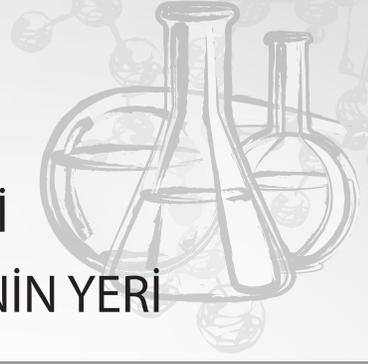


2. BÖLÜM

İLAÇ KEŞFİ VE GELİŞTİRİLMESİ SÜRECİNDE MİKROBİYOLOJİNİN YERİ



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GİRİŞ VE TARİHÇE

Günümüzde fizyolojik sistemleri veya patolojik durumları kullananın yararına değiştirmek veya incelemek amacıyla uygulanan veya uygulanması öngörülen madde veya ürün olarak tanımlanan ilacın geçmişi neredeyse insanlık tarihi kadar eskidir (Eşkazan, 2015). Yapılan araştırmalar, çok eski tarihlerde yaşamış olan uygarlıkların toksik madde farkındalıklarının bulunduğunu ve o dönemin koşullarına uygun olarak geleneksel ilaç yapımı ve kullanımı konusunda tecrübe sahibi olduklarını göstermektedir. Günümüzden yaklaşık iki yüz bin yıl önce yaşamış insan türü olarak bilinen Neandertallerin bir mağarada bulunan iskelet kalıntılarının yakınında bulunan ağaç parçaları ve bitkisel kalıntılar bu konuya verilebilecek bilinen en eski örneklerdendir. Neandertallerin ağrı kesici özelliği bulunan salisilik asit içeren kavak ağacını ve antibiyotiğin keşfinden binlerce yıl önce antibiyotik oluşturan *Penicillium* küfünü tükettikleri yapılan çalışmalarla gösterilmiştir (Edmeads, 1999; Weyrich, Duchene ve ark., 2017).

Yaklaşık 5300 yıl öncesine ait ve antropoloji literatürüne “İceman” olarak geçmiş erkek bedeninin bağırsaklarında *Trichuris trichiura* parazit yumurtalarına rastlanılmıştır. Bu kişinin giysileri arasında pürgatif özellikli bir madde olan agarik asit türevlerini içeren *Piptoporus betulinus* (huş mantarı) adı verilen ağaç mantarını taşıdığı belirlenmiştir. Mantarların toksik ve antibakteriyel etkili bile-

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mesini inhibe eden en düşük antimikrobiyal etkili madde konsantrasyonu MİK değeri olarak kaydedilir (Gür, 2016).

Agar dilüsyonu yöntemi genellikle anaeroblar ve *Helicobacter* spp. gibi güç üreyen mikroorganizmalar için önerilmektedir (Balouiri, Sadiki ve ark., 2016.)

SONUÇ VE ÖNERİLER

Canlılığın devamı için yaşamın her alanında önemli fonksiyonları olan mikroorganizmaların, yeni ilaçların keşfi ve geliştirilmesi süreçlerindeki rolü ve önemi yadsınamaz. Mikroorganizmalar hem oluşturdukları farklı biyolojik özellikler gösteren bileşikler nedeniyle doğal ilaç kaynağı olabilmeleri hem de ilaç üretiminin ve tüketiminin çeşitli aşamalarında kontaminasyona neden olmaları açısından önemlidir.

Günümüzün en önemli halk sağlığı tehditlerinden biri olan antimikrobiyal direncin çözümünde kullanılacak yeni terapötik ajanların acilen keşfedilmesi gereklidir. Aday molekülün antimikrobiyal etkisini araştırmaya yönelik mikrobiyolojik testler ilaç geliştirme sürecinin tarama testleri kapsamında yer almaktadır.

KAYNAKLAR

- Abbasoğlu U (1996). Antimikrobiyal Aktivite Araştırma Yöntemleri, *FABAD J. Pharm. Sci*, 22, 111-118.
- Alamgir ANM (2017). Drugs: Their Natural, Synthetic, and Biosynthetic Sources. In: Therapeutic Use of Medicinal Plants and Their Extracts: Volume 1. Progress in Drug Research, vol 73. Springer, Cham.
- Bábik I, Chalabala M, Sagáth J (1977). Mikrobiálna nezávadnosť liečiv. I. Vznik poziadavky mikrobiálnej nezávadnosti a výsledky hodnotenia mikrobiologickej akosti liečiv [Microbial purity of drugs. I. Development of requirements for microbial purity and results of evaluation of the microbial quality of drugs]. *Cesk Farm*. 26(8), 383-8.
- Balouiri M, Sadiki M, Ibsouda SK (2016). Methods for in vitro evaluating antimicrobial activity: A review. *Journal of Pharmaceutical Analysis*, 6, 71-79.
- Behal V (2006). Mode of action of microbial bioactive metabolites. *Folia Microbiologica*, 51(5), 359.
- Bremus C, Herrmann U, Bringer-Meyer S, ve ark. (2006). The use of microorganisms in L-ascorbic acid production. *Journal of Biotechnology*, 124, 196-205.
- Capasso L (1998). 5300 year ago the Ice Man used natural laxatives and antibiotics. *The Lancet*, 352.
- Cengiz G, Algın Yapar E (2020). Method decision for determining specific microorganisms in pharmaceutical products: An overview. *Universal Journal of Pharmaceutical Research* 5(5), 85-91.
- Chandwad S, Gutte S. (2019). Screening of Actinomycetes for α -amylase inhibitors production. *Current Enzyme Inhibition*, 15(1), 41-45.
- Chast F (2008). Chapter 1- A History of Drug Discovery: From first steps of chemistry to achievements in molecular pharmacology, Editor(s): Camille Georges Wermuth, The Practice of Medicinal Chemistry (Third Edition), Academic Press, Pages 1-62, ISBN 9780123741943.

- CLSI (2009). Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts, Approved Guideline-Second Edition. CLSI document M44-A2. Wayne, PA: Clinical and Laboratory Standards Institute.
- CLSI (2018). Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved Standard, 13th ed., CLSI document M02. Wayne, PA: Clinical and Laboratory Standards Institute.
- Code of Federal Regulations (2000). Title 21, Food and Drugs, "Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs," Part 210–211, US Printing Office, Washington, DC.
- Cohen J (2017). The Evolution of Koch's Postulates. *Infection Diseases (Fourth Edition)*. Edited by: Jonathan Cohen, William G. Powderly and Steven M. Opal. ISBN 978-0-7020-6285- Elsevier.
- Edmeads J (1999). History of migraine treatment. *Can. J. Clin. Pharmacol*, 6 Suppl A:5A-8A.
- EP-European Pharmacopoeia (2020). Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use, 5.1.4.
- Eryılmaz M, Gürpınar SS, Palabıyık İM, ve ark. (2018). Molecular identification and antimicrobial activity of vaginal *Lactobacillus* sp. *Current Pharmaceutical Biotechnology*, 19(15), 1241-1247.
- Eşkazan EE (2015). İlaçın doğuşu ve geliştirilmesinde ilk adımlar. *Yeni Tıp Tarihi Araştırmaları*, 21, 39-59.
- EUCAST (2020). Media Preparation for EUCAST Disk Diffusion Testing and For Determination of MIC Values by the Broth Microdilution Method. v 6.0, 2020. (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_test_documents/2020_manuals/Media_preparation_v_6.0_EUCAST_AST.pdf)
- EUCAST (2021a). Antimicrobial Susceptibility Testing. EUCAST Disk Diffusion Method. v 9.0, 2021. (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_test_documents/2021_manuals/Manual_v_9.0_EUCAST_Disk_Test_2021.pdf)
- EUCAST (2021b). EUCAST Reading Guide for Broth Microdilution. v 3.0, 2021. (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/MIC_testing/Reading_guide_BMD_v_3.0_2021.pdf)
- Evans AS (1976). Causation and disease: the Henle-Koch postulates revisited. *Yale J. Biol. Med.* 49(2), 175-195.
- Fabian SJ, Maust MD, Panaccione DG (2018). Ergot alkaloid synthesis capacity of *Penicillium camemberti*. *Applied and Environmental Microbiology*, 84(19).
- FDA (2021). The Drug Development Process. (<https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process>)
- Félix FKC, Letti LAJ, Pereira GVM, ve ark. (2019). L-lysine production improvement: a review of the state of the art and patent landscape focusing on strain development and fermentation technologies. *Critical Reviews in Biotechnology*, 39(8), 1031-1055.
- Frey EF (1985). The earliest medical texts. *Clio. Med.* 1985-1986;20(1-4), 79-90.
- Greco C, Keller NP, Rokas A (2019). Unearthing fungal chemodiversity and prospects for drug discovery. *Current Opinion in Microbiology*, 51, 22-29.
- Gür D (2016). Antibiyotik Duyarlılık Testleri, EUCAST: Uygulama, Yorum ve Uzman Kurallar, Türk Mikrobiyoloji Cemiyeti Dergisi, 46-Eksayı (http://tmc.dergisi.org/pdf/tmc_supplement_2016.pdf)
- Hallmann-Mikolajczak A (2004). Papyrus Ebersa. Księga wiedzy medycznej egipcjan z XVI w P.N.E [Ebers Papyrus. The book of medical knowledge of the 16th century B.C. Egyptians]. *Arch. Hist. Filoz. Med.* 67(1), 5-14. Polish.
- Hassan MA, Kamal YES, Ramlan Aziza, ve ark. (2012). Antibiotics as microbial secondary metabolites: Production and application. *International Journal of Engineering Science*, 59(1), 101-111.
- Heatley NG (1944). A method for the assay of penicillin, *Biochem. J.* 38:61-65.

- Hugerth L (1966). Mikrobiologiska föroreningar i läkemedel. Referat av en utredning [Microbiological contamination of drugs; report of an analysis]. *Sven Farm Tidskr.* 70(1), 9-14.
- Iacone R, Scanzano C, Santarpia L, *ve ark.* (2020). Macronutrients in Parenteral Nutrition: Amino Acids. *Nutrients*, 12(3), 772.
- ISO 20776-1 (2006). Clinical laboratory testing and in vitro diagnostic test systems - Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices - Part 1: Reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases.
- Jimenez L (2019). Analysis of FDA Enforcement Reports (2012-2019) to Determine the Microbial Diversity in Contaminated Non-Sterile and Sterile Drugs. American Pharmaceutical Review (<https://www.americanpharmaceuticalreview.com/Featured-Articles/518912-Analysis-of-FDA-Enforcement-Reports-2012-2019-to-Determine-the-Microbial-Diversity-in-Contaminated-Non-Sterile-and-Sterile-Drugs/>)
- Jones AW (2011). Early drug discovery and the rise of pharmaceutical chemistry. *Drug. Test. Anal.* 3(6), 337-44.
- Kallings LO, Ringertz O, Silverstolpe L (1966). Microbiological contamination of medical preparations. *Acta Pharm Suec.* 3(3), 219-28.
- Kaufmann, S (2008). Paul Ehrlich: founder of chemotherapy. *Nat Rev Drug Discov* 7, 373.
- Kramer SN (1963). *Sumerians: Their history, culture and character.* The University of Chicago.
- Kurek J (2019). Introductory Chapter: Alkaloids - Their Importance in Nature and for Human Life, Alkaloids - Their Importance in Nature and Human Life, IntechOpen.
- Lilienfeld DE (2008). The first pharmacoepidemiologic investigations: national drug safety policy in the United States, 1901-1902. *Perspect Biol Med.* Spring, 51(2), 188-98.
- Ludva J, Gajdos M (1977). Hodnocení mikrobiologické nezávadnosti sulfonamidů. Nálezy mikrobů a možnosti dekontaminace [Evaluation of the microbiological purity of sulfonamides. Findings of microbes and possibility of decontamination]. *Cesk Farm.* 26(8), 374-6.
- Mugoyela V, Mwambete KD (2010). Microbial contamination of nonsterile pharmaceuticals in public hospital settings. *Therapeutics and Clinical Risk Management*, 6, 443-448.
- Munita JM, Arias CA (2016). Mechanisms of antibiotic resistance. *Microbiology Spectrum.* 4(2), VMBF-0016-2015.
- Nargesi BM., Trachtmann N, Sprenger GA, *ve ark.* (2018). Production of p-amino-L-phenylalanine (L-PAPA) from Glycerol by Metabolic Grafting of *Escherichia coli*. *Microbial Cell Factories*, 17(1), 149.
- Nunn JF (1996). *Ancient Agyptian Medicine.* The Bath Press, Bath, pp 227.
- Rao N, Prabhu M, Xiao M, Li WJ (2017). Fungal and bacterial pigments: secondary metabolites with wide applications. *Frontiers in Microbiology*, 8(1113), 1-13.
- Ratajczak M, Kubicka MM, Kamińska D, Sawicka P, Długaszewska J (2015). Microbiological quality of non-sterile pharmaceutical products. *Saudi Pharm J.* 23(3), 303-307.
- Ratajczak M, Kubicka MM, Kamińska D, *ve ark.* (2015). Microbiological quality of non-sterile pharmaceutical products. *Saudi Pharm J.* 23(3), 303-307.
- Sandle T (2016). *Pharmaceutical Microbiology: Essentials for Quality Assurance and Quality Control*, Woodhead Publishing, Cambridge, UK.
- Singh R, Kumar M, Mittal A, *ve ark.* (2017). Microbial metabolites in nutrition, healthcare and agriculture. 3 *Biotech*, 7(15).
- Stavri N, Radu C (1979). Poluarea microbiologica a medicamentelor și implicațiile sale practice [Microbiological pollution of drugs and its practical implications]. *Rev Med Chir Soc Med Nat Iasi.* 83(3), 513-7.
- Tan, SY, Tatsumura Y. (2015). Alexander Fleming (1881-1955): Discoverer of penicillin. *Singapore Medical Journal*, 56(7), 366-367.

- Tröndle J, Trachtmann N, Sprenger GA, ve ark. (2018). Fed-batch Production of L-Tryptophan from Glycerol Using Recombinant *Escherichia coli*. *Biotechnology & Bioengineering*, 115(12), 2881-2892.
- Türk Farmakopisi 2017. (2018). Mikrobiyolojik Yöntemler. II. Cilt, sayfa 691-719. Türkiye İlaç ve Tıbbi Cihaz Kurumu.
- USP- United States Pharmacopoeia (2020). Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use, 1111.
- Ventola CL (2015). The antibiotic resistance crisis: part 1: causes and threats. *P T*. 40(4), 277-283.
- Wei G, Tan D, Chen C, Tong Q, Li XN, Huang J, Liu J, Xue Y, Wang J, Luo Z, Zhu H, Zhang Y (2017). Flavichalasin A-M, cytochalasin alkaloids from *Aspergillus flavipes*. *Scientific Reports*, 7, (42434).
- Weibel EK, Hadvary P, Hochuli E, ve ark. (1987). Lipstatin, an inhibitor of pancreatic lipase, produced by *Streptomyces toxytricini*. I. Producing organism, fermentation, isolation and biological activity. *The Journal of Antibiotics*, 40(8), 1081-1085.
- Wendisch VF, Jorge JMP, Pérez-García F, ve ark. (2016). Updates on industrial production of amino acids using *Corynebacterium glutamicum*. *World Journal of Microbiology and Biotechnology*, 32(6), 105.
- Weyrich LS, Duchene S, Soubrier J, ve ark. (2017). Neanderthal behaviour, diet, and disease inferred from ancient DNA in dental calculus. *Nature*, 20, 357-361.
- WHO (2015). Global Action Plan on Antimicrobial Resistance. (<https://www.who.int/publications/i/item/9789241509763>)
- WHO (2020). Antimicrobial resistance. (<https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>).
- Zaffiri L, Gardner J, Toledo-Pereyra LH (2012). History of antibiotics. From salvarsan to cephalosporins. *J. Invest. Surg.* 25(2), 67-77.
- Zhang Y, Lin J, Bai L, ve ark. (2018). Antioxidant capacities of *Bacillus endophyticus* ST-1 and *Ketogulonicigenium vulgare* 25B-1 in vitamin C fermentation. *Biotechnology & Biotechnological Equipment*, 32:(3), 628-637.
- Zhou J, Du G, Chen J (2012). Metabolic engineering of microorganisms for vitamin C production. Wang X., Chen J., Quinn P. (eds), *Reprogramming Microbial Metabolic Pathways*, 64, Springer, Dordrecht, 241-259.