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PREFACE

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Chapter 1

THE ROLE OF COMMUNITY PHARMACISTS IN THE TREATMENT OF MENTAL HEALTH DISORDERS

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1. INTRODUCTION

Chronic and enduring psychiatric disorders including psychotic disorders, bipolar disorder, schizophrenia, and major depression; any mental illness that adversely affects an individual's social connections, academic accomplishments, and work performance (1). Individuals living with these conditions have a life expectancy that is up to 25 years shorter than that of the general population. This primarily stems from modifiable lifestyle elements like tobacco use, absence of physical activity, poor eating habits, antipsychotic medication's adverse reactions, and the stress of living with a mental illness (2). In 2003, over 450 million individuals worldwide were reported to grapple with mental disorders; this number is much higher today, and it is emphasized that mental health medicines account for a significant proportion of the medicines prescribed by physicians (3). This group exhibits a notably elevated prevalence of coexisting avoidable chronic ailments, such as type 2 diabetes, and cardiovascular, and respiratory conditions. For this reason, they have been identified as a major burden on the US economy (2).

Considering the individual, societal, and financial consequences of people with untreated psychotic disorders, the involvement of primary healthcare professionals is essential to guarantee sufficient assistance for this demographic. Healthcare experts have recognized that people affected by mental health conditions as individuals presenting some of the most challenging cases for management (4). Moreover, these patients are 1.5 to 10 times more inclined to visit their pharmacist than their primary care physician (5). The treatment of more serious mental illnesses, such as schizophrenia, has leaned heavily on

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REFERENCES

1. Carey MP, Carey KB. Behavioral research on the severe and persistent mental illnesses. Behavior Therapy. 1999;30(3):345.
2. Ng R, El-Den S, Stewart V, Collins JC, Roennfeldt H, McMillan SS, et al. Pharmacist-led interventions for people living with severe and persistent mental illness: A systematic review. Australian & New Zealand Journal of Psychiatry. 2022;56(9):1080-103.
3. Bell S, McLachlan AJ, Chen TF, Whitehead P, Aslani P. Community pharmacy services to optimise the use of medications for mental illness: a systematic review. Australia and New Zealand Health Policy. 2005;2(1).
4. Chang E, Daly J, Bell P, Brown T, Allan J, Hancock K. A continuing educational initiative to develop nurses' mental health knowledge and skills in rural and remote areas. Nurse Education Today. 2002;22(7):542-51.
5. Tsuyuki RT, Beahm NP, Okada H, Al Hamarneh YN. Pharmacists as accessible primary health care providers: review of the evidence. Canadian Pharmacists Journal/ Revue des Pharmaciens du Canada. 2018;151(1):4-5.
6. Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. British medical bulletin. 2015;114(1):169-79.
7. Whiteford H, Buckingham B, Harris M, Diminic S, Stockings E, Degenhardt L. Estimating the number of adults with severe and persistent mental illness who have complex, multi-agency needs. Australian & New Zealand Journal of Psychiatry. 2017;51(8):799-809.
8. Finley PR, Crismon ML, Rush AJ. Evaluating the impact of pharmacists in mental health: a systematic review. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2003;23(12):1634-44.
9. Finley PR, Rens HR, Pont JT, Gess SL, Louie C, Bull SA, et al. Impact of a collaborative care model on depression in a primary care setting: a randomized controlled trial. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2003;23(9):1175-85.
10. Gisev N, Bell JS, O'Reilly CL, Rosen A, Chen TF. An expert panel assessment of comprehensive medication reviews for clients of community mental health teams. Social Psychiatry and Psychiatric Epidemiology. 2010;45:1071-9.
11. Rubio-Valera M, Chen TF, O'Reilly CL. New roles for pharmacists in community mental health care: a narrative review. International Journal of Environmental Research and Public Health. 2014;11(10):10967-90.
12. Eltorki Y, Abdallah O, Omar N, Zolezzi M. Perceptions and expectations of health care providers towards clinical pharmacy services in a mental health hospital in Qatar. Asian journal of psychiatry. 2019;42:62-6.
13. Haslam L, Gardner DM, Murphy AL. A retrospective analysis of patient care activities in a community pharmacy mental illness and addictions program. Research in Social and Administrative Pharmacy. 2020;16(4):522-8.
14. Everard M. Improving access and use of psychotropic medicines: World Health Organization; 2005.
15. Davis B, Qian J, Ngorsuraches S, Jeminiwa R, Garza KB. The clinical impact of pharmacist services on mental health collaborative teams: A systematic review. Journal of the American Pharmacists Association. 2020;60(5):S44-S53.

16. Landes SJ, Smith MG, Lam JC, Watt TC, Curran GM. Rural community pharmacists' perceptions of implementing mental health interventions to reach underserved populations. Journal of Rural Mental Health. 2022.
17. Kohan S, Chung SY, Stone J. Expanding the pharmacist's role in a psychiatric hospital. Psychiatric Services. 1973;24(3):164-6.
18. Jenkins MH, Bond C. The impact of clinical pharmacists on psychiatric patients. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 1996;16(4):708-14.
19. Kyle JA. The role of the community pharmacist in mental health. US Pharm. 2018;43(11):13-20.
20. Scott CL, Scott NW, Johnston M, de Bruin M, Nkansah N, Bond CM, et al. Pharmacist services for non-hospitalised patients. Cochrane Database of Systematic Reviews. 2018(9).
21. Bell JS, Rosen A, Aslani P, Whitehead P, Chen TF. Developing the role of pharmacists as members of community mental health teams: perspectives of pharmacists and mental health professionals. Research in Social and Administrative Pharmacy. 2007;3(4):392-409.
22. Bell JS, Whitehead P, Aslani P, McLachlan AJ, Chen TF. Drug-related problems in the community setting: pharmacists' findings and recommendations for people with mental illnesses. Clinical Drug Investigation. 2006;26:415-25.
23. Gardner DM. Collaborative mental health care: effective and rewarding. SAGE Publications Sage CA: Los Angeles, CA; 2007. p. S11-S.
24. De las Cuevas C, De Leon J, Peñate W, Betancort M. Factors influencing adherence to psychopharmacological medications in psychiatric patients: a structural equation modeling approach. Patient preference and adherence. 2017:681-90.
25. Chong WW, Aslani P, Chen TF. Adherence to antidepressant medications: an evaluation of community pharmacists' counseling practices. Patient preference and adherence. 2013:813-25.
26. Chong W, Aslani P, Chen T. Effectiveness of interventions to improve antidepressant medication adherence: a systematic review. International journal of clinical practice. 2011;65(9):954-75.
27. Sud D, Laughton E, McAskill R, Bradley E, Maidment I. The role of pharmacy in the management of cardiometabolic risk, metabolic syndrome and related diseases in severe mental illness: a mixed-methods systematic literature review. Systematic reviews. 2021;10:1-35.
28. Stimmel GL, McGhan WF, Wincor MZ, Deandrea DM. Comparison of pharmacist and physician prescribing for psychiatric inpatients. American Journal of Hospital Pharmacy. 1982;39(9):1483-6.
29. Brook O, Van Hout H, Nieuwenhuyse H, Heerdink E. Impact of coaching by community pharmacists on drug attitude of depressive primary care patients and acceptability to patients; a randomized controlled trial. European Neuropsychopharmacology. 2003;13(1):1-9.
30. Brook OH, Van Hout H, Stalman W, Nieuwenhuyse H, Bakker B, Heerdink E, et al. A pharmacy-based coaching program to improve adherence to antidepressant treatment among primary care patients. Psychiatric Services. 2005;56(4):487-9.

31. Finley PR, Rens HR, Pont JT, Gess SL, Louie C, Bull SA, et al. Impact of a collaborative pharmacy practice model on the treatment of depression in primary care. American Journal of Health-System Pharmacy. 2002;59(16):1518-26.
32. Rosen CE, Holmes S. Pharmacist's impact on chronic psychiatric outpatients in community mental health. American Journal of Health-System Pharmacy. 1978;35(6):704-8.
33. Razali M, Yahya H. Compliance with treatment in schizophrenia: a drug intervention program in a developing country. Acta Psychiatrica Scandinavica. 1995;91(5):331-5.
34. Shaw H, Mackie CA, Sharkie I. Evaluation of effect of pharmacy discharge planning on medication problems experienced by discharged acute admission mental health patients. International Journal of Pharmacy Practice. 2000;8(2):144-53.
35. Gisev N, Bell JS, McLachlan AJ, Chetty M, Chen TF. Psychiatric drug use among patients of a community mental health service: patterns and implications. Disease Management & Health Outcomes. 2006;14:369-76.
36. Aburamadan H, Sridhar S, Tadross T. Intensive monitoring of adverse drug reactions to antipsychotic medications in the inpatient psychiatry department of a secondary care hospital of UAE. International Journal of Pharmaceutical Investigation. 2018;8(3):151-.
37. Hashimoto Y, Tensho M. The need for educating patients with schizophrenia about the adverse effects of medications. Australasian Psychiatry. 2016;24(4):352-5.
38. Kaukab I, Nasir B, Abrar MA, Muneer S, Kanwal N, Shah SN, et al. Effect of pharmacist-led patient education on management of depression in drug resistance tuberculosis patients using cycloserine. A prospective study. Lat Am J Pharm. 2015;34(7):1403-10.
39. Lin C, Strauss R, Hong J, Hamper JG, Hoy ES, Lazar AA, et al. Impact of a pharmacist-administered long-acting injectable antipsychotic service in a supermarket-based community pharmacy on medication adherence. Journal of the American College of Clinical Pharmacy. 2019;2(4):343-8.
40. Mishra A, Krishna GS, Alla S, Kurian TD, Kurian J, Ramesh M, et al. Impact of pharmacist–psychiatrist collaborative patient education on medication adherence and quality of life (QOL) of Bipolar Affective Disorder (BPAD) patients. Frontiers in pharmacology. 2017;8:722.
41. Yalçin N, Ak S, Gürel SC, Çeliker A. Compliance in schizophrenia spectrum disorders: the role of clinical pharmacist. International Clinical Psychopharmacology. 2019;34(6):298-304.
42. Alves L, Carlos J, Rosana M, Carneiro C, Alberto L, Regina A. Assessment of the effectiveness of pharmacotherapy follow-up in patients treated for depression. Journal of Managed Care Pharmacy. 2013;19(3):218-27.
43. Raynsford J, Dada C, Stansfield D, Cullen T. Impact of a specialist mental health pharmacy team on medicines optimisation in primary care for patients on a severe mental illness register: a pilot study. European Journal of Hospital Pharmacy. 2020;27(1):31-5.
44. Gorton HC, Littlewood D, Lotfallah C, Spreadbury M, Wong KL, Gooding P, et al. Current and potential contributions of community pharmacy teams to self-harm and suicide prevention: A qualitative interview study. PloS One. 2019;14(9):e0222132.

45. Chike-Obuekwe S, Gray NJ, Gorton HC. Suicide Prevention in Nigeria: Can Community Pharmacists Have a Role? Pharmacy. 2022;10(5):109.
46. Black E, Murphy AL, Gardner DM. Community pharmacist services for people with mental illnesses: preferences, satisfaction, and stigma. Psychiatric Services. 2009;60(8):1123-7.
47. McMillan SS, El-Den S, O'Reilly CL, Roennfeldt H, Theodorus T, Chapman J, et al. A training programme for community pharmacists to support people living with severe and persistent mental illness: Intervention mapping in the context of a pandemic. Health Education Journal. 2022;81(8):964-81.
48. Samorinha C, Saidawi W, Saddik B, Abduelkarem AR, Alzoubi KH, Abu-Gharbieh E, et al. How is mental health care provided through community pharmacies? A quest for improvement. Pharmacy Practice. 2022;20(2):1-12.
49. Finley PR, Rens HR, Gess S, Louie C. Case management of depression by clinical pharmacists in a primary care setting. Formulary. 1999;34(10).
50. O'Reilly CL, Wong E, Chen TF. A feasibility study of community pharmacists performing depression screening services. Research in Social and Administrative Pharmacy. 2015;11(3):364-81.

Chapter 2

A COMPREHENSIVE REVIEW OF ETHNOBOTANICAL STUDIES IN GAZİANTEP PROVINCE

Seher YILDIRIM[1]
Songül KARAKAYA[2]

INTRODUCTION

All animals, plants, and humans in nature are the result of a delicate balance. In mythology, plants have been regarded as the most valuable gift given to humans by the gods. All plants serve humanity, and the relationship between humans and plants has existed since the beginning of human existence. Archaeological findings dating back to ancient times indicate that humans primarily relied on plants to obtain food and address health issues. The Neanderthal remains found in the Shanidar Cave in Northern Iraq during excavations carried out between 1957 and 1961, along with the objects discovered in the graves, are considered the earliest evidence of the plant-human relationship's inception. In a burial site believed to belong to a shaman and dating back 60,000 years, various plant species such as yarrow, henbane, purple hyacinth, hollyhock, marigold, and ephedra were identified. It is believed that these plants, which were placed in the grave with the belief that the deceased would use them upon returning to life, may indicate a differentiation between edible plants and medicinal plants. These plant species are still significant today, particularly in the field of herbal medicine (1).

The term "ethnobotany" is derived from the combination of "ethno," referring to studies related to humans, and "botany," which represents the science of plants. Ethnobotany carries the meaning of plant-human relationships in culturally diverse human communities from a broader perspective. The term "ethnobotany" was first used by American botanist John Harshberger in 1895. In the late 19th century, ethnobotany began to develop as a scientific discipline, and major pharmaceutical companies, including the World Health Organization (WHO),

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use of plants has also been observed in addressing concerns related to sperm count, infertility, and hormonal issues affecting menstrual regularity. However, it is worth noting that in hormonal problems, alternative techniques are also employed alongside herbal remedies.

Based on the ethnobotanical examination of plants used among the people in Gaziantep, it is evident that a wide variety of plants from different families have been utilized for various purposes. The results provide valuable insights into the traditional uses of 134 plants belonging to 42 families. The study highlights the extensive use of plants in all aspects of life in Gaziantep. The Asteraceae, Lamiaceae, and Rosaceae families are the most commonly utilized in terms of numerical representation. Medical applications stand out as the primary purpose of plant usage, particularly for conditions such as diabetes, liver and kidney diseases, wounds, and gastrointestinal problems. It is noteworthy that some traditional uses of plants align with existing literature, while others showcase unique local practices. Additionally, the findings indicate that certain plants are employed for the management of chronic diseases like heart conditions, blood pressure, and cholesterol, often without medical consultation.

REFERENCES

1. Faydaoğlu E, Sürücüoğlu MS. Geçmişten Günümüze Tıbbi ve Aromatik Bitkilerin Kullanılması ve Ekonomik Önemi. Kastamonu Üni., Orman Fakültesi Dergisi; 2011;11(1): 52- 67.
2. Kocabaş YZ, Gedik O. Kahramanmaraş İl Merkezi Semt Pazarlarında Satılan Bitkiler Hakkında Etnobotanik Araştırmalar. Iğdır Üni. Fen Bilimleri Enst. Der.; 2016;6(4):41-50. DOI: 10.21597/jist.2016624154.
3. Yiğit SŞ. Gaziantep ili Aktarlarında Satılan Bitkiler ve Etnobotanik Özellikleri, Fen Bilimleri Enstitüsü, Biyoloji Bölümü. Yüksek Lisans Tezi, Gaziantep: Gaziantep Üniversitesi, 2014.
4. Taş D. Anadolu Geleneksel Halk Hekimliği https://slideplayer.biz.tr/slide/2841511/. 09.12. 2023.
5. Kaya A. Tıbbi bitkiler ve etnobotanik çalışmalar. Bitkilerle tedavi sempozyumu; 2010; 5(6):11-18.
6. Faydaoğlu E, Sürücüoğlu MS. Geçmişten günümüze tıbbi ve aromatik bitkilerin kullanılması ve ekonomik önemi. Kastamonu University Journal of Forestry Faculty; 2011;11(1):52-67.
7. Vural N. Toksikoloji. A.Ü. Eczacılık Fak. Yayınları; NO: 73; 2005.
8. Güner U. Toksikoloji. Trakya Üniversitesi Fen Fakültesi; 2014; 2:186-189.
9. Karabaş M. Tarihte Zeytin, Üzüm Ve İncir https://www.academia.edu/download/91098545/Tarihte_Zeytin_J_Uzum_ve_Incir.pdf. 02.01. 2023.
10. Avcı M. Çeşitlilik ve Endemizm Açısından Türkiye'nin Bitki Örtüsü. İstanbul Üniversitesi Edebiyat Fakültesi Coğrafya Bölümü Coğrafya Dergisi; 2005;13:27–55.

11. Türkiye Tohumcular Birliği. Dünyadaki bitki türleri sayıldı. https://www.turktob.org.tr/en/dunyadaki-bitki-turleri-sayildi/22095. 15.11.2022.
12. Dinçer D, Bekçi B, Bekiryazıcı F. Türkiye'deki Doğal Bitki Türlerinin Üretiminde Doku Kültürü Tekniklerinin Kullanımı. Nevşehir Bilim ve Teknoloji Dergisi; 2016; Özel Sayı:295-302. DOI: 10.17100/nevbiltek.211012
13. Avcı M. Türkiye Bitki Örtüsünün Çeşitlilik ve Endemizm Açısından Bir Değerlendirmesi. Ulusal Coğrafya Kongresi; 2005; İstanbul; Bildiri Kitabı, 73–85.
14. Bulut E, Şimşek MY. Kırsal Turizm ve Gaziantep Arkeolojik Değerleri. Türk Bilimsel Derlemeler Dergisi;2014;2:38-44.
15. T. C. Kültür ve Turizm Bakanlığı/Gaziantep İl Kültür Ve Turizm Müdürlüğü. Tarihçe. https://gaziantep.ktb.gov.tr/TR-52292/tarihce.html. 12 Aralık 2022
16. Kalkan GP. "Gaziantep" Adı Üzerine. Kilis 7 Aralık Üniversitesi Sosyal Bilimler Dergisi;2015;5(9):101-107.
17. Uçar M. Gaziantep Tarihi Su Sisteminin Osmanlı Dönemindeki Yönetimi. MEGARON; 2017;12(1):157-169. DOI: 10.5505/megaron.2016.93898
18. Kalkan Gp. "Gaziantep" Adı Üzerine. Sosyal Bilimler Dergisi; 2015;5(9):101-107.
19. Baydar C. Gaziantep Yöresi Bilmece Sorma Geleneği Ve Gaziantep Bilmeceleri. Çağ Üniversitesi Sosyal Bilimler Enstitüsü Türk Dili Ve Edebiyatı Anabilim Dalı Mersin, 2019.
20. Gaziantep İl Çevre Durum Raporu T.C. Gaziantep Valiliği İl Çevre Ve Orman Müdürlüğü, Çed Ve Planlama Şube Müdürlüğü, Gaziantep - 2011.
21. Pehlivan M. Huzurlu Yaylası (Gaziantep) otsu bitkilerin floristik incelenmesi. Fen Bilimleri Enstitüsü, Biyoloji Bölümü. Yüksek lisans tezi, Gaziantep: Gaziantep Üniversitesi, 2005.
22. İncik FN. Gaziantep florasında bulunan Quercus L. (meşe) türlerinin tespiti ve biyoekolojik özelliklerinin incelenmesi.Fen Bilimleri Enstitüsü, Biyoloji Bölümü. Yüksek lisans tezi, Gaziantep: Gaziantep Üniversitesi, 2004.
23. Özuslu E. Gaziantep Üniversitesi Kampüs Florası.. Ekoloji; 2004;14(53):25-32.
24. Türkiye İstatistik Kurumu. Coğrafi İstatistik Portalı https://cip.tuik.gov.tr/. 04.02. 2023
25. Türkiye Nüfusu İl İlçe Mahalle Köy Nüfusları. Gaziantep Nüfusu. https://www.nufusune.com/gaziantep-nufusu. 01.03. 2023
26. Geniş Ş, Adağ EB. Demographic and Socio-economic Structure of Gaziantep City Population: Notes from a Fieldwork. Gaziantep Üniversitesi Sosyal Bilimler Dergisi; 2011;10(1):293-321.
27. Özer H, Türkmen N. Investigation of plants with ethnobotanical use in Gaziantep province (Turkey). GSC Biological and Pharmaceutical Sciences;2019;07(02):071–078. DOI: 10.30574/gscbps.2019.7.2.0076
28. Şığva HÖ, Seçmen Ö. Ethnobotanic survey of Işıklı (Çarpın), Dağdancık and Tokdemir in Gaziantep, Turkey. European Journal of Biology;2009;68(1):19-26.
29. Bulut G, Korkmaz A, Tuzlacı E. The ethnobotanical notes from Nizip (Gaziantep-Turkey). Istanbul Journal of Pharmacy; 2017;47(2):57-62. DOI: 10.5152/IstanbulJPharm.2017.009
30. Akgünlü S.B. Kilis ve Gaziantep yöresinde tüketilen bazı yabani sebzelerin mineral içerikleri ve mikrobiyolojik analizleri.Fen Bilimleri Enstitüsü, Biyoloji Anabilim Dalı. Yüksek lisans tezi, Kilis: Kilis 7 Aralık Üniversitesi, 2014.

Chapter 3

PHENOLIC CHALCONE MANNICH BASES AND THEIR CYTOTOXIC ACTIVITY

Mehtap TUGRAK SAKARYA[1]*
Halise İnci GUL[2]

1. INTRODUCTION

Cancer is a disease that can affect everyone, regardless of age, gender, nationality or ethnicity. According to the International Cancer Institute, it is a disease that ranks second among the causes of death with the highest mortality rate in the world. Although costly research and new treatment options are increasing rapidly in this field, the recovery rate of cancer patients can only be achieved by 20-25% (1). While the main aim of treatment should be to cure the cancer completely, this is very unlikely to be achieved. The realistic goal may be to increase the patient's life expectancy and quality. Today, surgery and radiation therapy are frequently used primarily in the treatment of a cancer patient. In addition to these treatments, chemotherapy is also frequently applied. Chemotherapy is a treatment with a large number of drugs to kill cancer cells. Chemotherapy uses drugs that destroy cancer cells. The ideal drug is expected to kill only cancer cells without harming normal cells, but this property is not present in most drugs currently used in clinical practice. Because there is not much difference in terms of quantity between malignant cancer cell and normal human cell. Cancer treatments often damage healthy cells and tissues. Side effects basically depend on the type and extent of the treatment and do not occur in the same way for everyone, and may even vary from one session to the next in the same person. For example, treatment with cytotoxic drugs often causes nausea, vomiting, loss of appetite, weakness, fatigue and anemia, and a decrease in blood cells leading to an increased risk of infection. While most people undergoing chemotherapy lose their hair, other side effects vary according to the type of drug. As a result, no chemical compound has

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publications on Mannich bases' antiproliferative effects have been published. This tendency has been expanded by the examination of aminomethylated derivatives of phenolic chalcone analogues, which was established by seminal research into the anticancer activity of Mannich bases produced from α,β-unsaturated ketones. With the inclusion of previously unknown examples of Mannich bases with potent activity, the production of cytotoxic compounds via aminomethylation of natural flavonoids and structurally related substrates continues to rise significantly. The information summarized in this update confirms the Mannich reaction's relevance in the design and synthesis of antiproliferative compounds, and hopefully provides the interested reader with structure information as well as the analytical tools needed for further advances in this ever-growing line of research.

REFERENCES

1. Palaska E. Antikanser ilaçlar. 2nd ed. Ankara: Hacettepe Üniversitesi Yayınları; 2004.
2. Dimmock JR, Kumar P. Anticancer and cytotoxic properties of Mannich bases. Current Medicinal Chemistry; 1997;4(1):1-22. doi: 10.1002/CHIN.199745335
3. Kandepu NM. Mannich bases of chalcones and cyclohexanones as candidate cytotoxic agents. Ottawa: University of Saskatchewan; 1999.
4. Dollinger M, Rosenbaum EH, Tempero M, et al. Everyone's Guide to Cancer Therapy. 4th ed. Bethesda, Maryland: Andrews McMeel; 2002.
5. Anand P, Sundaram C, Jhurani S, et al. Curcumin and cancer: an "old-age" disease with an "age-old" solution. Cancer Letters; 2008;267(1):133-164. doi: 10.1016/j.canlet.2008.03.025
6. Albert AA. Selective Toxicity: The Physico-Chemical Basis of Therapy. Baskı. New York, Chapman and Hall, 1985.
7. Frei E. Effect of Dose and Schedule on Response, Cancer Medicine. Philadelphia, Lea and Febiger, 1974: 117
8. Dowling MD, Krakoff IH, Karnofsky DD. Mechanism of Action of Anti-Cancer Drugs, Chemoteraphy of Cancer. Phidelphia, Lea and Febiger, 1970.
9. Ertan M. Antikanser Ðlaçlar. 1st ed. Ankara: Hacettepe Üniversitesi Yayınları; 2000
10. Ashby J. Potential carcinogenicity of alkylating agents. Chemistry in Britian; 1978; 14: 595.
11. Dimmock JR, Raghavan SK, Bigam GE. Evaluation of Mannich-bases of 2-arylidene-1,3-diketones versus murine P388 leukemia. European Journal of Medicinal Chemistry; 1988;23(2):111-117. doi:10.1016/0223-5234(88)90182-1
12. Farmer PB. Monitoring for human exposure to carcinogens. Chemistry in Britian; 1982; 18: 790-4. Accession Number: WOS:A1982PQ29200010
13. Cairns J. Efficiency of the adaptive response of Escherichia coli to alkylating agents. Nature; 1980;286(5769):176-178. doi: 10.1038/286176a0.
14. Waddell TG, Gebert PH, Tait DL. Michael type reactionsof tenulin, a biologically active sesquiterpene lactone. Journal of Pharmaceutical Sciences; 1983;72:1474-1476. doi: 10.1002/jps.2600721228

15. Baluja G, Municio AM, Vega S. Reactivity of some α,β-unsaturated ketones towards sulphydryl compounds and their antifungal activity. Chemical Industry; 1964;3:2053-2054.
16. Stern H. Sulphydryl groups and cell division. Science; 1956;124:1292-1293. doi: 10.1126/science.124.3235.1292-a.
17. Kostanecki, S.; Tambor, J. Ueber die sechs isomeren Monooxybenzalacetophenone (Monooxychalkone). Berichte der Deutschen Chemischen Gesellschaft; 1899; 32: 1921–1926 . doi:10.1002/cber.18990320293
18. Dimmock JR, Elias DW, Beazely MA, et al. Bioactivities of chalcones. Current Medicinal Chemistry; 1999;6(12):1125-1149.
19. Lahtchev KL, Batovska DI, Parushev SP, et al. Antifungal activity of chalcones: A mechanistic study using various yeast strains. European Journal of Medicinal Chemistry; 2008;43(10):2220-2228. doi: 10.1016/j.ejmech.2007.12.027
20. Tomar V, Kamaluddin BG, Rajakumar S, et al. Synthesis of new chalcone derivatives containing acridinyl moiety with potential antimalarial activity. European Journal of Medicinal Chemistry; 2010;45(2):745-751. doi: 10.1016/j.ejmech.2009.11.022
21. Nakamura C, Kawasaki N, Miyataka H, et al. Synthesis and biological activities of fluorinated chalcone derivatives. Bioorganic and Medicinal Chemistry; 2002;10(3):699-706. doi: 10.1016/S0968-0896(01)00319-4
22. Wu J, Li J, Cai Y, et al. Evaluation and discovery of novel synthetic chalcone derivatives as anti-inflammatory agents. Journal of Medicinal Chemistry; 2011;54:8110-8123. doi: 10.1021/jm200946h
23. Israf DA, Khaizurin TA, Syahida A, et al. Cardamonin inhibits COX and iNOS expression via inhibition of p65NF-kappaB nuclear translocation and Ikappa-B phosphorylation in RAW 264.7 macrophage cells. Molecular Immunology; 2007;44(5):673-679. doi: 10.1016/j.molimm.2006.04.025
24. Abdullah MI, Mahmood A, Madni M, et al. Synthesis, characterization, theoretical, anti-bacterial and molecular docking studies of quinoline based chalcones as a DNA gyrase inhibitor. Bioorganic Chemistry; 2014;54:31-37. doi: 10.1016/j.bioorg.2014.03.006
25. Mahapatra DK, Asati V, Baharti SK. Chalcones and their therapeutic targets for the management of diabetes: structural and pharmacological perspectives. European Journal of Medicinal Chemistry; 2015;92:839-865. doi: 10.1016/j.ejmech.2015.01.051
26. Claisen L, Claparède A. "Condensationen von Ketonen mit Aldehyden" [Condensations of ketones with aldehydes]. Berichte der Deutschen Chemischen Gesellschaft; 1881; 14 (1): 2460–2468. doi:10.1002/cber.188101402192.
27. Schmidt JG. "Ueber die Einwirkung von Aceton auf Furfurol und auf Bittermandelöl in Gegenwart von Alkalilauge" [On the effect of acetone on furfural and on bitter almond oil (benzaldehyde) in the presence of alkali hydroxides]. Berichte der Deutschen Chemischen Gesellschaft; 1881; 14 (1): 1459–1461. doi:10.1002/cber.188101401306.
28. Micheli F, Degiorgis F, Feriani A, et al. A combinatorial approach to [1,5]benzothiazepine derivates as potential antibacterial agents. Journal of Combinatorial Chemistry; 2001;3:224-228. doi: 10.1021/cc0000949
29. Alcantara AR, Marinas JM, Sinisterra JV. Synthesis of 2'-hydroxychalcones and related-compounds in interfacial solid-liquid conditions. Tetrahedron Letters; 1987;28:1515-1518. doi: 10.1016/S0040-4039(01)81030-3

30. Daskiewicz JB, Comte G, Barron D, et al. Organolithium mediated synthesis of prenylchalcones as potential inhibitors of chemoresistance. Tetrahedron Letters; 1999;40:7095-7098. doi: 10.1016/S0040-4039(99)01461-6
31. Mahapatra DK, Bharti SK, Asati V. Anti-cancer chalcones: Structural and molecular target perspectives. European Journal of Medicinal Chemistry; 2015;98:69-114. doi: 10.1016/j.ejmech.2015.05.004.
32. Iwata S, Nishino T, Nagata N, et al. Antitumorigenic activities of chalcones. I. Inhibitory effects of chalcone derivatives on 32Pi-incorporation into phospholipids of HeLa cells promoted by 12-O-tetradecanoyl-phorbol 13-acetate (TPA). Biological and Pharmaceutical Bulletin; 1995;18(12):1710-1713. doi: 10.1248/bpb.18.1710.
33. Yit CC, Das NP. Cytotoxic effect of butein on human colon adenocarcinoma cell proliferation. Cancer Letters; 1994;82(1):65-72. doi: 10.1016/0304-3835(94)90147-3.
34. Post JFM, Varma RS. Growth inhibitory effects of bioflavonoids and related compounds on human leukemic CEM-Cl and CEM-C7 cells. Cancer Letters; 1992;67:207-213. doi: 10.1016/0304-3835(92)90145-l.
35. Blicke FF, editor. Mannich Reaction. New York: John Wiley and Sons; 1942.
36. Mannich C, Krosche W. Ueber ein kondensations produkt aus formaldehyd, ammoniak und antipyrin. Archiv der Pharmazie; 1912;250:647-647. doi: 10.1002/ardp.1912250015
37. Davioud-Charvet E, McLeish MJ, Veine DM, et al. Mechanism-based inactivation of thioredoxin reductase from plasmodium falciparum by Mannich bases. Implication for cytotoxicity. Biochemistry; 2003;42:13319-13330. doi: 10.1021/bi0353629.
38. Roman G. Mannich bases in medicinal chemistry and drug design. European Journal of Medicinal Chemistry, 2015;89:743-816. doi: 10.1016/j.ejmech.2014.10.076
39. Tugrak M, Gul HI, Sakagami H. Synthesis and cytotoxicities of 2-[4-hydroxy-(3,5-bis-aminomethyl)-benzylidene]-indan-1-ones. Letter Drug Design and Discovery; 2015;12:806-812. doi: 10.2174/1570180812666150430002002
40. Tugrak M, Yamali C, Sakagami H, et al. Synthesis of mono Mannich bases of 2-(4-hydroxybenzylidene)-2,3-dihydroinden-1-one and evaluation of their cytotoxicities. Journal of Enzyme Inhibition and Medicinal Chemistry; 2016;31(5):818-823. doi: 10.3109/14756366.2015.1070263.
41. Chen Y, Cass SL, Kutty SK, et al. Synthesis, biological evaluation and structure-activity relationship studies of isoflavene based Mannich bases with potent anti-cancer activity. Bioorganci and Medicinal Chemistry Letters; 2015;25:5377-5383. doi: 10.1016/j.bmcl.2015.09.027.
42. Sivakumar KK, Rajasekaran A, Senthilkumar P, et al. Conventional and microwave assisted synthesis of pyrazolone Mannich bases possessing anti-inflammatory, analgesic, ulcerogenic effect and antimicrobial properties. Bioorganic and Medicinal Chemistry Letters; 2014;24:2940-2944. doi: 10.1016/j.bmcl.2014.04.067.
43. Koksal M, Yarim M, Erdal A, et al Synthesis and anti-inflammatory activities of novel 5-(3,4-dichlorophenyl)-3-[(4-substitutedpiperazin-1-yl)methyl]-1,3,4-oxadiaxole-2(3H)-thiones. Drug Research; 2014;64:66-72. doi: 10.1055/s-0033-1353184
44. Lee CM, Plattner JJ, Ours CW et al. [(Aminomethyl)aryloxy]acetic acid esters. A new class of high-ceiling diuretics. 1. effect of nitrogen and aromatic nuclear substitution. Journal of Medicinal Chemistry; 1984:1579-1587. doi: 10.1021/jm00378a010

45. Erciyas E, Erkaleli HI, Cosar G. Antimicrobial evaluation of some stryl ketone derivatives and related thiol adducts. Journal of Pharmaceutical Sciences; 1984;83:545-548. doi: 10.1002/jps.2600830420
46. Gul HI, Calis U, Ozturk Z, et al. Evaluation of anticonvulsant activities of bis(3-aryl-3-oxo-propyl) ethylamine hydrochlorides and 4-aryl-3-arylcarbonyl-1-ethyl-4-piperidinol hydrochlorides. Arzneimittelforschung; 2007;57:133-136. doi: 10.1055/s-0031-1296595
47. Reddy MVB, Su CR, Chiou WF, et al. Design, synthesis, and biological evaluation of Mannich bases of heterocyclic chalcone analogs as cytotoxic agents. Bioorganic and Medicinal Chemistry; 2008;16:7358-7370. doi: 10.1016/j.bmc.2008.06.018
48. Dimmock JR, Kandepu NM, Hetherington M, et al. Cytotoxic activities of Mannich bases of chalcones and related compounds. Journal of Medicinal Chemistry; 1998;41:1014-1026. doi: 10.1021/jm970432t
49. Kandeel MM, Abdou NA, Kadry HH, et al. Synthesis and in vitro antitumor activity of some new Mannich bases. International Journal of ChemTech Research; 2013;5:401-408.
50. Tugrak M, Gul HI, Bandow K, et al. Synthesis and biological evaluation of some new mono Mannich bases with piperazines as possible anticancer agents and carbonic anhydrase inhibitors. Bioorganic Chemistry; 2019;90:103095. doi: 10.1016/j.bioorg.2019.103095
51. Chen Y, Cass SL, Kutty SK et al. Synthesis, biological evaluation and structure–activity relationship studies of isoflavene based Mannich bases with potent anti-cancer activity. Bioorganic and Medicinal Chemistry Letters; 2015; 25:5377–5383. doi:10.1016/j.bmcl.2015.09.027
52. Pape VFS, Palkó R, Tóth S et al. Structure–activity relationships of 8-hydroxyquinoline-derived Mannich bases with tertiary amines targeting multidrug-resistant cancer. Journal of Medicinal Chemistry; 2022; 65: 7729-7745. doi: 10.1021/acs.jmedchem.2c00076
53. Yamali C, Gul HI, Sakagami H et al. Synthesis and bioactivities of halogen bearing phenolic chalcones and their corresponding bis Mannich bases. Journal of Enzyme Inhibition and Medicinal Chemistry; 2016; 31(S4): 125–131. doi: 10.1080/14756366.2016.1221825

Chapter 4

ANALYSIS OF ANTIOXIDANT CAPACITY OF COMMERCIAL *Myrtus communis* ESSENTIAL OIL BY SPECTROPHOTOMETRIC METHOD

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INTRODUCTION

Myrtus communis L. belongs to the Myrtaceae family. The Myrtaceae family includes 145 genera and 5500 species (1). It is a plant species belonging to West Asia, Southern Europe, and North Africa (2, 3). It is common in the Mediterranean region. Myrtle is an endemic plant known as murt or hambelis (4). *M. communis* is one of the prominent medicinal and aromatic species in the Myrtaceae family (5). *M. communis* can reach an average height of 2-4 meters. Its leaves are hairless, glossy, dark green, perennial herbs. Its fruits are hairless, pea-sized, hard, and oval in appearance. The flowering period of the *M. communis* plant is in the summer months. Ripe fruits taste sweeter than unripe fruits. It is drought resistant because it needs very little water (3, 6-10). Its flowers are star-shaped, white or pink in appearance, and fragrant (11). The leaves, fruits, and underground roots of *M. communis* are the parts traditionally recommended for use in folk medicine (12). Traditional medicinal uses of *M. communis* leaves in Algeria include the treatment of sinusitis, otitis, respiratory disorders, bronchitis, hemorrhoid, and diarrhea (13). *M. communis* leaves are generally preferred in the cosmetics industry in Turkey, and its fruits are also preferred in villages as an antiseptic (14). Some studies reveal the sedative effect of *M. communis* due to its anxiolytic and muscle relaxant properties without anticonvulsant effects (15, 16). The aroma of the essential oil (EO), which is present in the plant's abundant

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extract showed higher antioxidant activity than the essential oil included in this study (88). This difference may be due to the methods used while obtaining the essential oil, or to the use of leaves only.

4. CONCLUSION

Myrtle EO has been utilized for centuries as a disinfectant, antiseptic, and in the treatment of various diseases. After it was revealed that myrtle EO has antioxidant properties, it has taken its place in the food industry. In this study, the antioxidant properties of commercially available *M. communis* EO were investigated. In this study, which we conducted using the DPPH method, the IC_{50} value was examined and EC_{50}, ARP, and AEAC values were calculated according to this result. When the results were examined, it was seen that *M. communis* EO was a natural antioxidant source.

Instead of commercially procuring *M. communis* EO, the EO can be obtained and studied by using distillation, extraction, or mechanical methods. However, for this, the periods when the EO content in the leaves of the plant is at the highest level should be preferred. Evaluation of the antioxidant capacity of EO using different methods will contribute to the literature.

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5. REFERENCE

1. Snow N. et al. Morphological and molecular evidence of polyphyly in Rhodomyrtus (Myrtaceae: Myrteae). Systematic Botany; 2011;36;(2):390-404 doi:10.1600/036364411X569570
2. Nadkarni K. Indian Materia Medica, 3rd Edn, Popular Prakashan Pvt. Ltd., Bombay; 1989;1:838
3. Satyavati G, Raina M Sharma M, Medicinal plants of India. Vol. 2. 1987: Indian Council of Medical Research.
4. Atzei AD, Le piante nella tradizione popolare della Sardegna: documentazione sugli usi alimentari, aromatizzanti, profumieri, artigianali, cosmetici, medicinali, veterinari, magici, ornamentali, rituali, religiosi, tintori, antiparassitari e vari, delle piante. 2003: Carlo Delfino Editore.
5. Mendes M, Gazarini L Rodrigues M. Acclimation of Myrtus communis to contrasting Mediterranean light environments—effects on structure and chemical composition of foliage and plant water relations. Environmental and experimental botany; 2001;45;(2):165-178 doi:10.1016/S0098-8472(01)00073-9
6. Kirtikar K Basu B. Indian medicinal plants. Indian Medicinal Plants.; 1935

7. Maheshwari P Singh U. Dictionary of economic plants in India. Dictionary of economic plants in India.; 1965
8. Sastri B. The Wealth of India. A Dictionary of Indian Raw Materials and Industrial Products. Raw Materials, Vol. 6: LM.1962
9. Shah C Qadry J, A textbook of pharmacognosy. 1971: Messrs BS Shah.
10. Stuart M, The encyclopedia of herbs and herbalism. 1981: Crescent.
11. Charles D. Antioxidant properties of spices shells and other. London: John Willey; 2013
12. Farah A. et al. Fractional distillation effect on the chemical composition of Moroccan myrtle (Myrtus communis L.) essential oils. Flavour and fragrance Journal; 2006;21;(2):351-354 doi:10.1002/ffj.1651
13. Beloued A. Plantes médicinales d'Algérie. Office des publications universitaires. Alger, 184p; 1998
14. Baytop T. Therapy with medicinal plants in Turkey (past and present). Publication of the istanbul University; 1999;312
15. Hajiaghaee R. et al. Hydroalcoholic extract of Myrtus communis can alter anxiety and sleep parameters: a behavioural and EEG sleep pattern study in mice and rats. Pharmaceutical biology; 2016;54;(10):2141-2148 doi:10.3109/13880209.2016.1148175
16. Mulas M Cani MR. Germplasm evaluation of spontaneous myrtle (Myrtus communis L.) for cultivar selection and crop development. Journal of herbs, spices & medicinal plants; 1999;6;(3):31-49 doi:10.1300/J044v06n03_04
17. Gardeli C. et al. Essential oil composition of Pistacia lentiscus L. and Myrtus communis L.: Evaluation of antioxidant capacity of methanolic extracts. Food chemistry; 2008;107;(3):1120-1130 doi:10.1016/j.foodchem.2007.09.036
18. Bradesi P. et al. Chemical composition of myrtle leaf essential oil from Corsica (France). Journal of essential oil Research; 1997;9;(3):283-288 doi:10.1080/10412905.1997.10554245
19. Boelens MH Jimenez R. The chemical composition of Spanish myrtle oils. Part II. Journal of Essential Oil Research; 1992;4;(4):349-353 doi:10.1080/10412905.1992.9698084
20. Bouzouita N, Kachouri F, Hamdi M Chaabouni MM. Antimicrobial activity of essential oils from Tunisian aromatic plants. Flavour and fragrance journal; 2003;18;(5):380-383 doi:10.1002/ffj.1200
21. Yadegarinia D. et al. Biochemical activities of Iranian Mentha piperita L. and Myrtus communis L. essential oils. Phytochemistry; 2006;67;(12):1249-1255 doi:10.1016/j.phytochem.2006.04.025
22. Hayder N. et al. Antimutagenic activity of Myrtus communis L. using the Salmonella microsome assay. South african journal of botany; 2008;74;(1):121-125 doi:10.1016/j.sajb.2007.10.001
23. Hayder N. et al. Anti-genotoxic and free-radical scavenging activities of extracts from (Tunisian) Myrtus communis. Mutation Research/Genetic Toxicology and Environmental Mutagenesis; 2004;564;(1):89-95 doi:10.1016/j.mrgentox.2004.08.001
24. Urios A Blanco M. Specificity of spontaneous and t-butyl hydroperoxide-induced mutations in ΔoxyR strains of Escherichia coli differing with respect to the SOS mutagenesis proficiency and to the MutY and MutM functions. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis; 1996;354;(1):95-101 doi:10.1016/0027-5107(96)00043-7

25. Lawrence BM, Hogg JW Terhune SJ. Essential oils and their constituents: III. Some new trace constituents in the essential oil of Salvia lavandulaefolia, Vahl. Journal of Chromatography A; 1970;50:59-65 doi:10.1076/phbi.35.3.218.13295
26. Mazza G. Gas chromatographic—mass spectrometric investigations of the volatile components of myrtle berries (Myrtus communis L.). Journal of Chromatography A; 1983;264:304-311 doi:10.1016/S0021-9673(01)95036-8
27. Elfellah M, Akhter M Khan M. Anti-hyperglycaemic effect of an extract of Myrtus communis in streptozotocin-induced diabetes in mice. Journal of ethnopharmacology; 1984;11;(3):275-281 doi:10.1016/0378-8741(84)90073-4
28. Gortzi O, Lalas S, Chinou I Tsaknis J. Reevaluation of bioactivity and antioxidant activity of Myrtus communis extract before and after encapsulation in liposomes. European food research and technology; 2008;226;(3):583-590 doi:10.1007/s00217-007-0592-1
29. Maccioni S, Tomei P Rizzo A. L'uso medicinale delle specie vegetali selvatiche e coltivate nella tradizione popolare della bassa Val di Magra. 1995
30. Serce S. et al. Antioxidant activities and fatty acid composition of wild grown myrtle (Myrtus communis L.) fruits. Pharmacognosy magazine; 2010;6;(21):9 doi:10.4103/0973-1296.59960
31. Hakeem M Mufradat B. Idara Tarraqui Urdu Publications, Lucknow. 1895
32. Clark AM. Natural products as a resource for new drugs. Pharmaceutical research; 1996;13;(8):1133-1141 doi:10.1023/A:1016091631721
33. Messaoud C, Laabidi A Boussaid M. Myrtus communis L. infusions: the effect of infusion time on phytochemical composition, antioxidant, and antimicrobial activities. Journal of food science; 2012;77;(9):C941-C947 doi:10.1111/j.1750-3841.2012.02849.x
34. Chalchat J-C, Garry R-P Michet A. Essential oils of myrtle (Myrtus communis L.) of the Mediterranean littoral. Journal of essential oil Research; 1998;10;(6):613-617 doi: 10.1080/10412905.1998.9700988
35. Ziyyat A. et al. Phytotherapy of hypertension and diabetes in oriental Morocco. Journal of ethnopharmacology; 1997;58;(1):45-54 doi:10.1016/S0378-8741(97)00077-9
36. Le Floc'h E. Contribution aune étude ethnobotanique de la flore tunisienne. Imprimerie Officielle de la Republique Tunisienne, Tunis; 1983
37. Flamini G. et al. Phytochemical typologies in some populations of Myrtus communis L. on Caprione Promontory (East Liguria, Italy). Food chemistry; 2004;85;(4):599-604 doi:10.1016/j.foodchem.2003.08.005
38. Sumbul S, Ahmad MA, Asif M Akhtar M. Myrtus communis Linn.-A review. 2011
39. Feißt C, Franke L, Appendino G Werz O. Identification of molecular targets of the oligomeric nonprenylated acylphloroglucinols from Myrtus communis and their implication as anti-inflammatory compounds. Journal of Pharmacology and Experimental therapeutics; 2005;315;(1):389-396 doi:10.1124/jpet.105.090720
40. Traboulsi AF. et al. Insecticidal properties of essential plant oils against the mosquito Culex pipiens molestus (Diptera: Culicidae). Pest management science; 2002;58;(5):491-495 doi:10.1002/ps.486
41. Gautheir R AAaGM. Activity of the extracts of Myrtus communis against Pediculus humanis capitis. Plant Med Phytother; 1988;23;(2):25-108
42. Amensour M. et al. Antioxidant activity and total phenolic compounds of myrtle extracts Actividad antioxidante y contenido de compuestos fenólicos totales en extractos de myrtus. CyTA–Journal of Food; 2010;8;(2):95-101 doi:10.1080/19476330903161335

43. Sepici A, Gürbüz I, Çevik C Yesilada E. Hypoglycaemic effects of myrtle oil in normal and alloxan-diabetic rabbits. Journal of ethnopharmacology; 2004;93;(2-3):311-318 doi:10.1016/j.jep.2004.03.049
44. Sumbul S. et al. Evaluation of Myrtus communis Linn. berries (common myrtle) in experimental ulcer models in rats. Human & experimental toxicology; 2010;29;(11):935-944 doi:10.1177/0960327110364154
45. Alem G, Mekonnen Y, Tiruneh M Mulu A. Invitro antibacterial activity of crude preparation of myrtle (Myrtus communis) on common human pathogens. Ethiopian medical journal; 2008;46;(1):63-69
46. Mansouri S, Foroumadi A, Ghaneie T Najar AG. Antibacterial activity of the crude extracts and fractionated constituents of Myrtus communis. Pharmaceutical biology; 2001;39;(5):399-401 doi:10.1076/phbi.39.5.399.5889
47. Fleming ET. PDR for Herbal Medicines, 2nd ad. Montvale, NJ:-Medical Economics Company; 2000:656-657
48. Ormancey X. Formulation of essential oils in functional perfumery. Parfums, Cosmetiques, Actualites; 2001;157:30-40
49. Sawamura M. Aroma and functional properties of Japanese yuzu (Citrus junos Tanaka) essential oil. Aroma Research; 2000;1;(1):14-19
50. Gupta V. et al. Pharmacological potential of Matricaria recutita-A review. Int J Pharm Sci Drug Res; 2010;2;(1):12-16
51. Martín Á, Varona S, Navarrete A Cocero MJ. Encapsulation and co-precipitation processes with supercritical fluids: applications with essential oils. The Open Chemical Engineering Journal; 2010;4;(1) doi:10.2174/1874123101004010031
52. Andrade EHA. et al. Variability in essential oil composition of Piper dilatatum LC Rich. Biochemical systematics and ecology; 2011;39;(4-6):669-675 doi:10.1016/j.bse.2011.05.021
53. Griffin SG, Wyllie SG, Markham JL Leach DN. The role of structure and molecular properties of terpenoids in determining their antimicrobial activity. Flavour and Fragrance Journal; 1999;14;(5):322-332 doi:10.1002/(SICI)1099-1026(199909/10)14:5<322::AID-FFJ837>3.0.CO;2-4
54. De Sousa DP. Analgesic-like activity of essential oils constituents. Molecules; 2011;16;(3):2233-2252 doi:10.3390/molecules16032233
55. Lis-Balchin M. Essential oils and'aromatherapy': their modern role in healing. Journal of the royal society of health; 1997;117;(5):324-329 doi:10.1177/146642409711700511
56. Sangwan N, Farooqi A, Shabih F Sangwan R. Regulation of essential oil production in plants. Plant growth regulation; 2001;34;(1):3-21 doi:10.1023/A:1013386921596
57. Caballero B, Trugo LC Finglas PM, Encyclopedia of food sciences and nutrition. 2003: Academic.
58. Hyldgaard M, Mygind T Meyer RL. Essential oils in food preservation: mode of action, synergies, and interactions with food matrix components. Frontiers in microbiology; 2012;3:12 doi:10.3389/fmicb.2012.00012/full
59. Pereira P, Cebola M-J Bernardo-Gil MG. Comparison of antioxidant activity in extracts of Myrtus communis L. obtained by SFE vs. solvent extraction. Journal of Environmental Science and Engineering. A; 2012;1;(1A)
60. Young I Woodside J. Antioxidants in health and disease. Journal of clinical pathology; 2001;54;(3):176-186

61. Reynolds J. Martindale–The Extra Pharmacopoeia 31st edition London. Royal Pharmaceutical society of Great Britain; 1996
62. Lis-Balchin M Deans S. Bioactivity of selected plant essential oils against Listeria monocytogenes. Journal of applied microbiology; 1997;82;(6):759-762 doi:10.1046/j.1365-2672.1997.00153.x
63. Burt S. Essential oils: their antibacterial properties and potential applications in foods—a review. International journal of food microbiology; 2004;94;(3):223-253 doi:10.1016/j.ijfoodmicro.2004.03.022
64. Wang H. et al. Antioxidant and antiinflammatory activities of anthocyanins and their aglycon, cyanidin, from tart cherries. Journal of natural products; 1999;62;(2):294-296 10.1021/np980501m
65. Wang SY Stretch AW. Antioxidant capacity in cranberry is influenced by cultivar and storage temperature. Journal of Agricultural and Food Chemistry; 2001;49;(2):969-974 doi:10.1021/jf001206m
66. Zheng W Wang SY. Oxygen radical absorbing capacity of phenolics in blueberries, cranberries, chokeberries, and lingonberries. Journal of agricultural and food chemistry; 2003;51;(2):502-509 doi:10.1021/jf020728u
67. Hayder N. et al. In vitro antioxidant and antigenotoxic potentials of myricetin-3-o-galactoside and myricetin-3-o-rhamnoside from Myrtus communis: Modulation of expression of genes involved in cell defence system using cDNA microarray. Toxicology in vitro; 2008;22;(3):567-581 doi:10.1016/j.tiv.2007.11.015
68. Romani A. et al. Evaluation of antioxidant effect of different extracts of Myrtus communis L. Free radical research; 2004;38;(1):97-103 doi:10.1080/10715760310001625609
69. Rosa A. et al. Protective effect of the oligomeric acylphloroglucinols from Myrtus communis on cholesterol and human low density lipoprotein oxidation. Chemistry and physics of lipids; 2008;155;(1):16-23 doi:10.1016/j.chemphyslip.2008.04.005
70. Alamanni M Cossu M. Radical scavenging activity and antioxidant activity of liquors of myrtle (myrtus communis l.) Berries and leaves. Italian journal of food science; 2004;16;(2) doi:10.1016/j.chemphyslip.2008.04.005
71. Vacca V. et al. Changes in phenolic compounds, colour and antioxidant activity in industrial red myrtle liqueurs during storage. Food/Nahrung; 2003;47;(6):442-447 doi:10.1002/food.200390098
72. Tuberoso CI. et al. Myrtle hydroalcoholic extracts obtained from different selections of Myrtus communis L. Food Chemistry; 2007;101;(2):806-811 doi:10.1016/j.foodchem.2006.02.039
73. Angioni A. et al. Effects of cold storage on quality traits of Sardinian Myrtle (Mytrus communis L.) berries and their alcoholic extracts. 2011
74. Miguel MG. Antioxidant activity of medicinal and aromatic plants. A review. Flavour and Fragrance Journal; 2010;25;(5):291-312 doi:10.1002/ffj.1961
75. Moon J-K Shibamoto T. Antioxidant assays for plant and food components. Journal of agricultural and food chemistry; 2009;57;(5):1655-1666 doi:10.1021/jf803537k
76. Joshi SC, Verma AR Mathela CS. Antioxidant and antibacterial activities of the leaf essential oils of Himalayan Lauraceae species. Food and Chemical Toxicology; 2010;48;(1):37-40 doi:10.1016/j.fct.2009.09.011

77. Blois MS. Antioxidant determinations by the use of a stable free radical. Nature; 1958;181;(4617):1199-1200
78. Brand-Williams W, Cuvelier M-E Berset C. Use of a free radical method to evaluate antioxidant activity. LWT-Food science and Technology; 1995;28;(1):25-30 doi:10.1016/S0023-6438(95)80008-5
79. Wróblewska KB, Baby AR, Guaratini MTG Moreno PRH. In vitro antioxidant and photoprotective activity of five native Brazilian bamboo species. Industrial Crops and Products; 2019;130:208-215 doi:10.1016/j.indcrop.2018.12.081
80. Ghasemi K, Ghasemi Y Ebrahimzadeh MA. Antioxidant activity, phenol and flavonoid contents of 13 citrus species peels and tissues. Pak J Pharm Sci; 2009;22;(3):277-281
81. Kroyer GT. Red clover extract as antioxidant active and functional food ingredient. Innovative Food Science & Emerging Technologies; 2004;5;(1):101-105 doi:10.1016/S1466-8564(03)00040-7
82. Sasaki YF. et al. The comet assay with 8 mouse organs: results with 39 currently used food additives. Mutation Research/Genetic Toxicology and Environmental Mutagenesis; 2002;519;(1-2):103-119 doi:10.1016/S1383-5718(02)00128-6
83. Djeridane A. et al. Antioxidant activity of some Algerian medicinal plants extracts containing phenolic compounds. Food chemistry; 2006;97;(4):654-660 doi:10.1016/j.foodchem.2005.04.028
84. Wannes WA. et al. Antioxidant activities of the essential oils and methanol extracts from myrtle (Myrtus communis var. italica L.) leaf, stem and flower. Food and chemical toxicology; 2010;48;(5):1362-1370 doi:10.1016/j.fct.2010.03.002
85. Belmimoun A, Meddah B, Meddah A Sonnet P. Antibacterial and antioxidant activities of the essential oils and phenolic extracts of Myrtus communis and Zygophylum album from Algeria. Journal of Fundamental and Applied Sciences; 2016;8;(2):510-524 doi:10.4314/jfas.v8i2.22
86. Mimica-Dukić N. et al. Essential oil of Myrtus communis L. as a potential antioxidant and antimutagenic agents. Molecules; 2010;15;(4):2759-2770 doi:10.3390/molecules15042759
87. Wannes WA Marzouk B. Characterization of myrtle seed (Myrtus communis var. baetica) as a source of lipids, phenolics, and antioxidant activities. journal of food and drug analysis; 2016;24;(2):316-323 doi:10.1016/j.jfda.2015.11.001
88. Benchikh F, Amira S Benabdallah H. The evaluation of antioxidant capacity of different fractions of Myrtus communis L. leaves. Annual Research & Review in Biology; 2018:1-14

Chapter 5

ANALYSIS OF ANTIOXIDANT CAPACITY OF COMMERCIAL *Citrus lemon* ESSENTIAL OIL BY SPECTROPHOTOMETRIC METHOD

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INTRODUCTION

Citrus lemon (lemon) is a valuable therapeutic and aromatic plant from the Rutaceae family. It has yellow and elliptical edible fruit and is evergreen. The term lemon actually comes from the old French word for "lemon" and is expressed in different terms in different languages. While it is expressed with the terms "lamun" in Arabic and "lmun" in Persian; it goes by the names "lemon" in English, "zitrone" in German, and "le citron" in French. (1, 2). Soils that tend to be acidic, have a wide pH range, are successful in terms of drainage, and can retain moisture provide the most suitable conditions for the growth of C. lemon (3). Although it is unclear what C. lemon's precise native environment was, it has spread from Southeast Asia to Northeast India and then to China and has been cultivated since ancient times (4).

The main component of C. lemon is vitamin C, and it also contains terpenes, hydrocarbons, flavonoids, minerals, and essential oils. Scurvy is treated with vitamin C. llemon juice was employed in the treatment of scurvy disease even before vitamin C was discovered (5). In addition, in traditional medicine, lemon juice, which is rich in vitamin C content, is used to relieve hypertension, colds, sore throat, fever and chest pain; The essential oil (EO) of C. lemon has been used for cough since ancient times (6). In ancient Rome, the essential oil of C. lemon

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4. CONCLUSION

According to the needs of consumers, the demand for natural substances is increasing in the food, cosmetics, and pharmaceutical sectors. Consequently, research on essential oils is vital in addition to determining the components of essential oils as well as linking those components with the bioactive qualities of essential oils. The protective impact that essential oils have against oxidative damage is something that has to be investigated in great detail. With regards to the present investigation, the antioxidant capacity of C. lemon essential oil and ascorbic acid prepared in methanol using the DPPH method were compared. According to the data obtained and other studies in the sources, the radical scavenging effect of C. lemon essential oil was found to be lower than that of ascorbic acid. This is thought to be due to the fact that ascorbic acid is a potent antioxidant and the differences in the amount of phenolic component that provides antioxidant properties in C. lemon content. Our study suggests that C. lemon essential oil can be used as an auxiliary supplement as a result of the experiments and literature reviews.

Differences in phenolic content are likely to vary depending on the growing location, rainfall, temperature, humidity, the mineral content of the soil, time of harvest, method of obtaining the essential oil, and from which part of the plant it is obtained. This will cause differences in the results of antioxidant activity. In new studies on essential oils, compounds that affect antioxidant capacity can be determined by performing phenolic content analyses.

In this study, the evaluation of C. lemon essential oil by dissolving in solvents of different polarities (ethyl acetate, ethanol), examining its antioxidant capacity using different methods, studying the essential oils and extracts obtained from fruits and leaves grown at different maturity, climatic conditions, and soil yield, Determining their flavonoid contents and examining their antioxidant activities will also contribute to the literature.

REFERENCES

1. Kamal G. et al. Yield and chemical composition of Citrus essential oils as affected by drying pretreatment of peels. International Food Research Journal; 201
1;18;(4)
2. Klimek-Szczykutowicz M, Szopa A Ekiert H. Citrus limon (Lemon) phenomenon—a review of the chemistry, pharmacological properties, applications in the modern pharmaceutical, food, and cosmetics industries, and biotechnological studies. Plants; 2020;9;(1):119 doi:10.3390/plants9010119

3. Goetz P. Citrus limon (L.) Burm. f.(Rutacées) citronnier. Phytothérapie; 2014;12;(2):116-121 doi:10.1007/s10298-014-0854-6
4. Al-Qudah TS. et al. Lemon as a source of functional and medicinal ingredient: A review. International Journal of Chemical and Biochemical Science; 2018;14:55-61
5. Mabberley DJ. Citrus (Rutaceae): a review of recent advances in etymology, systematics and medical applications. Blumea-Biodiversity, Evolution and Biogeography of Plants; 2004;49;(2-3):481-498 doi:10.3767/000651904X484432
6. Balogun FO Ashafa AOT. A review of plants used in South African traditional medicine for the management and treatment of hypertension. Planta medica; 2019;85;(04):312-334 doi:10.1055/a-0801-8771
7. Papp N, Bartha S, Boris G Balogh L. Traditional uses of medicinal plants for respiratory diseases in Transylvania. Natural Product Communications; 2011;6;(10):1934578X1100601012 doi:10.1177/1934578X1100601
8. Clement Y, Baksh-Comeau Y Seaforth C. An ethnobotanical survey of medicinal plants in Trinidad. Journal of ethnobiology and ethnomedicine; 2015;11;(1):1-28 doi:10.1186/s13002-015-0052-0
9. Gulsen O Roose ML. Lemons: diversity and relationships with selected Citrus genotypes as measured with nuclear genome markers. Journal of the American Society for Horticultural Science; 2001;126;(3):309-317 doi:10.21273/JASHS.126.3.309
10. Talon M Gmitter FG. Citrus genomics. International journal of plant genomics; 2008;2008 doi:10.1155/2008/528361
11. Jia S-S. et al. Induction of apoptosis by D-limonene is mediated by inactivation of Akt in LS174T human colon cancer cells. Oncology reports; 2013;29;(1):349-354 doi:10.3892/or.2012.2093
12. Amorim JL. et al. Anti-inflammatory properties and chemical characterization of the essential oils of four citrus species. PloS one; 2016;11;(4):e0153643 doi:10.1371/journal.pone.0153643
13. Hamdan D. et al. Chemical composition of the essential oils of variegated pink-fleshed lemon (Citrus x limon L. Burm. f.) and their anti-inflammatory and antimicrobial activities. Zeitschrift für Naturforschung C; 2013;68;(7-8):275-284 10.1515/znc-2013-7-804
14. Millet F. Huiles essentielles et essence de citronnier (Citrus limon (L.) Burm. f.). Phytotherapie; 2014;12;(2):89-97 doi:10.1007/s10298-014-0857-3
15. Espina L. et al. Inactivation of Escherichia coli O157: H7 in fruit juices by combined treatments of citrus fruit essential oils and heat. International Journal of Food Microbiology; 2012;159;(1):9-16 doi:10.1016/j.ijfoodmicro.2012.07.020
16. Minami M. et al. The inhibitory effect of essential oils on herpes simplex virus type-1 replication in vitro. Microbiology and immunology; 2003;47;(9):681-684 doi:10.1111/j.1348-0421.2003.tb03431.x
17. Aboelhadid S. et al. In vitro and in vivo effect of Citrus limon essential oil against sarcoptic mange in rabbits. Parasitology research; 2016;115;(8):3013-3020 doi:10.1007/s00436-016-5056-8
18. Elegbede JA, Maltzman TH, Elson CE Gould MN. Effects of anticarcinogenic monoterpenes on phase II hepatic metabolizing enzymes. Carcinogenesis; 1993;14;(6):1221-1223 doi:10.1093/carcin/14.6.1221

19. Murali R Saravanan R. Antidiabetic effect of d-limonene, a monoterpene in streptozotocin-induced diabetic rats. Biomedicine & preventive nutrition; 2012;2;(4):269-275 doi:10.1016/j.bionut.2012.08.008
20. Jing L. et al. Preventive and ameliorating effects of citrus D-limonene on dyslipidemia and hyperglycemia in mice with high-fat diet-induced obesity. European journal of pharmacology; 2013;715;(1-3):46-55 doi:10.1016/j.ejphar.2013.06.022
21. Komiya M, Takeuchi T Harada E. Lemon oil vapor causes an anti-stress effect via modulating the 5-HT and DA activities in mice. Behavioural brain research; 2006;172;(2):240-249 doi:10.1016/j.bbr.2006.05.006
22. Kim J, Jayaprakasha GK, Uckoo RM Patil BS. Evaluation of chemopreventive and cytotoxic effect of lemon seed extracts on human breast cancer (MCF-7) cells. Food and chemical toxicology; 2012;50;(2):423-430 doi:10.1016/j.fct.2011.10.057
23. Parhiz H. et al. Antioxidant and anti-inflammatory properties of the citrus flavonoids hesperidin and hesperetin: an updated review of their molecular mechanisms and experimental models. Phytotherapy Research; 2015;29;(3):323-331 doi:10.1002/ptr.5256
24. Xavier S. et al. Vitamin C antioxidant effects in hippocampus of adult Wistar rats after seizures and status epilepticus induced by pilocarpine. Neuroscience letters; 2007;420;(1):76-79 doi:10.1016/j.neulet.2007.04.056
25. European Directorate for the Quality of Medicines. European Pharmacopoeia 9.2, Lemon Oil; European Directorate for the Quality of Medicines: Strasburg, Germany. 9.2 ed. 2017.
26. The United States Pharmacopeial Convention. United States Pharmacopoeia. National Formulary; The United States Pharmacopeial Convention. 2009
27. Ministry of Health and Faily Welfare. Citrus limon (Lilnn) Burm. f. In The Ayurvedic Pharmacopoeia of India (IV); Ministry of Health and Faily Welfare, Government of India. 2017.
28. Agence Nationale de Sécurité du Médicament et des Produits de Santé, France. French Pharmacopoeia, 10th ed.; Citrus limon Flavedo; Agence Nationale de Sécurité du Médicament et des Produits de Santé. 1998
29. Alman Komisyonu E, Fitoterapi. 2022 9.10.2022]; Available from: https://buecher.heilpflanzen-welt.de/BGACommission-E-Monographs/0043.htm
30. Kozmetik Bileşen Veritabanı (CosIng). 2022 9.10.2022]; Available from: https://ec.europa.eu/growth/sectors/cosmetics/cosing_en.
31. Hu J, Li X, Liu X Zhang W. Inhibitory effect of lemon essential oil on mushroom tyrosinase activity in vitro. Mod. Food Sci. Technol; 2015;31:97-105 doi:10.13982/j.mfst.1673-9078.2015.6.016
32. Valgimigli L. et al. Lemon (Citrus limon, Burm. f.) essential oil enhances the transepidermal release of lipid-(A, E) and water-(B6, C) soluble vitamins from topical emulsions in reconstructed human epidermis. International journal of cosmetic science; 2012;34;(4):347-356 doi:10.1111/j.1468-2494.2012.00725.x
33. Otang W Afolayan A. Antimicrobial and antioxidant efficacy of Citrus limon L. peel extracts used for skin diseases by Xhosa tribe of Amathole District, Eastern Cape, South Africa. South African Journal of Botany; 2016;102:46-49 doi:10.1016/j.sajb.2015.08.005

34. Avrupa Gıda Güvenliği Otoritesi (EFSA). 2022 9.10.2022]; Available from: http://www.efsa.europa.eu/.
35. Tisserand R Young R, Essential oil safety: a guide for health care professionals. 2013: Elsevier Health Sciences.
36. Volpato GT. et al. Effect of essential oil from Citrus aurantium in maternal reproductive outcome and fetal anomaly frequency in rats. Anais da Academia Brasileira de Ciências; 2015;87:407-415 doi:10.1590/0001-3765201520140354
37. Opdyke D DLJ O. Monographs on fragrance raw materials. 1974 doi:10.1016/S0015-6264(75)80165-9
38. Naganuma M. et al. A study of the phototoxicity of lemon oil. Archives of dermatological research; 1985;278;(1):31-36 doi:10.1007/BF00412492
39. Vekiari SA. et al. Composition and seasonal variation of the essential oil from leaves and peel of a Cretan lemon variety. Journal of Agricultural and Food Chemistry; 2002;50;(1):147-153 doi:10.1021/jf001369a
40. Robards K Antolovich M. Analytical chemistry of fruit bioflavonoidsA review. Analyst; 1997;122;(2):11R-34R doi:10.1039/A606499J
41. Russo M. et al. Reduced time HPLC analyses for fast quality control of citrus essential oils. Journal of Essential Oil Research; 2015;27;(4):307-315 doi:10.1080/10412905.2015.1027419
42. Kaskoos RA. Essential oil analysis by GC-MS and analgesic activity of Lippia citriodora and Citrus limon. Journal of essential oil bearing plants; 2019;22;(1):273-281 doi:10.1080/0972060X.2019.1603123
43. González-Molina E, Domínguez-Perles R, Moreno D García-Viguera C. Natural bioactive compounds of Citrus limon for food and health. Journal of pharmaceutical and biomedical analysis; 2010;51;(2):327-345 doi:10.1016/j.jpba.2009.07.027
44. Jing L. et al. Metabolite profiles of essential oils in citrus peels and their taxonomic implications. Metabolomics; 2015;11;(4):952-963 doi:10.1007/s11306-014-0751-x
45. Owolabi MS. et al. Chemical composition of Citrus limon (L.) Osbeck growing in Southwestern Nigeria: Essential oil chemotypes of both peel and leaf of lemon. Am. J. Essent. Oils Nat. Prod; 2018;6:36-40
46. Masson J. et al. Oxygenated heterocyclic compounds to differentiate Citrus spp. essential oils through metabolomic strategies. Food Chemistry; 2016;206:223-233 doi:10.1016/j.foodchem.2016.03.057
47. Valgimigli L Pratt DA. Antioxidants in chemistry and biology. Encyclopedia of radicals in chemistry, biology and materials; 2012 doi:10.1002/9781119953678.rad055
48. Amorati R, Foti MC Valgimigli L. Antioxidant activity of essential oils. Journal of agricultural and food chemistry; 2013;61;(46):10835-10847 doi:10.1021/jf403496k
49. Abuin E, Lissi E, Ortiz P Henriquez C. Uric acid reaction with DPPH radicals at the micellar interface. Boletín de la Sociedad Chilena de Química; 2002;47;(2):145-149 doi:10.4067/S0366-16442002000200010
50. Brand-Williams W, Cuvelier M-E Berset C. Use of a free radical method to evaluate antioxidant activity. LWT-Food science and Technology; 1995;28;(1):25-30 doi:10.1016/S0023-6438(95)80008-5
51. Gupta D. Methods for determination of antioxidant capacity: A review. International Journal of Pharmaceutical Sciences and Research; 2015;6;(2):546 doi:10.13040/IJPSR.0975-8232.6(2).546-66

52. Re R. et al. Antioxidant activity applying an improved ABTS radical cation decolorization assay. Free radical biology and medicine; 1999;26;(9-10):1231-1237 doi:10.1016/S0891-5849(98)00315-3
53. Miller NJ. et al. A novel method for measuring antioxidant capacity and its application to monitoring the antioxidant status in premature neonates. Clinical science (London, England: 1979); 1993;84;(4):407-412 doi:10.1042/cs0840407
54. Miller NJ Rice-Evans CA. Factors influencing the antioxidant activity determined by the ABTS•+ radical cation assay. Free radical research; 1997;26;(3):195-199 doi:10.3109/10715769709097799
55. Contreras-Guzmán ES Strong III FC. Determination of tocopherols (vitamin E) by reduction of cupric ion. Journal of the Association of Official Analytical Chemists; 1982;65;(5):1215-1221 doi:10.1093/jaoac/65.5.1215
56. Blois MS. Antioxidant determinations by the use of a stable free radical. Nature; 1958;181;(4617):1199-1200
57. Sánchez-Moreno C. Methods used to evaluate the free radical scavenging activity in foods and biological systems. Food science and technology international; 2002;8;(3):121-137 doi:10.1106/10820130202677
58. Wróblewska KB, Baby AR, Guaratini MTG Moreno PRH. In vitro antioxidant and photoprotective activity of five native Brazilian bamboo species. Industrial Crops and Products; 2019;130:208-215 doi:10.1016/j.indcrop.2018.12.081
59. Kroyer GT. Red clover extract as antioxidant active and functional food ingredient. Innovative Food Science & Emerging Technologies; 2004;5;(1):101-105 doi:10.1016/S1466-8564(03)00040-7
60. Thompson D Moldéus P. Cytotoxicity of butylated hydroxyanisole and butylated hydroxytoluene in isolated rat hepatocytes. Biochemical pharmacology; 1988;37;(11):2201-2207 doi:10.1016/0006-2952(88)90582-5
61. Kang H. et al. Studies on the development of functional powder from citrus peel. Bioresource technology; 2006;97;(4):614-620 doi:10.1016/j.biortech.2005.03.037
62. Choi H-S, Song HS, Ukeda H Sawamura M. Radical-scavenging activities of citrus essential oils and their components: detection using 1, 1-diphenyl-2-picrylhydrazyl. Journal of agricultural and food chemistry; 2000;48;(9):4156-4161 doi:10.1021/jf000227d
63. Frassinetti S. et al. Antibacterial and antioxidant activity of essential oils from Citrus spp. Journal of Essential Oil Research; 2011;23;(1):27-31 doi:10.1080/10412905.2011.9700427
64. Loizzo MR. et al. Chemical profile and antioxidant properties of extracts and essential oils from Citrus× limon (L.) burm. Cv. Femminello comune. Chemistry & biodiversity; 2016;13;(5):571-581 doi:10.1002/cbdv.201500186
65. İnan Ö, Özcan MM Aljuhaimi F. Effect of location and Citrus species on total phenolic, antioxidant, and radical scavenging activities of some Citrus seed and oils. Journal of Food Processing and Preservation; 2018;42;(3):e13555 doi:10.1111/jfpp.13555
66. Di Vaio C. et al. Essential oils content and antioxidant properties of peel ethanol extract in 18 lemon cultivars. Scientia Horticulturae; 2010;126;(1):50-55 doi:10.1016/j.scienta.2010.06.010
67. Hojjati M Barzegar H. Chemical composition and biological activities of lemon (Citrus limon) leaf essential oil. Nutrition and Food Sciences Research; 2017;4;(4):15-24 doi:10.29252/nfsr.4.4.3

68. Saeb S, Amin M, Gooybari RS Aghel N. Evaluation of antibacterial activities of Citrus limon, Citrus reticulata, and Citrus grandis against pathogenic bacteria. International Journal of Enteric Pathogens; 2016;4;(4):3-37103 doi:10.15171/ijep.2016.13
69. Vinson JA, Proch J Bose P. Determination of quantity and quality of polyphenol antioxidants in foods and beverages. Methods in Enzymology; 2001;335:103-114 doi:10.1016/s0076-6879(01)35235-7
70. Proteggente AR. et al. The antioxidant activity of regularly consumed fruit and vegetables reflects their phenolic and vitamin C composition. Free radical research; 2002;36;(2):217-233 doi:10.1080/10715760290006484
71. Wilmsen PK, Spada DS Salvador M. Antioxidant activity of the flavonoid hesperidin in chemical and biological systems. Journal of agricultural and food chemistry; 2005;53;(12):4757-4761 doi:10.1021/jf0502000
72. Nijveldt RJ. et al. Flavonoids: a review of probable mechanisms of action and potential applications. The American journal of clinical nutrition; 2001;74;(4):418-425 doi:10.1093/ajcn/74.4.418
73. Jung HA. et al. Inhibitory activity of flavonoids fromPrunus davidiana and other flavonoids on total ROS and hydroxyl radical generation. Archives of pharmacal research; 2003;26;(10):809-815 doi:10.1007/BF02980025
74. Park Y-S. et al. Quality Characteristics and Antioxidant Potential of Lemon (Citrus limon Burm. f.) seed oil extracted by different methods. Frontiers in Nutrition; 2021;8 doi:10.3389/fnut.2021.644406
75. González-Molina E, Moreno DA García-Viguera C. Genotype and harvest time influence the phytochemical quality of Fino lemon juice (Citrus limon (L.) Burm. F.) for industrial use. Journal of agricultural and food chemistry; 2008;56;(5):1669-1675 doi:10.1021/jf073282w

Chapter 6

OVERVIEW OF MICELLES FOR ANTIFUNGAL THERAPY

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1. INTRODUCTION

Over the past two decades, the incidence of fungal infections has increased significantly. Worldwide, more than 1.6 million people die each year from fungal infections, and more than 300 million people currently suffer from serious fungal infections. In addition, the widespread use of antifungal drugs has had serious consequences for antifungal therapy. Resistant strains have emerged, leading to treatment failures. The current antifungal options are limited by the existence of toxicities and drug-resistant strains. There are many approaches to develop antifungal therapy, including the synthesis of new compounds, the use of biological extracts, the modification of the delivery methods or forms of antifungal drugs, and the combination of known antifungals with other drugs/agents. Nanotechnology is a promising strategy for reasons such as providing a high spectrum, overcoming the issues in toxicity, and providing better diffusion and effectiveness. Micelles are spherical amphiphilic colloidal structures with a hydrophobic core and a hydrophilic shell and their particle diameters range from 5 to 100 nm. Recently, micelles have attracted attention in the pharmaceutical field due to their unique properties, size, shape and biocompatibility, which enhance drug loading and modified release. This review focuses on providing an overview of the role and importance of micelles in antifungal therapy.

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Due to the advantages of nanotechnology and micelles in antifungal therapy, various investigations are being undertaken on these topics. In the study by Suwan et al.(47), silver nanoparticles with Psidium guajava aqueous extract were developed using green synthesis. Although these nanoparticles show a particle size of 96±4 nm, aggregation is observed over time. For this reason, micelles produced by direct mixture of Poloxamer 407 (F127) polymer were used to stabilize these nanoparticles. The particle size of micelle-coating nanoparticles was found in the range of 70.4±0.8 nm to 258.6±11.4 nm, and zeta potential values were observed below -22 mV. In the in vitro inhibition study against Candida albicans, micelle-coating nanoparticles showed a 2-fold higher inhibition area at the end of 90 days than those not coated with micelles.

5. CONCLUSION

Micellar systems stands out in antifungal treatment because of their unique properties, size, shape and biocompatibility, which enhanced drug loading and modified release. The studies have shown that micelles loaded with antifungal agents could increase efficacy and reduce dosage and side effects. Even so, further studies are needed to evaluate how they behave biologically and to assess safety.

REFERENCES

1. Mahdi BM. Review of Fungal Infection in Human Beings and Role of COVID-19 Pandemic. Indian Journal of Forensic Medicine & Toxicology. 2021;15(4):887–897. doi.org/10.37506/ijfmt.v15i4.16815
2. Roemer T, Krysan DJ. Antifungal drug development: challenges, unmet clinical needs, and new approaches. Cold Spring Harb Perspect Med. 2014;4(5):a019703. doi: 10.1101/cshperspect.a019703
3. Durdu M, Ilkit M, Tamadon Y, Tolooe A, Rafati H, Seyedmousavi S. Topical and systemic antifungals in dermatology practice. Expert Rev Clin Pharmacol. 2017;10(2):225–237. doi: 10.1080/17512433.2017.1263564
4. Nivoix Y, Ledoux MP, Herbrecht R. Antifungal Therapy: New and Evolving Therapies. Semin Respir Crit Care Med. 2020;41(1):158–174. doi: 10.1055/s-0039-3400291
5. Mueller SW, Kedzior SK, Miller MA, Reynolds PM, Kiser TH, Krsak M, et al. An overview of current and emerging antifungal pharmacotherapy for invasive fungal infections. Expert Opin Pharmacother. 2021;22(10):1355–1371. doi.org/10.1080/14656566.2021.1892075
6. Ito K. Inhaled antifungal therapy: benefits, challenges, and clinical applications. Expert Opin Drug Deliv. 2022;19(7):755–769. doi: 10.1080/17425247.2022.2084530
7. Zhang Q, Liu F, Zeng M, Mao Y, Song Z. Drug repurposing strategies in the development of potential antifungal agents. Appl Microbiol Biotechnol. 2021;105(13):5259–5279. doi.org/10.1007/s00253-021-11407-7

8. Houšť J, Spížek J, Havlíček V. Antifungal Drugs. Metabolites. 2020;10(3):106. doi.org/10.3390/metabo10030106
9. Van Daele R, Spriet I, Wauters J, Maertens J, Mercier T, Van Hecke S, et al. Antifungal drugs: What brings the future? Med Mycol. 2019;57(3):328–343. doi: 10.1093/mmy/myz012
10. Chang YL, Yu SJ, Heitman J, Wellington M, Chen YL. New facets of antifungal therapy. Virulence. 2017;8(2):222–236. doi.org/10.1080/21505594.2016.1257457
11. Robbins N, Wright GD, Cowen LE. Antifungal Drugs: The Current Armamentarium and Development of New Agents. Microbiol Spectr. 2016;4(5). doi.org/10.1128/microbiolspec.funk-0002-2016
12. Nett JE, Andes DR. Antifungal Agents: Spectrum of Activity, Pharmacology, and Clinical Indications. Infect Dis Clin North Am. 2016;30(1):51–83. dx.doi.org/10.1016/j.idc.2015.10.012
13. Fuentefria AM, Pippi B, Dalla Lana DF, Donato KK, de Andrade SF. Antifungals discovery: an insight into new strategies to combat antifungal resistance. Lett Appl Microbiol. 2018;66(1):2–13. doi:10.1111/lam.12820
14. Perfect JR. Is there an emerging need for new antifungals?. Expert Opinion on Emerging Drugs. 2016;21(2):129–131. doi.org/10.1517/14728214.2016.1155554
15. Osanloo M, Assadpour S, Mehravaran A, Abastabar M, Akhtari J. Niosome-loaded antifungal drugs as an effective nanocarrier system: A mini review. Curr Med Mycol. 2018;4(4):31–36. doi: 10.18502/cmm.4.4.384
16. Lengert EV, Talnikova EE, Tuchin VV, Svenskaya YI. Prospective Nanotechnology-Based Strategies for Enhanced Intra- and Transdermal Delivery of Antifungal Drugs. Skin Pharmacol Physiol. 2020;33(5):261–269. doi: 10.1159/000511038
17. Johal HS, Garg T, Rath G, Goyal AK. Advanced topical drug delivery system for the management of vaginal candidiasis. Drug Deliv. 2016;23(2):550–563. doi.org/10.3109/10717544.2014.928760
18. Martínez-Montelongo JH, Medina-Ramírez IE, Romo-Lozano Y, González-Gutiérrez A, Macías-Díaz JE. Development of Nano-Antifungal Therapy for Systemic and Endemic Mycoses. J Fungi (Basel). 2021;7(2):158. doi.org/10.3390/jof7020158
19. Ghezzi M, Pescina S, Padula C, Santi P, Del Favero E, Cantù L, et al. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. J Control Release. 2021;332:312–336. doi.org/10.1016/j.jconrel.2021.02.031
20. Jones M, Leroux J. Polymeric micelles - a new generation of colloidal drug carriers. Eur J Pharm Biopharm. 1999;48(2):101–111. doi: 10.1016/s0939-6411(99)00039-9
21. Kwon GS, Okano T. Polymeric micelles as new drug carriers. Advanced Drug Delivery Reviews. 1996 Sep 16;21(2):107–116. doi.org/10.1016/S0169-409X(96)00401-2
22. Hwang D, Ramsey JD, Kabanov AV. Polymeric micelles for the delivery of poorly soluble drugs: From nanoformulation to clinical approval. Adv Drug Deliv Rev. 2020;156:80–118. doi: 10.1016/j.addr.2020.09.009
23. Deshmukh AS, Chauhan PN, Noolvi MN, Chaturvedi K, Ganguly K, Shukla SS, et al. Polymeric micelles: Basic research to clinical practice. Int J Pharm. 2017;532(1):249–268. doi: 10.1016/j.ijpharm.2017.09.005
24. Kedar U, Phutane P, Shidhaye S, Kadam V. Advances in polymeric micelles for drug delivery and tumor targeting. Nanomedicine. 2010;6(6):714–729. doi: 10.1016/j.nano.2010.05.005

25. Perumal S, Atchudan R, Lee W. A Review of Polymeric Micelles and Their Applications. Polymers. 2022;14(12):2510. doi.org/10.3390/polym14122510
26. Hanafy NAN, El-Kemary M, Leporatti S. Micelles Structure Development as a Strategy to Improve Smart Cancer Therapy. Cancers. 2018;10(7):238. doi: 10.3390/cancers10070238
27. Lu Y, Park K. Polymeric micelles and alternative nanonized delivery vehicles for poorly soluble drugs. Int J Pharm. 2013;453(1):198–214. doi: 10.1016/j.ijpharm.2012.08.042
28. Yokoyama M. Polymeric micelles as a new drug carrier system and their required considerations for clinical trials. Expert Opin Drug Deliv. 2010;7(2):145–158. doi: 10.1517/17425240903436479
29. Zhou L, Zhang P, Chen Z, Cai S, Jing T, Fan H, et al. Preparation, characterization, and evaluation of amphotericin B-loaded MPEG-PCL-g-PEI micelles for local treatment of oral Candida albicans. Int J Nanomedicine. 2017;12:4269–4283. doi: 10.2147/IJN.S124264
30. Okonogi S, Phumat P, Khongkhunthian S, Suttiat K, Chaijareenont P. Denture-Soaking Solution Containing Piper betle Extract-Loaded Polymeric Micelles; Inhibition of Candida albicans, Clinical Study, and Effects on Denture Base Resin. Antibiotics (Basel). 2021;10(4):440. doi.org/10.3390/antibiotics10040440
31. Tonglairoum P, Woraphatphadung T, Ngawhirunpat T, Rojanarata T, Akkaramongkolporn P, Sajomsang W, et al. Development and evaluation of N-naphthyl-N,O-succinyl chitosan micelles containing clotrimazole for oral candidiasis treatment. Pharm Dev Technol. 2017;22(2):184–190. doi: 10.3109/10837450.2016.1163391
32. Zhou L, Li A, Wang H, Sun W, Zuo S, Li C. Preparation and characterization of luteolin-loaded MPEG-PCL-g-PEI micelles for oral Candida albicans infection. Journal of Drug Delivery Science and Technology. 2021;63:102454. doi: 10.1016/j.jddst.2021.102454
33. Badr-Eldin SM, Aldawsari HM, Fahmy UA, Ahmed OAA, Alhakamy NA, Elfaky MA, et al. Optimized D-α-tocopherol polyethylene glycol succinate/phospholipid self-assembled mixed micelles: A promising lipid-based nanoplatform for augmenting the antifungal activity of fluconazole. Acta Pharm. 2022;72(4):547–560. doi: 10.2478/acph-2022-0028
34. Gou S, Monod M, Salomon D, Kalia YN. Simultaneous Delivery of Econazole, Terbinafine and Amorolfine with Improved Cutaneous Bioavailability: A Novel Micelle-Based Antifungal "Tri-Therapy." Pharmaceutics. 2022;14(2):271. doi.org/10.3390/pharmaceutics14020271
35. Teng F, Deng P, Song Z, Zhou F, Feng R. Enhanced effect in combination of curcumin- and ketoconazole-loaded methoxy poly (ethylene glycol)-poly (ε-caprolactone) micelles. Biomed Pharmacother. 2017;88:43–51. doi: 10.1016/j.biopha.2017.01.033
36. Suksiriworapong J, Mingkwan T, Chantasart D. Enhanced transmucosal delivery of itraconazole by thiolated d-α-tocopheryl poly(ethylene glycol) 1000 succinate micelles for the treatment of Candida albicans. Eur J Pharm Biopharm. 2017;120:107–115. doi: 10.1016/j.ejpb.2017.08.012
37. Sayed S, Elsayed I, Ismail MM. Optimization of β-cyclodextrin consolidated micellar dispersion for promoting the transcorneal permeation of a practically insoluble drug. Int J Pharm. 2018;549(1–2):249–260. doi: 10.1016/j.ijpharm.2018.08.001

38. Guo Y, Karimi F, Fu Q, G Qiao G, Zhang H. Reduced administration frequency for the treatment of fungal keratitis: a sustained natamycin release from a micellar solution. Expert Opin Drug Deliv. 2020;17(3):407–421. doi: 10.1080/17425247.2020.1719995
39. Durgun ME, Kahraman E, Hacıoğlu M, Güngör S, Özsoy Y. Posaconazole micelles for ocular delivery: in vitro permeation, ocular irritation and antifungal activity studies. Drug Deliv Transl Res. 2022;12(3):662–675. doi: 10.1007/s13346-021-00974-x
40. Younes NF, Abdel-Halim SA, Elassasy AI. Solutol HS15 based binary mixed micelles with penetration enhancers for augmented corneal delivery of sertaconazole nitrate: optimization, in vitro, ex vivo and in vivo characterization. Drug Deliv. 2018;25(1):1706–1717. doi: 10.1080/10717544.2018.1497107
41. Osouli M, Abdollahizad E, Alavi S, Mahboubi A, Abbasian Z, Haeri A, et al. Biocompatible phospholipid-based mixed micelles for posaconazole ocular delivery: Development, characterization, and in - vitro antifungal activity. J Biomater Appl. 2023;37(6):969–978. doi.org/10.1177/08853282221141962
42. Banshoya K, Kaneo Y, Tanaka T, Yamamoto S, Maeda H. Development of an amphotericin B micellar formulation using cholesterol-conjugated styrene-maleic acid copolymer for enhancement of blood circulation and antifungal selectivity. Int J Pharm. 2020;589:119813. doi: 10.1016/j.ijpharm.2020.119813
43. Moreno-Rodríguez AC, Torrado-Durán S, Molero G, García-Rodríguez JJ, Torrado-Santiago S. Efficacy and toxicity evaluation of new amphotericin B micelle systems for brain fungal infections. Int J Pharm. 2015;494(1):17–22. doi: 10.1016/j.ijpharm.2015.08.003
44. Leonhard V, Comini LR, Alasino RV, Cometto MJ, Bierbrauer KL, Beltramo DM. Self-Assembled Teicoplanin Micelles as Amphotericin B Nanocarrier. J Pharm Sci. 2023;112(4):1081–1088. DOI: 10.1016/j.xphs.2022.12.007
45. Song Z, Zhu L, Xu H, Wen Y, Feng R. Phenylboronic acid-installed poly(isobutene-alt-maleic anhydride) polymeric micelles for pH-dependent release of amphotericin B. Journal of Drug Delivery Science and Technology. 2023;81:104225. doi: 10.1016/j.colsurfb.2022.112559
46. Althomali NM, Alshammari RS, Al-atawi TS, Aljohani AA, Safwat MA, Soliman GM. Impact of Biocompatible Poly(ethylene glycol)-block-Poly(ε-caprolactone) Nano-Micelles on the Antifungal Efficacy of Voriconazole. Biointerface Res Appl Chem. 2022;13(1):62. doi.org/10.33263/BRIAC131.062
47. Suwan T, Khongkhunthian S, Okonogi S. Antifungal activity of polymeric micelles of silver nanoparticles prepared from Psidium guajava aqueous extract. J Control Release. 2021;332:312-336. doi: 10.1016/j.jconrel.2021.02.031

Chapter 7

DEGRADABLE SYNTHETIC BIOPOLYMERS IN MEDICINE

Timur PAÇACI[1]

1.INTRODUCTION

Biopolymers can be examined in three parts as natural, semi-natural and synthetic. Rather than natural and semi-natural polymers, in this section, synthetic degradable biopolymers in medicine and their properties are tried to be explained.

Biopolymers was founded in 1963 and gain importance in the medicine industry with their low toxicity, different physical and chemical properties. Biopolymers are divided into two as degradable and non-degradable polymers in nature. Degradable and non-degradable polymers are preferred depending on the usage life and place in metabolism. Their common point is that they are compatible with living metabolism. Biocompatibility, growth ability, production in large quantities and specific areas of use have given importance to synthetic biopolymers in the health sector. In this section, the properties of degradable synthetic biopolymers and their use in the field of medicine are emphasized.

2.DEGRADABLE SYNTHETIC BIOPOLYMERS IN MEDICINE

Today, studies are carried out on 10 different biodegradable synthetic polymers: polylactic acid, polyglycolic acid, polycaproalctone, polyhydroxybutyrate, polybutylene succinate, polyvinyl alcohol, polyethylene adipate, polyether sulfone, polyurethane and polyvinylpyrrolidone. Biodegradable polymers derived from these polymers are frequently emphasized by scientists due to their tensile and impact strength, low toxicity, ease of production on a large scale allowing the production of polymers with different physical properties with mixtures and their derivatives can be handled.

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3.CONCLUSION

Biodegradable polymers, which have been produced for use in the medical field since the 1960s, are gaining more and more importance. This is evident in the number of publications. However, the fact that they do not have the desired level of physical and chemical resistance has made the development of biopolymers necessary. Biopolymers with biodegradable properties, on the other hand, are finding more and more medical uses with their easy dissolution in nature, high number of derivatives, biocompatibility, sufficient physical and chemical resistance. In this context, it is an inevitable fact that the newly developed biodegradable polymers will create more economic and wider usage areas thanks to their advanced physical and chemical properties. Oxygen concentration in polymers significantly affects their degradability and changes in chain length are important in the physical strength of polymers. The most striking disadvantage of degradable biopolymers is that they do not have sufficient physical strength depending on the place of use. The reasons for this are based on insufficient chain length or unsuitable crystal/amorphous region ratios (elasticity) in polymers.

In this section, the general properties of synthetic biodegradable polymers, which are frequently studied, and their usage areas in the medical sector are tried to be explained. Apart from these polymers, synthetic nondegradable biopolymers and natural biopolymers are also used in different ways in the medical field. It is promising for the future to make nondegradable polymers degredable by adding side groups or to develop semi-synthetic polymers with sufficient physical strength by changing the chain structures of natural polymers.

REFRENCES

1. Drumright RE, Gruber PR, Henton DE. Polylactic Acid Technology. Advanced Materials; 2000;12(23): 1841–1846. doi.org/10.1002/1521-4095(200012)12:23<1841::AID-ADMA1841>3.0.CO;2-E
2. Van de Velde K, Kiekens P. Biopolymers: overview of several properties and consequences on their applications, Department of Textiles, Ghent University; 2002;21: 433–442. doi.org/10.1016/S0142-9418(01)00107-6
3. Hartmann MH. High Molecular Weight Polylactic Acid Polymers. In: Kaplan, D.L. (eds) Biopolymers from Renewable Resources. Macromolecular Systems — Materials Approach. Springer, Berlin, Heidelberg, 1998.
4. Nijenhuis AJ, Du YJ, Van Aert HAM, Bastiaansen C. ABA Type Copolymers of Lactide with Poly(ethylene glycol). Kinetic, Mechanistic, and Model Studies. Macromolecules; 1995;28(7): 2124-2132. doi.org/10.1021/ma00111a004
5. Lasprilla AJR, Martinez GAR, Lunelli BH, Jardini AL, Filho RM. Poly-lactic acid synthesis for application in biomedical devices. A review. Biotechnology Advances; 2012;30(1):321–328. doi.org/10.1016/j.biotechadv.2011.06.019

6. Fukushima K, Kimura Y. Stereocomplexed polylactides (Neo-PLA) as high-performance bio-based polymers: their formation, properties, and application. Polymer International; 2006;55(6):626–642. https://doi.org/10.1002/pi.2010
7. Tracy MA, Ward KL. Firouzabadian, L.; Wang, Y.; Dong, N.; Qian, R.; Zhang, Y. Factors affecting the degradation rate of poly (lactide-co-glycolide) microspheres in vivo and in vitro. Biomaterials; 1999;20(11): 1057–1062. https://doi.org/10.1016/S0142-9612(99)00002-2
8. Liu L, Li S, Garreau H, Vert M. Selective Enzymatic Degradations of Poly(l-lactide) and poly(E-caprolactone) blend films. Biomacromolecules; 2000;1(3): 350–359. doi.org/10.1021/bm000046k
9. Soni S, Gupta H, Kumar N, Nishad D, Mittal G, Bhatnagar A. Biodegradable biomaterials; 2010;3(1): 30–40.
10. Nakafuku C, Yoshimura H. Melting parameters of poly(glycolic acid). Polymer (Guildf); 2004;45(11): 3583–3585. doi.org/10.1016/j.polymer.2004.03.041
11. Polyglycolic Acid (PGA) Market Research Report - Global Forecast till 2030. https://www.marketresearchfuture.com/reports/ polyglycolic-acid-market-5749 (Accessed: August 2023)
12. Jahno VD. Síntese e caracterização do Poli (L-Ácido Láctico) para uso como biomaterial, 2005.
13. Nair LS, Laurencin CT. Biodegradable polymers as biomaterials. Progress in Polymer Science; 2007;32(8-9):762–98. doi.org/10.1016/j.progpolymsci.2007.05.017
14. Hayashi T. Biodegradable polymers for biomedical uses. Progress in Polymer Science; 1994;19(4): 663–702. doi.org/10.1016/0079-6700(94)90030-2
15. Sinha VR, Bansal K, Kaushik R, Kumria R, Trehan A. Poly-ϵ-caprolactone microspheres and nanospheres: an overview. International Joyrnal of Pharmaceutics; 2004;278(1): 1–23. doi.org/10.1016/j.ijpharm.2004.01.044
16. Woodruff MA, Hutmacher DW. The return of a forgotten polymer—Polycaprolactone in the 21st century. Progress in Polymer Science; 2010;35(10): 1217–1256. doi.org/10.1016/j.progpolymsci.2010.04.002
17. Lohmeijer BGG, Pratt RC, Leibfarth F, Logan JW, Long DA, Dove AP, Nederberg F, Choi Wade C, Waymouth RM, Hedrick JL. Guanidine and amidine organocatalysts for ring-opening polymerization of cyclic esters. Macromolecules; 2006;39(25): 8574–8583. doi.org/10.1021/ma0619381
18. Yuan M, Xiong C, Deng X. Ring-opening polymerization of ε-caprolactone initiated by cyclopentadienyl sodium. Journal of Applied Polymer Science; 1998;67(7): 1273–1276. doi.org/10.1002/(SICI)1097-4628(19980214)67:7<1273::AID-APP17>3.0.CO;2-2
19. Kowalski A, Duda A, Penczek S. Kinetics and Mechanism of Cyclic Esters Polymerization Initiated with Tin(II) Octoate. 3.† Polymerization of l,l-Dilactide. Macromolecular Rapid Communications; 2000;33(20) 77359-7370. doi.org/10.1021/ma000125o
20. Yamashita M, Takemoto Y, Ihara E,Yasuda H., Organolanthanide-Initiated Living Polymerizations of ε-Caprolactone, δ-Valerolactone, and β-Propiolactone. Macromolecules; 1996;29(5), 1798-1806. doi.org/10.1021/ma951400n
21. Williams MD, Rahn JA, Sherman DH. Production of a polyhydroxyalkanoate biopolymer in insect cells with a modified eucaryotic fatty acid sythase. Applied and Environmental Microbiology; 1996;62(7): 2540-2546. doi.org/10.1128/aem.62.7.2540-2546.1996

22. Patnaik P. "Intelligent" descriptions of microbial kinetics in finitely dispersed bioreactors: neural and cybernetic modelsfor PHB biosynthesis by Ralstonia eutropha. Microbial Cell Factories; 2007;6: 23-25. doi.org/10.1186/1475-2859-6-23
23. Lee C, Song B, Jegal J, Kimura Y. Cell adhesion and surface chemistry of biodegradable aliphatic polyesters: discovery of particularly low cell adhesion behavior on poly (3-RS.-hydroxybutyrate. Macromolecular Research; 2003;21: 305–1313. doi.org/10.1007/s13233-013-1181-8
24. Simon F, Martin DP. Applications of PHAs in medicine and pharmacy. In: Y. Doi, A. Steinbuchel (eds) Biopolymers, 4th edn. Wiley-VCH, Weinham; 2002;91–103.
25. Yagmurlu MF, Korkusuz F, Gursel I, Korkusuz P, Ors U, Hasirci V. Sulbactamcefoperazone polyhydroxybutyrate-co-hydroxyvalerate (PHBV) local antibiotic delivery system: in vivo effectiveness and biocompatibility in the treatment of implant-related experimental osteomyelitis. Journal of Biomedical Materials Research; 1999; 46(4): 494–503. doi.org/10.1002/(SICI)1097-4636(19990915)46:4<494::AID-JBM7>3.0.CO;2-E
26. Xu J, Guo BH. Poly(butylene succinate) and its copolymers: Research, development and industrialization. Biotechnology Journal; 2010;5(11): 1149–1163. doi.org/10.1002/biot.201000136
27. Ishioka R, Kitakuni E, Ichikawa Y. Aliphatic polyesters: "Bionolle". In: Doi,Y., Steinbüchel,A. (Eds.), Biopolymers, Polyesters III Applications and Commercial Products; 2002;4:275–297. doi.org/10.1002/3527600035.bpol4010
28. Platnieks O, Gaidukovs S, Thakur VK, Barkane A, Beluns S. Bio-based poly (butylene succinate): Recent progress, challenges and future opportunities. European Polymer Journal; 2021;161:110855. doi.org/10.1016/j.eurpolymj.2021.110855.
29. Mtibe A, Muniyasamy S, Mokhena TC, Ofosu O, Ojijo V, John M. Recent insight into the biomedical applications of polybutylene succinate and polybutylene succinate-based materials. Express Polymer Letters; 2023;17(1): 2–28. doi.org/10.3144/expresspolymlett.2023.2
30. Cicero L, Licciardi M, Cirincione R, Puleio R, Giammona G, Giglia G, Sardo P, Vigni GE, Cioffi A, Sanfilippo A, Cassata G. Polybutylene succinate artificial scaffold for peripheral nerve regeneration. Journal of Biomedical Materials Research Part B Applied Biomaterials; 2022;110(1): 125–134. doi.org/10.1002/jbm.b.34896
31. Mtibe A, Motloung MP, Bandyopadhyay J, Ray SS. Synthetic biopolymers and their composites: Advantages and limitations – An Overview. Macromolecular Rapid Communications; 2021;42(15): 2100130. doi.org/10.1002/marc.202100130
32. Das R, Kundu D. Structural and Transport Properties of Norbornene-Functionalized Poly(vinyl alcohol) "Click" Hydrogel: A Molecular Dynamics Study. ACS Sustainable Chemistry & Engineering; 2023;11(29): 10812-10824. doi.org/10.1021/acssuschemeng.3c01948
33. Hassan CM, Peppas NA. Structure and Applications of Poly(vinyl alcohol) Hydrogels Produced by Conventional Crosslinking or by Freezing/Thawing Methods. In: Biopolymers · PVA Hydrogels, Anionic Polymerisation Nanocomposites. Advances in Polymer Science; 2000;153:37-65. doi.org/10.1007/3-540-46414-X_2
34. Wan WK, Campbell G, Zhang ZF, Hui AJ, Boughner DR. Optimizing the tensile properties of polyvinyl alcohol hydrogel for the construction of a bioprosthetic heart valve stent. Journal of Biomedical Materials Research; 2002;63(6): 854-61. doi.org/10.1002/jbm.10333

35. Peppas NA, Benner RE. Proposed method of intracordal injection and gelation of poly (vinyl alcohol) solution in vocal cords: polymer considerations. Biomaterials; 1980;1(3):158-62. doi.org/10.1016/0142-9612(80)90039-3
36. Paul W, Sharma CP. Polyacrylonitrile-reinforced poly(vinyl alcohol) membranes: Mechanical and dialysis performance. Journal of Applied Polymer Science; 1995;57(12): 1447–1454. doi.org/10.1002/app.1995.070571204
37. https://www.rxlist.com/ (access date:08.16.2023)
38. McNeil C, Basan S. Thermal degradation of blends of PVC with poly(ethylene adipate). Polymer Degradation and Stability; 1993;41(3): 311-17. doi.org/10.1016/0141-3910(93)90077-V
39. Monvisade P, Loungvanidprapa P. Synthesis of poly(ethylene adipate) and poly(ethylene adipate-co-terephthalate) via ring-opening polymerization. European Polymer Journal; 2007;43(8): 3408-3414. doi.org/10.1016/j.eurpolymj.2007.05.009
40. Chen L, Xu J, Xue W, Zeng Z. Mechanism and kinetics of esterification of adipic acid and ethylene glycol by tetrabutyl titanate catalyst. Korean Journal of Chemical Engineering; 2017;35(1): 82–88. doi.org/10.1007/s11814-017-0276-x
41. Jin HJ, Lee BY, Kim MN,Yoon JS. Properties and biodegradation of poly(ethylene adipate) and poly(butylene succinate) containing styrene glycol units. European Polymer Journal; 2000;36(12): 2693–2698. https://doi.org/10.1016/S0014-3057(00)00057-4
42. Atanase LI, Salhi S, Cucoveica O, Ponjavic M, Nikodinovic-Runic J, Delaite C. Biodegradability Assessment of Polyester Copolymers Based on Poly(ethylene adipate) and Poly(ε-caprolactone). Polymers; 2022;14(18): 3736. https://doi.org/10.3390/polym14183736
43. Atkins TW. Biodegradation of poly(ethylene adipate) microcapsules in physiological media. Biomaterials; 1998;19(1–3): 61-67. https://doi.org/10.1016/S0142-9612(97)00156-7
44. Anthierens T, Billiet L, Devlieghere F, Du Prez F. Poly(butylene adipate) functionalized with quaternary phosphonium groups as potential antimicrobial packaging material. Innovative Food Science & Emerging Technologies, 2012;15: 81–85. https://doi.org/10.1016/j.ifset.2012.02.010
45. Bikiaris D, Karavelidis V, Karavas E. Novel Biodegradable Polyesters. Synthesis and Application as Drug Carriers for the Preparation of Raloxifene HCl Loaded Nanoparticles. Molecules; 2009;14(7): 2410-2430. https://doi.org/10.3390/molecules14072410
46. Rahimpour A, Madaeni SS, Mehdipour-Ataei S. Synthesis of a novel poly (amide-imide)(PAI) and preparation and characterization of PAI blended polyethersulfone (PES) membranes. Journal of Membrane Science; 2008;311(1–2):349–359. https://doi.org/10.1016/j.memsci.2007.12.038
47. https://omnexus.specialchem.com/selection-guide/polyethersulfone-pesthermoplastic/key-applications (access date: 09.02.2023)
48. Burg KJL, Shalaby SW. PES and PEEK. Encyclopedia of Materials: Science and Technology; 2001;6837–6839. 10.1016/B0-08-043152-6/01212-2
49. Lelah MD, Cooper JL. Polyurethanes in Medicine. Boca Raton, FL: CRC Press, ISBN: 0849363071,1987.
50. Tatai L, Moore TG, Adhikari R, Malherbe F, Jayasekara R, Griffiths I, Gunatillake PA. Thermoplastic biodegradable polyurethanes: The effect of chain extender structure on properties and in-vitro degradation. Biomaterials; 2007;28(36): 5407–5417. doi.org/10.1016/j.biomaterials.2007.08.035

51. Cohn D, Lando G, Sosnik A, Garty S, Levi A. PEOPPO-PEO-based poly(ether ester urethane)s as degradable reverse thermo-responsive multiblock copolymers. Biomaterials; 2006;27(9): 1718. https://doi.org/10.1016/j.biomaterials.2005.10.035
52. Loomis K, McNeeley K, Bellamkonda V. Nanoparticles with targeting, triggered release, and imaging functionality for cancer applications. Soft Matter; 2011;7(3): 839–856. DOI: 10.1039/c0sm00534g
53. Guelcher SA. Biodegradable Polyurethanes: Synthesis and Applications in Regenerative Medicine. Tissue Engineering Part B: Reviews, 2008;14(1): 3–17. doi.org/10.1089/teb.2007.0133
54. Santerre JP, Woodhouse K, Laroche G, Labow RS. Understanding the biodegradation of polyurethanes: From classical implants to tissue engineering materials. Biomaterials; 2005;26: 7457–7470. https://doi.org/10.1016/j.biomaterials.2005.05.079
55. Ding M, Li J, Tan H, Fu Q. Self-assembly of biodegradable polyurethanes for controlled delivery applications. Soft Matter; 2012;8(20): 5414. DOI: 10.1039/c2sm07402h
56. Kurakula M, Rao GSNK. Type of Article: REVIEW Pharmaceutical Assessment of Polyvinylpyrrolidone (PVP): As Excipient from Conventional to Controlled Delivery Systems with a Spotlight on COVID-19 Inhibition. Journal of Drug Delivery Science and Technology; 2020;60: 102046. https://doi.org/10.1016/j.jddst.2020.102046
57. Christensen M, Johansen P, Hau C. Storage of polyvinylpyrrolidone (PVP) in tissues following long-term treatment with a PVP-containing vasopressin preparation. Acta Medica Scandinavica; 1978;204(1-6): 295–298. https://doi.org/10.1111/j.0954-6820.1978.tb08442.x
58. Bühler V. Polyvinylpyrrolidone – Excipients for Pharmaceuticals: Povidone, Crospovidone and Copovidone, Illustrate, Springer-Verlag, Berlin Heidelberg, New York, 2005;67.