wounds with Red betel 20% And 40% to bacterial numbers in diabetic foot infection (DFI) patients. *Journal Of Nursing Practice*, *4*(1), 51–60. https://doi.org/10.30994/jnp.v4i1.108

Surbakti, D., & Sianturi, N. S. (2015). *Analisis komponen kimia dan uji aktifitas antibakteri minyak atsiri daun sirih merah*.

Suri, M. A., Azizah, Z., & Asra, R. (2019). A review: Traditional use, phytochemical and pharmacological review of red betel leaves (Piper crocatum Ruiz & Pav). *Asian Journal of Pharmaceutical Research and Development*, *9*(1), 159–163. http://dx.doi.org/10.22270/ajprd.v9i1.000

Sutrisno, S., & Hidayat, D. P. (2018). Efektivitas penggunaan daun jambu biji (Psidium guajava) dan daun sirih merah (Piper crocatum) terhadap pengontrolan odour (bau) pada pasien dengan luka diabetes mellitus di Fatchul wound care. *The Shine Cahaya Dunia Ners*, *3*(1), 11–18. https://doi.org/10.35720/tscners.v3i1.57

Syarif, R. A., Wahyuningsih, M. S. H., Mustofa, M., & Ngatidjan, N. (2018). Antiplasmodial and onset speed of growth inhibitory activities of Tithonia diversifolia (Hemsley) A Gray leaf fractions against Plasmodium falciparum. *Tropical Journal of Pharmaceutical Research*, *17*(November), 2213–2218. https://doi.org/10.4314/tjpr.v17i11.15

Tesfaye, S., Boulton, A. J. M., Dyck, P. J., Freeman, R., Horowitz, M., Kempler, P., Lauria, G., Malik, R. A., Spallone, V., Vinik, A., Bernardi, L., Valensi, P., Albers, J. W., Amarenco, G., Anderson, H., Arezzo, J., Backonja, M. M., Biessels, G. J., Bril, V., … Jones, T. (2010). Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*, *33*(10), 2285–2293. https://doi.org/10.2337/dc10-1303

Tombulturk, F. K., Soydas, T., Sarac, E. Y., Tuncdemir, M., Coskunpinar, E., Polat, E., Sirekbasan, S., & Kanigur-Sultuybek, G. (2019). Regulation of MMP 2 and MMP 9 expressions modulated by AP-1 (c-jun) in wound healing : improving role of Lucilia sericata in diabetic rats. *Acta Diabetologica*, *56*(2), 177–186. https://doi.org/10.1007/s00592-018-1237-5

UNIVERSITAS GADJAH MADA
**Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts**
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Tonahi, J. M. M., Nuryanti, S., & Suherman, S. (2014). Antioksidan dari daun sirih merah (Piper Crocatum). *Jurnal Akademika Kimia*, *3*(3), 158–164. http://jurnal.untad.ac.id/jurnal/index.php/JAK/article/view/7796

Trindade, L. C. T., Matias, J. E. F., Aio, C. P. P. S., Farias, R. E., & Biondo-Simões, M. D. L. P. (2019). Differentiation of myofibroblasts in wounds after topical use of metronidazole: An experimental study. *Revista Do Colegio Brasileiro de Cirurgioes*, *46*(1), 1–11. https://doi.org/10.1590/0100-6991e-20192015

Truong, D., Nguyen, D. H., Anh Ta, N. T., Bui, A. V., Do, T. H., & Nguyen, H. C. (2019). Evaluation of the use of different solvents for phytochemical constituents, antioxidants, and in vitro anti-inflammatory activities of Severinia buxifolia. *Journal of Food Quality*, *2019*. https://doi.org/10.1155/2019/8178294

Tsourdi, E., Barthel, a, Rietzsch, H., Reichel, a, & Bornstein, S. R. (2013). Current aspects in the pathophysiology and treatment of chronic wounds in diabetes mellitus. *Biomed Res Int*, *2013*, 385641. https://doi.org/10.1155/2013/385641

Uccioli, L., Izzo, V., Meloni, M., Vainieri, E., Ruotolo, V., & Giurato, L. (2015). Non-healing foot ulcers in diabetic patients: general and local interfering conditions and management options with advanced wound dressings. *Journal of Wound Care*, *24*(4 Suppl), 35–42. https://doi.org/10.12968/jowc.2015.24.Sup4b.35

Ulviani, F., Yusriadi, & Khaerati, K. (2016). The effect of Red Betel leaf extract gel (Piper crocatum Ruiz & Pav) for healing burns in rabbits (Oryctolagus c). *GALENIKA Journal of Pharmacy*, *2*(2), 103–110. https://doi.org/2442-8744

Ungureanu, C., Marchal, L., Aurelia, A., & Foucault, A. (2013). Bioresource Technology Centrifugal partition extraction , a new method for direct metabolites recovery from culture broth : Case study of torularhodin recovery from Rhodotorula rubra. *Bioresource Technology*, *132*, 406–409. https://doi.org/10.1016/j.biortech.2012.11.105

Van de Vel, E., Sampers, I., & Raes, K. (2017). A review on influencing factors on the minimum inhibitory concentration of essential oils. *Critical Reviews in Food Science and Nutrition*, *August*, 1–22. https://doi.org/10.1080/10408398.2017.1371112

Van Putte, L., De Schrijver, S., & Moortgat, P. (2016). The effects of advanced glycation end products (AGEs) on dermal wound healing and scar formation: a systematic review. *Scars, Burns & Healing*. https://doi.org/10.1177/2059513116676828

Vande Berg, J. S., & Robson, M. C. (2003). Arresting cell cycles and the effect on wound healing. *Surgical Clinics of North America*, *83*(3), 509–520. https://doi.org/Arresting cell cycles and the effect on wound healing

Velnar, T., Bailey, T., & Smrkolj, V. (2009). The wound healing process: an overview of the cellular and molecular mechanisms. *The Journal of International Medical Research*, *37*(5), 1528–1542. https://doi.org/10.1177/147323000903700531

Venkatachalam, R. N., Singh, K., & Marar, T. (2012). Phytochemical screening in vitro antioxidant activity of psidium guajava. *Free Radicals and Antioxidants*, *2*(1), 31–36. https://doi.org/10.5530/ax.2012.2.7

Venter, C., & Niesler, C. U. (2019). Rapid quantification of cellular proliferation and migration

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

using ImageJ. *BioTechniques*, *66*(2), 99–102. www.BioTechniques.com

Verma, S., Gupta, M., Popli, H., & Aggarwal, G. (2018). Diabetes mellitus treatment using herbal drugs. *International Journal of Phytomedicine*, *10*(1), 01. https://doi.org/10.5138/09750185.2181

Vlad, A., & Timar, R. (2012). Pathogenesis of type 1 diabetes mellitus: A brief overview. *Romanian Journal of Diabetes, Nutrition and Metabolic Diseases*, *19*(1), 67–72. https://doi.org/10.2478/v10255-012-0009-1

Vowden, K., & Vowden, P. (2014). Wound dressings: principles and practice. *Surgery (Oxford)*, *32*(9), 462–467. https://doi.org/10.1016/j.mpsur.2014.07.001

Wade, L. . (2012). *Organic Chemistry* (8th Editio). Prentice Hall. https://books.google.co.id/books?hl=id&lr=&id=7sa4DwAAQBAJ&oi=fnd&pg=PR19&dq=Organic+Chemistry+8th+ed&ots=hLZM2_QGM8&sig=5UGHBI1y0rAV-MdxL71T6buAnnc&redir_esc=y#v=onepage&q=Organic Chemistry 8th ed&f=false

Wahyuningsih, M. S. H., Mubarika, S., Ganjar, I. G., Wahyuono, S., & Takeya, T. (2017). 5α-Oleandrin reduce Bcl-2 protein and increase Bax protein expression on Hela cervical cancer cell. *Universa Medicina*, *36*(2), 102. https://doi.org/10.18051/UnivMed.2017.v36.102-109

Wahyuningsih, M. S. H., Wirohadidjojo, Y. W., Hidayat, R., & Sadid, A. (2015). Antifibrotic effect of standardized ethanol extract of Tithonia diversifolia (Hemsley) A. Gray on keloid fibroblasts. *International Journal of Pharmacognosy and Phytochemical Research*, *7*(4), 642–647.

Wan, R., Weismann, J. P., Grundman, K., Lang, L., Gribowski, G., & Galiano, R. D. (2021). Diabetic wound healing: The impact of diabetes on myofibroblast activity and its potential therapeutic treatments. *The International Journal of Tissue Repair and Regeneration*, *29*(4), 573–581. https://doi.org/https://doi.org/10.1111/wrr.12954

Wang, Z., & Shi, C. (2020). Cellular senescence is a promising target for chronic wounds : a comprehensive review. *Burns& Trauma*, *8*, 1–8. https://doi.org/10.1093/burnst/tkaa021

Watanabe, K., Shibuya, S., Ozawa, Y., Toda, T., & Shimizu, T. (2021). Pathological relationship between intracellular superoxide metabolism and p53 signaling in mice. In *International Journal of Molecular Sciences* (Vol. 22, Issue 7). https://doi.org/10.3390/ijms22073548

Watkins, P. (2005). ABC of diabetes. In *Ethnicity and Disease* (Vol. 15, Issue 4). https://doi.org/10.1136/bmj.326.7395.924

Weller, M. G. (2012). A unifying review of bioassay-guided fractionation, effect-directed analysis and related techniques. *Sensors*, *12*, 9181–9209. https://doi.org/10.3390/s120709181

Widjiastuti, I. et al. (2016). Biocompatibility of red betel leaf extract (Piper crocatum) and 0,2 chlorhexidine gluconat toward BHK-21 fibroblast. *Conservative Dentistry Journal*, *4*(1), 6–11.

Wijaya, L., Budiyanto, A., & Astuti, I. (2019). Pathogenesis, evaluation, and recent management of diabetic foot ulcer. *Journal of the Medical Sciences*, *51*(1), 82–97.

Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

https://doi.org/10.19106/JMedSci005101201910

Wilkinson, H. N., & Hardman, M. J. (2020). Senescence in wound repair: emerging strategies to target chronic healing wounds. *Frontiers in Cell and Developmental Biology*, *8*(August), 1–13. https://doi.org/10.3389/fcell.2020.00773

Wu, H., Li, F., Shao, W., Gao, J., & Ling, D. (2019). Promoting angiogenesis in oxidative diabetic wound microenvironment using a nanozyme-reinforced self-protecting hydrogel. *ACS Central Science*, *5*(3), 477–485. https://doi.org/10.1021/acscentsci.8b00850

Wu, Z., Zheng, X., Gong, M., & Li, Y. (2016). Myricetin, a potent natural agent for treatment of diabetic skin damage by modulating TIMP/MMPs balance and oxidative stress. *Oncotarget*, *7*(44), 71754–71760. https://doi.org/10.18632/oncotarget.12330

Wulandari, N., Meiftasari, A., Fadliyah, H., & Jenie, R. I. (2018). Red Betel leaves methanolic extract (Piper crocatum Ruiz & Pav.) increases cytotoxic effect of Doxorubicin on WiDr colon cancer cells through apoptosis induction. *Indonesian Journal of Cancer Chemoprevention*, *9*(1), 1. https://doi.org/10.14499/indonesianjcanchemoprev9iss1pp1-8

Wurlina, Meles, D. K., Dewa Putu Anom Adnyana, I., Sasmita, R., & Putri, C. (2019). Biological study of piper crocatum leaves ethanol extract improving the skin histopathology of wistar rat wound infected by staphylococcus aureus. *EurAsian Journal of BioSciences*, *13*(1), 219–221.

Yagihashi, S., Mizukami, H., & Sugimoto, K. (2011). Mechanism of diabetic neuropathy: Where are we now and where to go? *Journal of Diabetes Investigation*, *2*(1), 18–32. https://doi.org/10.1111/j.2040-1124.2010.00070.x

Yan, H., Peng, K. J., Wang, Q. L., Gu, Z. Y., Lu, Y. Q., Zhao, J., Xu, F., Liu, Y. L., Tang, Y., Deng, F. M., Zhou, P., Jin, J. G., & Wang, X. C. (2013). Effect of pomegranate peel polyphenol gel on cutaneous wound healing in alloxan-induced diabetic rats. *Chinese Medical Journal*, *126*(9), 1700–1706. https://doi.org/10.3760/cma.j.issn.0366-6999.20122728

Yazdanpanah, L. (2015). Literature review on the management of diabetic foot ulcer. *World Journal of Diabetes*, *6*(1), 37. https://doi.org/10.4239/wjd.v6.i1.37

Yen, Y. H., Pu, C. M., Liu, C. W., Chen, Y. C., Chen, Y. C., Liang, C. J., Hsieh, J. H., Huang, H. F., & Chen, Y. L. (2018). Curcumin accelerates cutaneous wound healing via multiple biological actions: The involvement of TNF-α, MMP-9, α-SMA, and collagen. *International Wound Journal*, *15*(4), 605–617. https://doi.org/10.1111/iwj.12904

Yulianti, E., Sunarti, & Wahyuningsih, M. S. H. (2021). The effect of Kappaphycus alvarezii fraction on plasma glucose, advanced glycation end-products formation, and renal RAGE gene expression. *Heliyon*, *7*(October 2020). https://doi.org/10.1016/j.heliyon.2021.e05978

Zhu, Y., Doornebal, E. J., Pirtskhalava, T., Giorgadze, N., Wentworth, M., Fuhrmann-Stroissnigg, H., Niedernhofer, L. J., Robbins, P. D., Tchkonia, T., & Kirkland, J. L. (2017). New agents that target senescent cells: The flavone, fisetin, and the BCL-XL inhibitors, A1331852 and A1155463. *Aging*, *9*(3), 1–9. https://doi.org/10.18632/aging.101202

UNIVERSITAS
GADJAH MADA
**Efek Fraksi Aktif Piper crocatum Ruiz & Pav terhadap Deposisi Kolagen dan Wound Closure melalui
Regulasi Ekspresi p53, Alfa SMA, SOD1 dan E-cadherin pada Wounded Hyperglycemia Fibroblasts**
ANDINA SETYAWATI, Piper crocatum Ruiz & Pav, diabetic wound healing, mechanism, p53, Alpha SMA, SOD-
Universitas Gadjah Mada, 2022 | Diunduh dari http://etd.repository.ugm.ac.id/

Zulharini, M., Sutejo, I. R., Fadliyah, H., & Jenie, R. I. (2017). Methanolic extract of Red Betel Leaves (Piper crocatum Ruiz & Pav) perform cytotoxic effect and antimigration activity toward metastatic breast cancer. *Indonesian Journal of Cancer Chemoprevention*, *October*, 90–96.