

DAFTAR PUSTAKA

- AGC Biologics. (2023). Dynamic binding capacity: Create a more effective downstream process. <https://www.agcbio.com/biopharma-blog/dynamic-binding-capacity-benefits-and-strategies>
- Agin, A., Jeandidier, N., Gasser, F., Grucker, D., & Sapin, R. (2007). Glargin blood biotransformation: In vitro appraisal with human insulin immunoassay. *Diabetes & Metabolism*, 33(3): 205–212
- Ahmad, K. (2014). Insulin sources and types: A review of insulin in terms of its mode on diabetes mellitus. *Journal of Traditional Chinese Medicine*, 34: 234–237
- Ahmad, M., Hirz, M., Pichler, H., & Schwab, H. (2014). Protein expression in *Pichia pastoris*: recent achievements and perspectives for heterologous protein production. *Applied Microbiology and Biotechnology*, 98(12): 5301-5317
- Allen D, Ruan CH, King B, Ruan KH. (2019). Recent advances and nearfuture of insulin production and therapy. *Future Med Chem*, 11: 1513–1517
- Asmat U, Abad K, Ismail K. (2016). Diabetes mellitus and oxidative stress—A concise review. *Saudi Pharmaceutical Journal*, 24, 547-553
- Baeshen N. A., Baeshen M.N., Sheikh A., Bora R.S., Ahmed M.M.M., Ramadan H.A.I., Saini K.S., Redwan E.M. (2014). Cell factories for insulin production. *Microbiology Cell Fact*, 13: 141-149
- Baynest H.W. (2015). Classification, pathophysiology, diagnosis and management of diabetes mellitus. *Journal Diabetes Metabolit*, 6: 541-550. <https://doi.org/10.4172/2155-6156.1000541>
- Badan Pengawas Obat dan Makanan Republik Indonesia. (2021). *Data Importasi BPOM RI 2021*. BPOM
- Becker, R. H. A. (2007). Insulin glargine: A once-daily basal insulin analog. *Clinical Therapeutics*, 29:183–197. <https://doi.org/10.1016/j.clinthera.2007.09.019>

- Bradford, M.M. (1976). A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Analytical Biochemistry*, 72: 248-254
- Brange, J., Langkjaer, L., Havelund, S., & Vølund, A. (1997). Chemical stability of insulin. *Diabetes Care*, 20: 65–77
- Brubaker, Patricia L., and Drucker, Daniel J. (2004). Minireview: Glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system. *Endocrinology*, 145(6): 2653–2659. <https://doi.org/10.1210/en.2004-0037>
- Carta, G., & Jungbauer, A. (2010). *Protein Chromatography: Process Development and Scale-Up*. Wiley-VCH.
- Çelik, E., & Çalık, P. (2012). Production of recombinant proteins by yeast cells. *Biotechnology Advances*, 30(5), 1108–1118. <https://doi.org/10.1016/j.biotechadv.2011.09.011>
- Cereghino, J. L., & Cregg, J. M. (2000). Heterologous protein expression in the methylotrophic yeast *Pichia pastoris*. *FEMS Microbiology Reviews*, 24(1): 45–66
- Cytiva. (2024). Optimize resolution and purity during ion exchange chromatography. Retrieved from <https://www.cytivalifesciences.com/en/us/knowledge-center/optimize-resolution-purity-during-iex>
- Dağışan, Selen & Erbas, Oytun. (2021). Insulin Structure, Function and Diabetes Models in Animals. *Journal of Experimental and Basic Medical Sciences*, 1(10): 56-60
- Daly, R., & Hearn, M.T.W. (2021). Expression of Insulin in *Pichia pastoris*: Strategies for Increased Yield and Functionality. *Biotechnology and Bioengineering*, 118(2): 553-565
- Datta Neelabh. (2023). The Use of Escherichia coli for Recombinant Human Insulin Production. *Indian Journal Pharmaceutical Biological Research*, 11(1): 1-3

- Ding JG, Fei J, Cui DF, Zhang YS. (2005). Expression Of Monomeric Insulin Precursor In *Pichia pastoris* And Its Conversion Into Monomeric B27 Lys Destripeptide Insulin By Tryptic Hydrolysis. *Acta Biochemical et Biophysical Sinica*, 37(4): 234–240
- Dini N., Hariyatun, Nuruliawaty Utami, Eko Wahyu Putro, Wien Kusharyoto. (2022). Enhancement in Human Insulin Precursor Secretion by *Pichia pastoris* through Modification of Expression Conditions. *Hayati Journal Bioscience*, 29:24-30
- Dodson, G., & Steiner, D. (1998). The role of assembly in insulin's biosynthesis. *Current Opinion in Structural Biology*, 8(2): 189–194. [https://doi.org/10.1016/S0959-440X\(98\)80103-5](https://doi.org/10.1016/S0959-440X(98)80103-5)
- Duyvesteyn, H. M. E., & Tully, T. (2021). SDS-PAGE: A Review of the Technique and Its Applications. *Journal of Biochemistry and Molecular Biology*, 54(6): 558-572
- Garland, O., Radaeva, M., Pandey, M., Cherkasov, A., & Lallous, N. (2023). PurificationDB: database of purification conditions for proteins. *Database*, 2023. <https://doi.org/10.1093/database/baad016>
- Given, B. D., Laird, W. J., Cashion, L. M., Chance, R. E., & Hoffman, J. A. (1985). High-level production of biologically active human proinsulin in *Escherichia coli*. *Journal of Biological Chemistry*, 260(10): 6641–6645. [https://doi.org/10.1016/S0021-9258\(17\)38888-4](https://doi.org/10.1016/S0021-9258(17)38888-4)
- Gross, J.H. (2017). *Mass Spectrometry: A Textbook*. Springer
- Gurramkonda, C., Polez, S., Skoko, N., Caserman, S., Ravnkar, M., Štrukelj, B., & Peternel, S. (2010). Application of simple fed-batch technique to high-level secretory production of insulin precursor using *Pichia pastoris* with subsequent purification and conversion to human insulin. *Microbial Cell Factories*, 9: 31-35. <https://doi.org/10.1186/1475-2859-9-31>
- Hardianto, D. (2020). Telaah Komprehensif Diabetes Mellitus: Klasifikasi, Gejala, Diagnosis, Pencegahan, Dan Pengobatan. *Journal Bioteknologi Biosains Indonesia*, 7: 304–317

- Hardianto, Dudi. (2021). Jurnal Bioteknologi & Biosains Indonesia Insulin: Production, Types, Analysis, and Routes of Delivery. *Jurnal Bioteknologi & Biosains Indonesia* (JBBI), 8: 321-331
- Hardianto, Dudi & Martius, E & Rostinawati, Tina & Safarrida, Anna & Ida Royani, Juwartina & Laziba, D & Assyifa, F. (2023). Detection of recombinant *Pichia pastoris* producing glargine. *IOP Conference Series: Earth and Environmental Science*, 127(1): 1755-1765
- Hardianto, Dudi & Safarrida, Anna & Prayoga, Gilang & Zr, Yufva & Munirah, & Martius, Efrida & ida royani, Juwartina & Hartuti, Endah. (2024). Increasing the production of insulin glargine in *Pichia pastoris* through medium modification. *BIO Web of Conferences*. 127:1051-1061
- Hazra, C., Basu, S., Ghosh, S., & Mandal, N. (2021). Efficient in vitro conversion of proinsulin glargine using trypsin and carboxypeptidase B. *Journal of Chromatography B*, 11739(12): 26-56. <https://doi.org/10.1016/j.jchromb.2021.122656>
- Hazra P, Adhikary L, Dave N, Khedkar A, Manjunath HS, Anantharaman R, Iyer H. (2010). Development of a process to manufacture PEGylated orally bioavailable insulin. *Biotechnol Prog*, 26(6):1695–1704
- Hazra P, Suma Sreenivas, Krishnamurthy Venkatesan, Mukesh B. Patale, Amarnath Chatterjee, N. Ramprabu, Ajamoddin M. Shaikh, Mutyalasetty Kusumanchi.(2021). A novel peptide design aids in the expression and its simplified process of manufacturing of Insulin Glargine in *Pichia pastoris*. *Applied Microbiology and Biotechnology*, 105: 3061–3074
- Heise, T., Mathieu, C., & Kapitza, C. (2017). Understanding the pharmacokinetics and pharmacodynamics of insulin glargine 300 U/mL vs 100 U/mL. *Diabetes, Obesity and Metabolism*, 19(7): 920–927. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5748718/>
- Holmes, William J, Darby, Richard AJ., Wilks, Martin DB., Smith, Rodney., Bill, Roslyn. 2009. Developing a Scalable Model of Recombinant

- Protein Yield from *Pichia Pastoris*: The Influence of Culture Conditions, Biomass and Induction Regime. *Microbial Cell Factories*, 8 (35): 1-14
- Institute for Health Metrics and Evaluation. (2021). *Penyebab Kematian di Inonesia Global Burden of Diseases*. <https://vizhub.healthdata.org/>
- Jahangir MA, Bhisht P, Muheem A, Imam SS. (2017). Diabetes: Pharmacological History and Future Management Strategies. *Pharmceutical Bioprocess*, 5: 54–65
- Jia, W., Lu, M., Liu, Y., Liang, Y., Xu, D., Yang, Z., & Zhang, Y. (2008). Structural studies of insulin glargine by mass spectrometry. *Journal of Pharmaceutical Sciences*, 97(2): 570–580.
- Jonasson, P., Liljeqvist, S., Nygren, P.-Å., & Ståhl, S. (1996). In vitro conversion of proinsulin to insulin using trypsin and carboxypeptidase B. *Protein Expression and Purification*, 8(3): 435–443. <https://doi.org/10.1006/prep.1996.0054>
- Jungbauer, A., & Hahn, R. (2009). Ion-exchange chromatography. *Methods in Enzymology*, 463: 349–371. [https://doi.org/10.1016/S0076-6879\(09\)63021-0](https://doi.org/10.1016/S0076-6879(09)63021-0)
- Kannan V, Narayanaswamy P, Gadamsetty D, Hazra P, Khedkar A, Iyer H. (2009). A tandem mass spectrometric approach to the identification of O-glycosylated glargine glycoforms in active pharmaceutical ingredient expressed in *Pichia pastoris*. *Rapid Communication Mass Spectrometer* 23(7):1035–1042
- Krishnamurthi, V. R., Niyonshuti, I. I., Chen, J., & Wang, Y. (2021). A new analysis method for evaluating bacterial growth with microplate readers. *PloS one*, 16(1): 245-250
- Kuhlmann M, Schmidt A. (2014). Production and Manufacturing Of Biosimilar Insulin: Implications for Patients, Physicians, And Health Care System. *Biosimilars* 4: 45–58
- Lemus, L., & Wolf, B. A. (2022). Biosynthesis and processing of insulin in pancreatic β -cells: Molecular mechanisms and pathophysiological

- implications. *Frontiers in Endocrinology*, 13: 926-934.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9267443/>
- Macauley-Patrick, S., Fazenda, M. L., McNeil, B., & Harvey, L. M. (2005). Heterologous protein production using the *Pichia pastoris* expression system. *Yeast*, 22(4), 249–270. <https://doi.org/10.1002/yea.1208>
- Mane K, Chaluvvaraju KC, Niranjana MS, Zaranappa, Manjuthaj TR. (2012). Review Of Insulin and Its Analogues in Diabetes Mellitus. *Journal Basic Clinic Pharmaceutical*, 3: 283–293
- Mirmiranpour, H., Khaghani, S., Torkashvand, F., & Zomorodipour, A. (2022). Production of insulin analogs: Recent advances and future prospects. *Biotechnology Advances*, 55(10): 78-80.
<https://doi.org/10.1016/j.biotechadv.2021.107880>
- Moser, A. C., Hage, D. S., & Hearn, M. T. (2019). High-performance ion-exchange chromatography of proteins: Recent developments and applications. *Journal of Chromatography B*, 11(20): 1–14.
<https://doi.org/10.1016/j.jchromb.2019.05.006>
- Mukhopadhyay, A., & Sen, S. (2023). A Review of the Biosynthesis and Structural Implications of Insulin. *Cells*, 12(7): 10-18.
<https://www.mdpi.com/2073-4409/12/7/1008>
- Nensa E., Fajar N, Hadi. (2022). Analysis of Hydroquinone Content in Whitening Cream by Spectrophotometry UV-Vis Method. *Journal Syifa Sciences and Clinical Research*, 4(3): 768 -777
- Owens DR. (2011). Insulin preparations with prolonged effect. *Diabetes Technology Therapeutics*, 13: 5–14
- Pace, C. N., & Scholtz, J. M. (1997). Measuring the conformational stability of a protein. In T. E. Creighton (Ed.), *Protein Structure: A Practical Approach*, 299–321. Oxford University Press
- Polez, S., Origi, D., Zahariev, S., Guarnaccia, C., Tisminetzky, S. G., Skoko, N., & Baralle, M. (2016). A Simplified and Efficient Process for Insulin Production in *Pichia pastoris*. *PloS one*, 11(12): 167-207

- Potvin, G., Ahmad, A., & Zhang, Z. (2012). Bioprocess engineering aspects of heterologous protein production in *Pichia pastoris*: a review. *Biochemical Engineering Journal*, 64: 91–105
- Proteo Genix. (2023). Protein purification by hydrophobic interaction chromatography. <https://www.proteogenix.science/protein-purification/no-tag-purification/hydrophobic-interaction-chromatography/>
- Putro, D Nurdiani, Hariyatun, N Utami and W Kusharyoto (2020). Capture and Intermediate Purification of Human Insulin Precursor from *Pichia pastoris* Culture Using Cation Exchange Chromatography. *IOP Conf. Series: Earth Enviromental Science*, 762 (1): 20-28
- Rahman MS, Hossain KS, Das S, Kundu S, Adegoke EO, Rahman MA, Hannan MA, Uddin MJ, Pang MG. (2021). Role Of Insulin in Health and Disease: An Update. *International Journal Molecular Science* 22(6): 40-30
- Rachdaoui N. (2020). Insulin: The friend and the foe in the development of type 2 diabetes mellitus. *International Journal Molecular Science*, 21: 7-17
- Rosenstock, J., Dailey, G., Massi-Benedetti, M., Fritsche, A., Lin, Z., & Salzman, A. (2000). Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with NPH insulin in type 2 diabetes. *Diabetes Care*, 24(4): 631–637.
- Roush, D., Iammarino, M., Chmielowski, R., Insaioo, F., McCoy, M., Ortigosa, A., & Rauscher, M. (2023). Insulin purification—Innovation continuum via synthesis of fundamentals, technology, and modeling. *Biotechnology and Bioengineering*, 121-130. <https://doi.org/10.1002/bit.28427>
- Saini, S. & Sharma, N. (2023). Advances in Protein Detection Using Coomassie Brilliant Blue Staining: A Review. *Journal of Proteomics and Bioinformatics*, 16(1): 50-65

- Schägger, H., & von Jagow, G. (1987). Tricine-SDS-PAGE for the separation of proteins in the range from 1 to 100 kDa. *Analytical Biochemistry*, 166(2): 368–379. [https://doi.org/10.1016/0003-2697\(87\)90587-2](https://doi.org/10.1016/0003-2697(87)90587-2)
- Shen Y, Prinyawiwatkul W, Xu Z. (2019). Insulin: A Review of Analytical Methods. *Analyst* 144: 4139–4148
- Shukla, A. A., Hubbard, B., Tressel, T., Guhan, S., & Low, D. (2007). Downstream processing of monoclonal antibodies—Application of platform approaches. *Journal of Chromatography B*, 848(1): 28–39. <https://doi.org/10.1016/j.jchromb.2006.09.037>
- Singh, R., Kumar, M., Mittal, A., & Mehta, P. K. (2020). Microbial enzymes: industrial progress in 21st century. 3 *Biotech*, 10(9): 386-394. <https://doi.org/10.1007/s13205-020-02385-4>
- Skoog, D.A., West, D.M., Holler, F.J., Crouch, S.R. (2017). *Fundamentals of Analytical Chemistry*. Boston: Cengage Learning
- Steiner DF. (2011). On the discovery of precursor processing. *Methods Molecular Biology (Clifton, NJ)*, 768: 3–11
- Thermo Fisher Scientific. (2010). *Pichia Expression Kit: pPICZαA Vector Manual*. Invitrogen™. Retrieved from <https://tools.thermofisher.com/content/sfs/manuals/pichiman.pdf>
- Vecchio I, Tornali C, Bragazzi NL, Martini M. (2018). The Discovery of Insulin: An Important Milestone In The History Of Medicine. *Front Endocrinol*, 9: 6-13
- Wahidin, M., Achadi, A., Besral, B., Kosen, S., Nadjib, M., Nurwahyuni, A., Ronoatmodjo, S., Rahajeng, E., Pane, M., & Kusuma, D. (2024). Projection Of Diabetes Morbidity And Mortality Till 2045 In Indonesia Based on Risk Factors and NCD Prevention and Control Programs. *Scientific Reports*, 14(1): 5424-5435
- Wanderley, M. S. O., Oliveira, C., Bruneska, D., Domingues, L., Lima Filho, J. L., Teixeira, J. A., & Mussatto, S. I. (2013). Influence of trace elements supplementation on the production of recombinant frutalin

- by *Pichia pastoris* KM71H in fed-batch process. *Chemical Papers*, 67(7): 682–687. <https://doi.org/10.2478/s11696-013-0363-3>
- Wang, W., Singh, S., Zeng, D. L., King, K., & Nema, S. (2007). Antibody structure, instability, and formulation. *Journal of Pharmaceutical Sciences*, 96(1): 1–26. <https://doi.org/10.1002/jps.20727>
- Waters Corporation. (2025). What is the buffering pH range of Ammonium Acetate? https://support.waters.com/KB_Chem/Other/WKB73768_What_is_the_buffering_pH_range_of_Ammonium_Acetate
- Wen Zhu, Renren Xu, Guihua Gong, Lei Xu, Youjia Hu, Liping Xie. (2021). Medium Optimization for High Yield Production of Human Serum Albumin in *Pichia pastoris* and its Efficient Purification. *Protein Expression and Purification*, 181: 1-11
- Wolfgang Kemmler, James D. Peterson, And Donald F. Steiner. (1971). Studies on the Conversion of Proinsulin to Insulin. *The Journal Of Biological Chemistry*, 246(22): 6786-6791
- Yang, Z.-H., Du, X., & Tang, J.-G. (1999). Separation and characterization of trypsin and carboxypeptidase B-digested products of Met-Lys-human proinsulin. *Applied Biochemistry and Biotechnology*, 76(2): 107–114. <https://doi.org/10.1385/ABAB:76:2:107>
- Zhao, H., & Arnold, F. H. (1999). Directed evolution converts subtilisin E into a functional equivalent of thermolysin. *Protein Engineering*, 12(1): 47–53. <https://doi.org/10.1093/protein/12.1.47>