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Sağlık Bilimleri Dergisi

Yüksek İhtisas University Journal of Health Sciences

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Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi Yüksek İhtisas Üniversitesi'nin bilimsel yayınıdır

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Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi *(Yüksek İhtisas University Journal of Health Sciences)* yılda üç sayı (Nisan, Ağustos ve Aralık) olarak yayımlanan hakemli bir dergidir

Yüksek İhtisas University Journal of Health Sciences (Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi) is a peer-reviewed journal published three times a year (April, August and December).

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The control of conformity with the journal standards and the typesetting of the articles in this journal, the control of the English/Turkish abstracts and references and the preparation of the journal for publishing were performed by BAYT Publishing.

Yüksek İhtisas Üniversitesi
Sağlık Bilimleri Dergisi
Yüksek İhtisas University Journal of Health Sciences

Yayın Kurulu / *Editorial Board*

**Soyadına göre sıralanmıştır (Sorted by last name)*

Amaç ve Kapsam

2020 yılında yayın hayatına başlayan Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi (YIU Saglik Bil Derg), bağımsız, tarafsız ve çift-kör hakemlik ilkelerine uygun olarak yayınlanan bilimsel, açık erişimli, basılı ve aynı zamanda çevrimiçi yayınlanan süreli yayındır.

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi, Yüksek İhtisas Üniversitesi'nin Nisan, Ağustos ve Aralık aylarında olmak üzere dört ayda bir yayımlanan bilimsel yayın organıdır.

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi, ülkemizin ilk sağlık konseptli üniversite dergisi olma ayrıcalığı ile akademisyenlere hizmet vermek amacı yanı sıra hedef kitlesi ulusal ve uluslararası düzeyde klinik araştırmacılar, tıp/sağlık profesyonelleri, öğrenciler, hemşirelik profesyonelleri, ilgili mesleki ve akademik kurum ve kuruluşlarıdır.

Dergide sağlık bilimleri alanında orijinal makaleler, literatür gözden geçirmeleri, olgu sunumları, derleme, teknik bildiriler ve uzman görüşleri İngilizce ve Türkçe dillerinde yayımlanır. Yüksek Ihtisas Üniversitesi Sağlık Bilimleri Dergisi hakemli bir dergidir ve en yüksek etik ve editöryal standartlara uyar.

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi EBSCOhost, Türkiye Atıf Dizini ve Türk Medline tarafından indekslenmektedir.

Baş Editör

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Yazarlara Bilgiler

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi *(Yüksek İhtisas University Journal of Health Sciences)* yılda üç kez (Nisan, Ağustos ve Aralık) yayınlanan açık erişimli ve hakemli bir dergidir. Dergide sağlık bilimleri alanında İngilizce ve Türkçe dillerinde özgün makaleler, derlemeler, olgu sunumları, teknik raporlar ve yorumlar yayımlanır.

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi (Journal of Yüksek İhtisas University Health Sciences) en yüksek etik ve editörlük standartlarına uyar. Editörlük ve yayım süreci, International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE) ve National Information Standards Organization (NISO) kılavuzlarına uygun olarak yapılır. Akademik Yayıncılıkta Şeffaflık ve En İyi Uygulama (doaj.org/bestpractice) ilkeleri gözetilir.

Derginin Editörleri WAME Yöneticiler Birliğinin onaylamış olduğu editörler politikasını destekler ve Uluslararası Tıp Dergisi Editörleri Komitesi'nin yayımlamış olduğu Biyomedikal Dergilere Gönderilen Makaleler İçin Gerekli Standartlar ile tam bir uyum gösterir (**http://www.icmje.org/icmjerecommendations**).

Makale Gönderme

Yazarlar makalelerini Ulakbim- DergiPark web sitesinde bulunan Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi alanından göndermelidir. Makaleler Word dokümanı (.doc) veya zengin metin biçimi (.rtf) olarak gönderilmelidir. Her makalenin başında yazı başlığı, öz ve "medline" kurallarına göre düzenlenmiş Türkçe ve İngilizce anahtar sözcükler yazılmalıdır. Makale için iletişim kuracak tüm yazarların gerekli iletişim bilgileri olmalıdır. Tüm şekil, tablo ve gerekli görülen ek dokümanlar da gönderilmelidir. Yazarlar aynı sistem üzerinden Telif Hakkı Devri ve Finansal Durumu belirten ve yazının orijinalliğinin beyan edildiği formu da gönderilere eklemelidir.

Editoryal Politika

Tüm makaleler bilimsel katkıları, orijinallikleri ve içerikleri açısından bilimsel kurul tarafından değerlendirilir. Yazarlar verilerin doğruluğundan sorumludur. Dergi gerekli gördüğü yerlerde dil ve yazım ile ilgili uygun düzeltmeleri yapma hakkını saklı tutar. Makaleler gerekli görüldüğünde revizyon yapılmak üzere sorumlu yazara geri gönderilebilir. Dergide basılan yazılar derginin malı haline gelir ve yazıların telif hakkı Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi *(Journal of Yuksek Ihtisas University Health Sciences)* adına alınır. Daha önce herhangi bir dilde basılmış olan yazılar dergide basılmak üzere değerlendirilmez. Yazarlar, Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi'ne *(Journal of Yuksek Ihtisas University Health Sciences)* gönderdikleri bir yazıyı başka bir dergiye gönderemezler.

Makaleler, ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmjerecommendations) ile uyumlu olarak hazırlanmalıdır. Randomize çalışmalar CONSORT, gözlemsel çalışmalar STROBE, tanısal değerli çalışmalar STARD, sistematik derleme ve meta- analizler PRISMA, hayvan deneyli çalışmalar ARRIVE ve randomize olmayan davranış ve halk sağlığıyla ilgili çalışmalar TREND kılavuzlarına uyumlu olmalıdır.

Makalelerin Hazırlanması

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi'ne (Journal of Yüksek Ihtisas University Health Science), gönderilen makaleler ICMJE'nin biyomedikal dergiler için belirlemiş olduğu standartlara göre hazırlanmış olmalıdır. Makalenin gönderilmesi sırasında yazarlar deney/araştırma tipini belirtmelidirler ve istatistik uygulamaların "Guidelines for statistical reporting in articlesfor medical journals: amplificationsand explanations" (Bailar JC III, Mosteller F, Ann InternMed 1988; 108:266 -73) kılavuzuna uygun olması gerekmektedir. Makale ile birlikte gönderilen üst yazıda makale içindeki bilgilerin herhangi bir kısmının daha önce elektronik ortam dâhil yayımlanıp yayımlanmadığı veya değerlendirilmek üzere gönderilip gönderilmediği bildirilmelidir. Çalışma için etik kurul kararı alınıp alınmadığı veya insan deneyleri ile ilgili 2018 yılında güncellenen Helsinki Bildirgesi'ne uyulup uyulmadığı belirtilmelidir, aksi durumlar açıklanmalıdır. Üst yazıda iletişim kurulacak yazarın adresi, telefonu, faks numarası ve e-posta adresi olmalıdır. Tüm başvurular benzerlik tespit yazılımı (iThenticate by CrossCheck) tarafından taranır. Yayın Kurulu, dergimize gönderilen çalışmalar hakkındaki intihal, atıf manipülasyonu ve veri sahteciliği iddia ve şüpheleri karşısında COPE kurallarına uygun olarak hareket etmektedir. Yazar olarak listelenen herkesin ICMJE (www.icmje.org) tarafından önerilen yazarlık kriterlerini karşılaması gerekir. ICMJE, yazarların aşağıdaki dört kriteri karşılamasını önermektedir:

1. Çalışmanın konseptine/tasarımına; ya da çalışma için verilerin toplanmasına, analiz edilmesine ve yorumlanmasına önemli katkı sağlamış olmak;
2. Yazı taslağını hazırlamış ya da önemli fikirsel içeriğin eleştirel incelemelerini yapmış olmak.
3. Yazının yayından önceki son halini gözden geçirmiş ve onaylamış olmak.
4. Çalışmanın herhangi bir bölümünün geçerliliği ve doğruluğuna ilişkin soruların uygun şekilde soruşturulduğunun ve çözümlendiğinin garantisini vermek amacıyla çalışmanın her yönünden sorumlu olmayı kabul etmek.

Bir yazar, çalışmada katkı sağladığı kısımların sorumluluğunu almasına ek olarak, diğer yazarların çalışmanın hangi kısımlarından sorumlu olduğunu da teşhis edebilmelidir. Ayrıca, yazarlar birbirlerinin katkılarının bütünlüğüne güven duymalıdırlar.

Makale Özellikleri

Araştırma Makalesi

Araştırma makalesi ana metni *"Öz", "Giriş", "Materyal ve Metodlar", "Bulgular" ,"Tartışma/ Sonuç" ve "Kaynaklar"* alt başlıklarını içermelidir. Araştırma makaleleri için sözcük sayısı sınırları Tablo 1'dedir.

Öz

Araştırma makalelerinin özü Giriş, Materyal ve Metodlar, Bulgular ve Sonuç bölümlerinden oluşmalıdır. Çalışma içeriğini ve çalışmanın dayandığı zemini aktarmalı, çalışmanın amaçlarını, ana bulguları ve ana sonuçları belirtmelidir. Ayrıca çalışma ve gözlemlerin yeni ve önemli yönlerini vurgulamalıdır.

Anahtar Sözcükler

Öz bölümünün altında verilmeli ve en fazla altı adet olmalıdır. Anahtar sözcüklerin Türkiye Bilim Terimleri'nden seçilmesine özen gösterilmelidir (http://www.bilimterimleri.com).

Giriş

Bu bölümde niçin bu çalışmayı yapmaya ihtiyaç duyulduğu ve yapılma amacı sadece önemli makalelere atıfta bulunularak belirtilmelidir.

Materyal ve Metodlar

Bu bölümde çalışma için yapılan plan, hastalar, deney hayvanları, materyal ve kontroller, kullanılan çalışma yöntemleri ve uygulanan istatistiksel yöntem açıklanmalıdır. Etik konularla ilgili izinler yukarıda açıklandığı gibi belirtilmeli; ilaçların jenerik isimleri ile birlikte üretici adı veüretildiği ülke ifade edilmelidir.

Bulgular

Bu bölümde istatistiksel metotlar ile desteklenen bulgular ayrıntılı olarak belirtilmelidir. Sadece en önemli bulgular vurgulanmalıdır. Şekil ve tablolar metin içinde verilen bulguları desteklemeli,tekrar etmemelidir; verinin metin, tablo veya şekil şeklindeki sunumların sadece birinde gösterilmesi yeterlidir.

Tablo 1. Makale türleri için kısıtlamalar

Makale türü	Sözcük sınırı	Öz sözcük sınırı	Kaynak sınırı	Tablo sınırı	Resim sınırı
Araştırma Makalesi	4000	250 (Yapılandırılmış)	30	6	15 resim
Derleme	5000	250	50	6	20 resim
Olgu Sunumu	1500	150	15	Tablo yok	20 resim
Editöre Mektup	1000	Öz yok	5	Tablo yok	Resim yok

Tartışma/ Sonuç

Kaynakların ışığında bulguların önemi ve farkları vurgulanmalıdır; ancak sonuç bölümünde sunulan detaylar tekrarlanmamalıdır. Görüşler, çalışmada elde edilen gerçeklerle desteklenecek şekilde sınırlanmalıdır; araştırılmayan ya da gösterilmeyen varsayımlar tartışmaya eklenmemelidir. Bulgular başka araştırmalarla karşılaştırılmalıdır. Bu bölümde bulgular bölümünde belirtilmemiş yeni veri sunulmamalıdır.

Kaynaklar

Kaynaklar, "Uluslararası Tıp Dergisi Editörleri Komitesi (ICMJE)" tarafından geliştirilen "Biyomedikal Dergilere Gönderilen Makaleler İçin Gerekli Standartlar" kurallarına göre düzenlenmelidir. Sık kullanılan referans türleri için bazı örnekler verilmiştir. https://www.icmje.org/icmje-recommendations.pdf linki, burada sağlanmayan diğer referans türlerine ilişkin rehberlik amacıyla kullanılmalıdır. Her kaynak metindeki sırasına göre numaralandırılmalı ve listelenmelidir. Metin içerisinde cümle sonlarında parantez içinde "(....)" şeklinde belirtilmelidir. Kaynakların doğruluğundan yazar(lar) sorumludur. Dergi başlıkları Index Medicus'a uygun olarak kısaltılmalıdır. Dergi adlarının kısaltmaları için "Index Medicus'ta İndekslenen Dergilerin Listesi"ne bakınız (http://www.nlm.nih.gov/tsd/serials/lji.html). Index Medicus'ta yer almayan dergilerde kısaltma kullanılmaz. Kaynaklar'da yalnızca yayınlanmış makaleler veya "baskıda" olan makaleler kullanılabilir. Tüm yazarların isimleri yazılmalıdır, "et al" ifadesi kullanılmamalıdır.

Dergiler:

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV- infected patients. N Engl J Med. 2002;347:284-7. PMID: 12140307 DOI: 10.1056/NEJMsb020632

Çevrimiçi yayınlanmış makale:

Yalçın Çakmaklı G, Ayhan Y, Yazıcı MK, Demirci M, Şahin G. Spectral analysis of lithium tremor. Arch Neuropsychiatry, 17 Ekim 2020. https://doi.org/10.29399/npa.27378. [E-pub ahead of print]

Kitaplar:

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Kitap Bölümleri:

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. 93-113.

Toplantı Sunumları:

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.l

Tablolar ve Şekiller

Tüm tablo ve şekiller "Windows" altında açılabilmelidir. Online gönderilen resimlerin çözünürlük kalitesi minimum (10x10 cm boyutunda) 300 dpi ve jpg formatında olmalıdır. Her tablo ve şekil ayrı bir sayfada sunulmalıdır. Tüm tablo ve şekiller Arabik numaralar ile belirtilmelidir. Her tablonun başlığı tablonun içeriği ve amacını belirtmelidir. Her şeklin üzerindeki işaret ve sembolleri açıklayan bir alt yazısı olmalıdır.

Derleme Yazıları

Belirli bir alanda uzmanlık potansiyeli olan yazarlar tarafından hazırlanan derlemeler memnuniyetle karşılanmaktadır. Derlemeler, klinik uygulamada bir konunun mevcut bilgi seviyesini tanımlamalı, tartışmalı, değerlendirmeli ve gelecekteki çalışmalara rehberlik etmelidir. Derleme yazılarının alt başlıkları yazarlar tarafından planlanmalıdır. Ancak, her derleme makalesi bir "Giriş" ve bir "Sonuç" bölümü içermelidir. Derleme makalelerinin sınırlamaları için Tablo 1'e bakınız.

Olgu Sunumu

Nadir görülen, yeni bir bulgunun ya da yeni bir birlikteliğin tanımlandığı, tanıda ve tedavide güçlük gösteren veya yeni bir tedavi yönteminin uygulandığı ilgi çekici ve öğretici sunular yayınlanabilir. Bu yazılar, "Giriş", "Olgu Sunumu" ve "Tartışma" alt başlıklarını içermelidir. Olgu sunumlarının sözcük sayısı sınırları Tablo 1'de belirtilmiştir.

Editöre Mektup

Dergide yayımlanmış bir makale hakkında konunun uzmanı olan veya makalenin değerlendirmesini yapmış olan hakemler görüş veya yorumlarını Editöre Mektupla bildirebilirler. Kabul edilen Mektuplar, yayımlanmalarından önce konu aldıkları makalenin yazarına gönderilir ve ek görüş bildirmek, cevap vermek isteyip istemedikleri sorulur. Bu tür yazılar mümkün oldukça ilgili yazının yazarlarının yanıtlarıyla birlikte yayımlanır.

Düzeltmeler

Düzeltme talepleri ve eleştiriler iletişim adresi belirtilen yazara gönderilir. Basımın gecikmemesi için istenen düzeltmeler en kısa zamanda cevaplandırılmalıdır. Revizyonların cevapları ile geri gönderilmesi en geç 15 gün içinde olmalıdır. Editörler kurulu 15 günden sonraya kalan revizyonlarda makaleyi reddetme hakkını saklı tutar. Tüm hakemlerin görüşlerine cevap yazılmalıdır ve yapılan düzeltmelerin sayfa numarası ile satır sırası belirtilmelidir. Yapılan tüm değişikliklerin metin üstünde koyu olarak belirtildiği bir kopya ile düzeltmeler yapıldıktan sonraki son halinin temiz bir kopyası birlikte gönderilmelidir. Sunulan kaynakların ve verilerin doğruluğundan yazarlar sorumludur. Hatalı, aldatıcı veya yanlış yönlendirici bilgilerin varlığı fark edildiğinde Baş-Editör makaleyi bilimsel literatürden çekme ve bunu duyurma hakkına sahiptir.

İletişim

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Aims and Scope

Yüksek İhtisas University Journal of Health Sciences (YIU J Health Sci), which started its publication life in 2020, is a scientific, open access, both printed and online periodical published in accordance with the principles of independent, impartial and double-blind refereeing.

Yüksek İhtisas University Journal of Health Sciences is the scientific publication of Yüksek İhtisas University, published quarterly in April, August and December.

With the privilege of being the first university journal with a health concept in our country, Yüksek İhtisas University Journal of Health Sciences aims to serve academics, and its target audience is clinical researchers, medical/health professionals, students, nursing professionals, related professional, and academic institutions and organizations at the national/international level.

In the journal; original articles, literature reviews, case reports, reviews, technical papers and expert opinions in the field of health sciences are published in English and Turkish. Yüksek İhtisas University Journal of Health Sciences is a peer-reviewed journal, and adheres to the highest ethical and editorial standards.

Yüksek İhtisas University Journal of Health Sciences is indexed by EBSCOhost, the Turkish Citation Index, and Turkish Medline.

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Instructions for Authors

Yüksek İhtisas University Journal of Health Sciences *(Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi)* is an open access journal, and published three times a year (April, August and December). The journal publishes original articles, reviews, case reports, technical reports and commentaries in the fields of health science in English and Turkish languages.

Journal of Yuksek İhtisas University Health Sciences is a peer- reviewed journal and adheres to the highest ethical and editorial standards. Editorial and publishing processes of the journal are in accordance with the guidelines of International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). Editorial and publishing processes of the Journal of Yüksek İhtisas University Health Science, comply with the principles of Transparency and Best Practice in Academic Publishing (doaj.org/bestpractice).

The Editorial Board of the Journal of Yüksek Ihtisas University Health Sciences endorses the editorial policy statements approved by the WAME Board of Directors. The journal is following the uniform requirements for manuscripts submitted to biomedical journals published by the International Committee of Medical Journal Editors (**http://www.icmje.org/icmjerecommendations**).

Submission of Manuscripts

Authors should submit their articles from the Journal of Yüksek İhtisas University Health Sciences on the Ulakbim- DergiPark website. Articles should be submitted as Word document (.doc) or rich text format (.rtf). At the beginning of each article, the title, abstract and Turkish and English keywords arranged according to the "medline" rules should be written. All authors who will contact for the article should have the necessary contact information. All figures, tables and additional documents deemed necessary should also be sent. Authors should also attach the form stating the Copyright Transfer and Financial Status and declaring the originality of the article to the submissions through the same system.

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The main text of the research article should include "Introduction", "Material and Method", "Results" and "Discussion/ Conclusion" subheadings. Word count limits for research articles are in Table 1.

Abstract

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Keywords

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State concisely the purpose and rationale for the study and cite only the most pertinent references as background.

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Describe the plan, the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed. Address "Institutional Review Board" issues as stated above. State the generic names of the drugs with the name and country of the manufactures

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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	4000	250 (Structured)	30	6	15 images
Review Article	5000	250	50	6	20 images
Case Report	1500	150	15	No tables	20 images
Letter to the Editor	1000	No abstract	5	No tables	No image

Results

Present the detailed findings supported with statistical methods. Emphasize only your Important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice.

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State the importance and significance of your findings but do not repeat the details given the results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your findings with those of others'. No new data are to be presented in this section.

References

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For Epub Ahead of Print Articles:

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Books:

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Book chapters:

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. 93-113.

Meeting announcements:

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Tables and Figures

Tables and figures should work under "Windows". Color figures or grayscale images must be at least 300 dpi. Figures using ".jpg" or ".pdf" should be saved separate from the text. All tables and figures should be prepared on separate pages. They should be numbered in Arabic numerals. Each table must have a title indicating the purpose or content of each table. Each figure must have an accompanying legend defining abbreviations or symbols found in the figure.

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Review articles by authors with potential expertise in a particular field are welcomed. Reviews should describe, discuss and evaluate the current level of knowledge of a topic in clinical practice, and be a guide for future studies. Subtitles of review articles should be planned by the authors. However, each review article must contain an "Introduction" and a "Conclusion" section. Please refer to Table1 for the limitations of the review articles.

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There is limited space for case reports in the journal. Reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for review. The text should include the subheadings Introduction, Case Presentation, and Discussion. Please check Table1 below for wordcount specifications.

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Molecular Docking Study for Phenazine Derivative Compounds: Cholinesterases and Alzheimer's disease

Fenazin Türevi Bileşikler İçin Moleküler Docking Çalışması: Kolinesterazlar ve Alzheimer Hastalığı

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with no definitive treatment to date. According to the cholinergic hypothesis, decreased acetylcholine (ACh) levels contribute to the cognitive symptoms of the disease. Therefore, inhibition of AChE and BChE enzymes is an important strategy in next-generation drug design. In this study, the inhibitory potentials of four phenazine-derived dyes (Safranin-O, Phenosafranine, Pyocyanine and Janus Green B) on AChE and BChE enzymes were evaluated by molecular docking method.

Material and Methods: Ligand structures were obtained from PubChem database and energy minimization was performed using MMFF94 force field with Avogadro software. The structures of target proteins, human AChE (PDB: 4M0E) and BChE (PDB: 6QAA), were obtained from RCSB Protein Data Bank and preprocessed to make them ready for docking analyses. Molecular docking analyses were performed with AutoDock Vina (v1.2.5). The complexes obtained were analyzed with Discovery Studio to evaluate binding energies and interaction types.

Results: Janus Green B showed the highest binding score for AChE (–9.2 kcal/mol). The strongest binding for BChE was obtained with Safranin-O (–9.1 kcal/mol). The interaction of Phenosafranine with BChE (–8.9 kcal/mol) is also remarkable. Molecular interaction analyses showed that aromatic residues such as TRP286, TYR341 and TYR124 for AChE and residues such as TRP82, PHE329 and HIS438 for BChE play a central role in ligand binding. All ligands exhibited hydrogen bonds, π-alkyl and electrostatic interactions in the active sites of the enzymes. The findings of the study show that phenazine-derived dyes, especially Janus Green B and Phenosafranine, exhibit strong binding to AChE and BChE enzymes. These molecules can be evaluated among the new inhibitor candidates to be developed against Alzheimer's disease. Although the findings are based on *in silico* data, they should be supported by further *in vitro* and *in vivo* studies for biological validity.

Keywords: Alzheimer's disease, phenazine, cholinesterase inhibition, acetylcholinesterase, butyrylcholinesterase

ÖZ

Giriş: Alzheimer hastalığı (AH), günümüzde kesin tedavisi bulunmayan, ilerleyici nörodejeneratif bir bozukluktur. Kolinerjik hipoteze göre, asetilkolin (ACh) düzeylerinin azalması hastalığın bilişsel belirtilerine katkıda bulunur. Bu nedenle AChE ve BChE enzimlerinin inhibisyonu, yeni nesil ilaç tasarımlarında önemli bir stratejidir. Bu çalışmada, fenazin türevi dört boyanın (Safranin-O, Phenosafranine, Pyocyanine ve Janus Green B) AChE ve BChE enzimleri üzerindeki inhibitör potansiyelleri moleküler yerleştirme (docking) yöntemiyle değerlendirilmiştir.

Materyal ve Metodlar: Ligand yapıları PubChem veri tabanından temin edilerek Avogadro yazılımı ile MMFF94 kuvvet alanı kullanılarak enerji minimizasyonu yapılmıştır. Hedef proteinler olan insan AChE (PDB: 4M0E) ve BChE (PDB: 6QAA) yapıları RCSB Protein Data Bank'tan elde edilmiş, ön işlemden geçirilerek docking analizlerine hazır hale getirilmiştir. Moleküler yerleştirme analizleri AutoDock Vina (v1.2.5) ile gerçekleştirilmiştir. Elde edilen kompleksler Discovery Studio ile analiz edilerek bağlanma enerjileri ve etkileşim tipleri değerlendirilmiştir.

Bulgular: Janus Green B, AChE için en yüksek bağlanma skorunu (–9.2 kcal/mol) göstermiştir. BChE için ise en güçlü bağlanma Safranin-O (–9.1 kcal/mol) ile elde edilmiştir. Phenosafranine'nin BChE ile etkileşimi (–8.9 kcal/mol) de dikkat çekicidir. Moleküler etkileşim analizleri; AChE için TRP286, TYR341 ve TYR124 gibi aromatik kalıntıların; BChE için TRP82, PHE329 ve HIS438 gibi kalıntıların ligand bağlanmasında merkezi rol oynadığını göstermiştir. Tüm ligandlar enzimlerin aktif bölgelerinde hidrojen bağları, π-alkil ve elektrostatik etkileşimler sergilemiştir. Çalışmanın bulguları, fenazin türevli boyaların, özellikle Janus Green B ve Phenosafranine'in, AChE ve BChE enzimlerine karşı güçlü bağlanma gösterdiğini ortaya koymaktadır. Bu moleküller, Alzheimer hastalığına karşı geliştirilecek yeni inhibitör adayları arasında değerlendirilebilir. Bulgular *in silico* verilere dayanmakla birlikte, biyolojik geçerlilik için ileri *in vitro* ve *in vivo* çalışmalarla desteklenmelidir.

Anahtar Sözcükler: Alzheimer hastalığı, fenazin, kolinesteraz inhibisyonu, asetilkolinesteraz, bütirilkolinesteraz

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Introduction

Alzheimer's disease (AD) is a progressive and ultimately terminal condition characterized by a decline in cognitive function and memory loss (1). Cerebral amyloid angiopathy may coexist with parenchymal abnormalities in the disease pathogenesis. Molecular investigations have revealed that the primary constituent of amyloid plaques is amyloid beta (Aβ) (2), whereas neurofibrillary tangles consist of tau protein (3). The loss of neurons and synapses constitutes essential pathological features of AD. Although the accurate mechanism of the disease has not been understood for 118 years since its discovery (4), the enzymes and cholinergic system that regulate the biochemical pathways related to the progression of the disease have been well documented by studies conducted to date (5). Acetylcholine (ACh), which is used by cholinergic neurons that are crucial both in the peripheral and central nervous systems and contributes to several physiological processes, including memory, emotional processing, and learning (6), is the first neurotransmitter to be identified (7). ACh is hydrolyzed by acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes (8). AChE performs hydrolysis more rapidly than BChE. These ChE enzymes are structurally very similar enzymes. The differences between them are (i) their tissues, (ii) substrates, and (iii) inhibitor sensitivities (9).

The cholinergic hypothesis, on which the mechanism of medicines used in the treatment of AD, is based suggests that a reduction in ACh levels in the cortex contributes to the etiology of AD (10). Blocking the AChE and BChE, which enable this neurotransmitter to break down into choline and acetate, is an attempt to compensate for cholinergic loss, increase cholinergic transmission, and increase the decreased ACh density caused by the increase in AChE enzyme in brain cholinergic synapses and neuromuscular junctions due to AD (10). Additionally, research has shown that amyloid plaques may include cholinergic activation and protein metabolism (11). Cortical amyloid plaques expand quickly after cholinergic nuclei lesions. In a comparable manner, cognitive dysfunction and amyloidogenic metabolism in AD are triggered by a reduction in cholinergic signaling (12). Rivastigmine, galantamine, and donepezil are three groups of cholinesterase (ChE) inhibitors that have received approval from the United States Food and Drug Administration (FDA) for the treatment of AD. These ChE inhibitors are believed to enhance cognitive functions; however, their efficacy is a topic of debate (13).

Phenazines are chromatic compounds characterized by a heterocyclic structure that incorporates two nitrogen atoms, generally synthesized spontaneously by microorganisms (14). Pyocyanin, the first known phenazine, was first used as a 'blue pigment' for treating infected wounds in 1859, despite its chemical structure being identified almost a century later (15). Both natural phenazines and synthetic decoration groups show broad biological activities due to their pyrazine ring structures, and their effects on biotechnological processes are being studied (16). An extensive range of pharmacological activities, including antibacterial, antitumor, antileprosy, antitubercular, antifungal, neuroprotective, insecticide, and radical scavenging activity, have been documented for phenazine compounds since their discovery (16, 17). In addition to all these activities, we focused on the inhibitory effects of phenazine-structured compounds on ChE activities. The results showed that methylene violet 3RAX resulted in linear competitive inhibition of BChE (K_i = 0.51 ± 0.006 μM) and hyperbolic noncompetitive inhibition of AChE (K_i = 1.58 ± 0.36 μM) (18). Safranin-O (SO) induced linear competitive inhibition (Ki = 0.44 ± 0.085 μM) on human plasma BChE and hyperbolic noncompetitive inhibition (Ki = 0.69 ± 0.13 μM) on human erythrocyte AChE (19). This study explores the interactions of two essential cholinesterase enzymes with three structurally distinct phenazine-based dyes: Phenosafranine, Pyocyanin, and Janus Green B. Our Molecular Docking results showed that Janus Green B had the highest binding scores to AChE. This finding indicates that Janus Green B and the phenazine ring may be valuable in the development of novel pharmaceuticals for AD.

Material and Methods

Preparation of Ligands

The molecular structures of Safranin-O and its related compounds Phenosafranine, Pyocyanine, and Janus Green B were obtained from the PubChem database (Safranin-O: PubChem ID 33345803; Phenosafranine: ID 4764; Pyocyanine: ID 6817; Janus Green B: ID 119049). Before proceeding with docking studies, their three-dimensional conformations were energy-minimized using Avogadro software (version 1.2.0) to ensure structural stability. This process was performed using the MMFF94 force field, which optimizes molecular geometry by accounting for both electrostatic and steric interactions. Default parameters, including convergence criteria and energy thresholds, were applied to prepare the ligands for reliable docking analysis (20).

Docking Procedure

The X-ray crystal structures of human acetylcholinesterase (AChE; PDB ID: 4M0E, resolution: 2.00 Å) (21) and butyrylcholinesterase (BChE; PDB ID: 6QAA, resolution: 1.90 Å) (22)were obtained from the RCSB Protein Data Bank. Prior to docking, the structures were prepared by removing all water molecules and non-essential heteroatoms. Hydrogen atoms were added to reflect physiological protonation states, and Gasteiger partial charges were applied to both proteins. For AChE, the active site was defined based on the coordinates of the co-crystallized ligand, with the grid box centered at x =-17.27, y =-42.32, z = 25.90. Similarly, for BChE, the grid center was positioned at x = 18.99, y = 42.61, z = 40.81. In both cases, a uniform grid box size of 20 Å × 20 Å × 20 Å was

used to ensure full coverage of the active site and accommodate ligand flexibility. Docking simulations were carried out using AutoDock Vina (version 1.2.5), employing default parameters and the Lamarckian Genetic Algorithm to predict the most favorable binding poses and estimate binding affinities (23, 24). To assess the reliability of the docking results, the RMSD values of the poses that yielded the best binding scores were analyzed. Redocking was performed to validate the docking protocol using RMSD (Root Mean Square Deviation) as a pose validation metric. The RMSD value obtained for AChE (PDB ID: 4MOE) was 0.42 Å, indicating high accuracy in reproducing the crystallographic pose. For BChE (PDB ID: 6QAA), the RMSD was 2.02 Å, which is considered acceptable and supports the reliability of the docking protocol.

Analysis of Molecular Interactions

Upon completion of the docking simulations, the binding interactions between AChE, BChE, and the compounds were analyzed to identify key interaction types. Using Discovery Studio software, we visualized and carefully examined hydrogen bonds, hydrophobic interactions, and other relevant binding forces. These analyses provided valuable insights into the mechanisms driving the interaction between AChE, BChE, and the selected compounds.

Statistical Analysis

Avogadro was employed to optimize molecular geometries and ensure stable conformations prior to docking by utilizing the default MMFF94 force field for energy minimization of the compounds. The stability and energy profiles of the minimized structures are assessed using default statistical methods during this step of the process. AutoDock Vina was employed to perform docking simulations, using its standard Lamarckian Genetic Algorithm to calculate binding affinities based on both energy considerations and geometric complementarity. The docking procedure incorporated default statistical methods to evaluate the reliability and significance of the computed binding affinities. Discovery Studio, offering standard features for analyzing binding affinities and interaction frequencies, was employed to visualize the results. This software enabled the identification of key interactions, including hydrogen bonds and hydrophobic contacts, and applied default statistical analyses for providing an understanding of the distribution and importance of these interactions.

Results

Active Site-Based Docking Simulations

The analyses were conducted using the active site coordinates of AChE and BChE obtained from a previously conducted Safranin-O inhibition study (19). The docking poses of the ligands are shown within the active sites of AChE and BChE, with each ligand positioned inside the defined grid box (Figure 1). The structures illustrate how the ligands were placed within the catalytic pockets of the enzymes during the docking simulations, confirming that the targeted binding sites were appropriately defined.

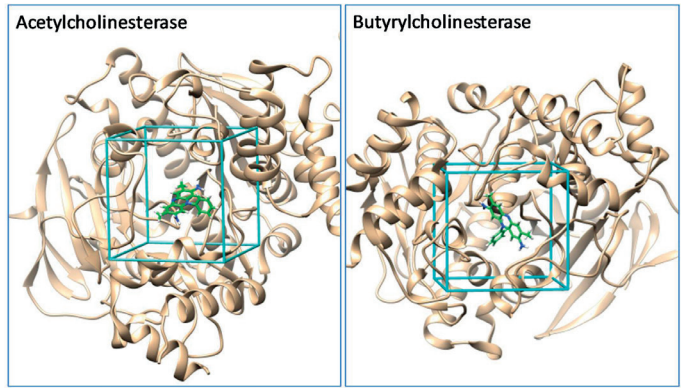


Figure 1. Binding site visualization of AChE and BChE with Safranin-O.

The docking results show how each compound fits within the active site of acetylcholinesterase (Figure 2). The binding orientations of Safranin-O, Phenosafranine, Pyocyanine, and Janus Green B are displayed to illustrate their spatial accommodation in the catalytic pocket. These visualizations support the docking scores by highlighting the ability of each ligand to interact with the active site region.

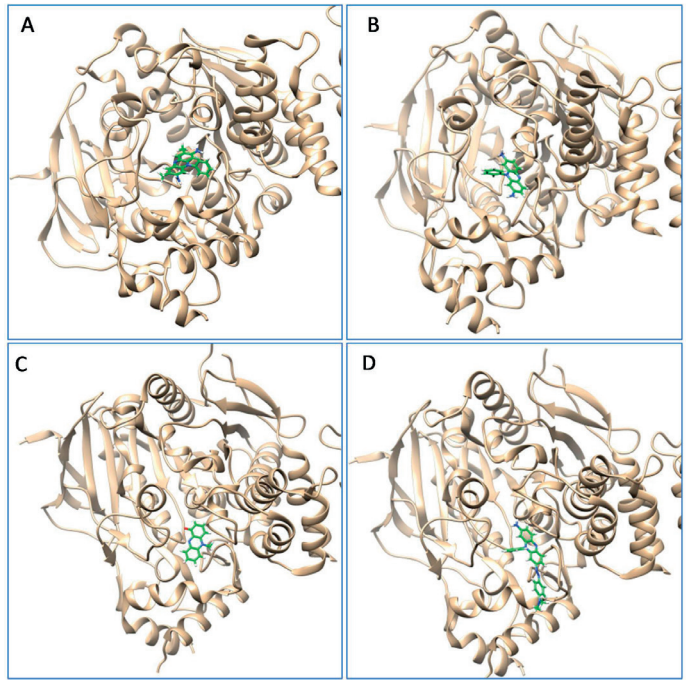


Figure 2. Docking poses of the compounds within the active site of AChE: A) Safranin-O, B) Phenosafranine, C) Pyocyanine, D) Janus Green B.

The docking results demonstrate how each compound fits into the active site of butyrylcholinesterase (Figure 3). The binding orientations of Safranin-O, Phenosafranine, Pyocyanine, and Janus Green B highlight their accommodation within the catalytic pocket, supporting the docking scores.

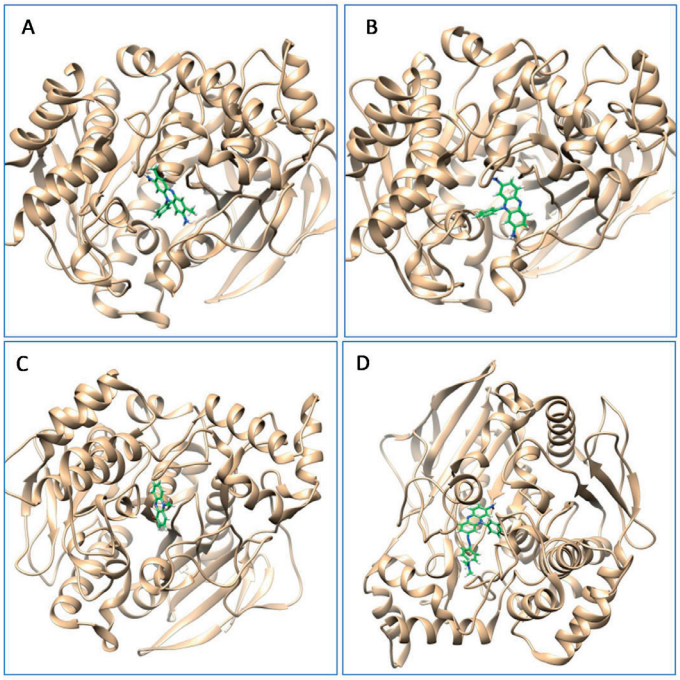
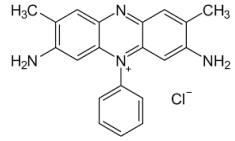
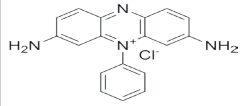
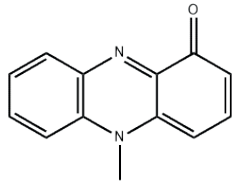
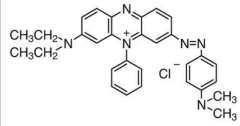


Figure 3. Docking poses of the compounds within the active site of BChE: A) Safranin-O, B) Phenosafranine, C) Pyocyanine, D) Janus Green B.

Table 1. Docking scores of compounds with AChE and BChE

Compound	Molecular Structure	Docking score for AChE (kcal/mol)	Docking score for BChE (kcal/mol)
Safranin-O		-7.6	-9.1
Phenosafranine		-8.2	-8.9
Pyocyanine		-8.3	-8.2
Janus Green B		-9.2	-8.8

Docking Results

According to the docking results, all four compounds exhibited notable binding affinities toward both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). The comparative docking scores for all compounds against both enzymes are summarized in Table 1. Janus Green B showed the strongest binding to AChE, with a docking score of –9.2 kcal/mol, indicating a favorable interaction within the enzyme's active site. For BChE, Safranin-O had the most favorable docking score at –9.1 kcal/mol, suggesting a strong potential for enzyme binding.

Analysis of Molecular Interactions

Molecular interactions revealed that Safranin-O, Phenosafranine, Pyocyanine, and Janus Green B interacted with key residues in the active site of AChE, as shown in Figure 4. Safranin-O (A) formed a hydrogen bond with HIS287 and π-alkyl interactions with TYR72, TRP286, and TYR341. Phenosafranine (B) showed hydrogen bonds with TYR124, TYR337, and PHE295, and π-alkyl interactions with TRP286, TYR341, and TYR72. Pyocyanine (C) interacted through a hydrogen bond with TYR124 and a carbon hydrogen bond with SER293, in addition to π-alkyl contacts with TRP286 and TYR341. Janus Green B (D) formed hydrogen bonds with TYR124 and TYR313, a carbon hydrogen bond with TYR341, and π-alkyl interactions with TRP286, TYR341, TYR72, and PHE337. These results suggest that all four compounds show promising binding potential to AChE, with strong and diverse interactions.

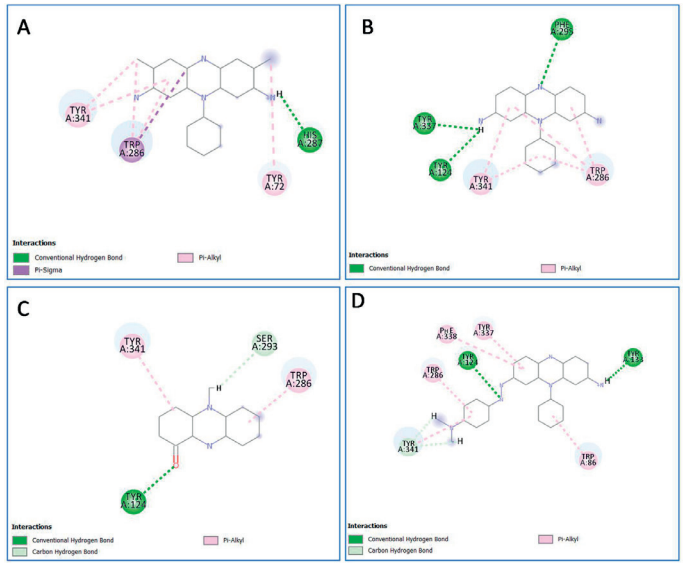


Figure 4. Molecular interactions of Safranin-O (A), Phenosafranine (B), Pyocyanine (C), and Janus Green B (D) with AChE active site

Molecular interactions revealed that Safranin-O, Phenosafranine, Pyocyanine, and Janus Green B interacted with key residues in the active site of BChE, as shown in Figure 5. Safranin-O (A) formed conventional hydrogen bonds with SER198, HIS438, and ASN83, and π-alkyl interactions with TRP82, PHE329, and LEU286. Additionally, an attractive charge interaction with ASP70 was observed. Phenosafranine (B) showed hydrogen bonds with THR120, SER79, and PRO285, along with π-alkyl interactions involving TYR332, PHE329, and ALA328. Pyocyanine (C) interacted through conventional hydrogen bonds with HIS438 and SER198, and displayed π-alkyl and alkyl

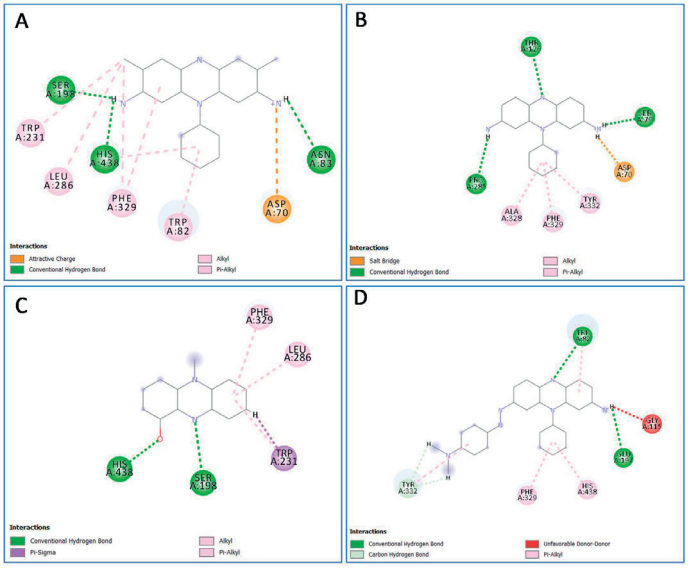


Figure 5. Molecular interactions of Safranin-O (A), Phenosafranine (B), Pyocyanine (C), and Janus Green B (D) with BChE active site

contacts with TRP231, LEU286, and PHE329. Janus Green B (D) formed hydrogen bonds with TRP82 and TYR332, a carbon hydrogen bond with GLU197, and π-alkyl interactions with TRP82, HIS438, and PHE329. Notably, an unfavorable donor–donor interaction was detected with GLY117. These findings indicate that all four compounds exhibit binding affinity towards BChE, with strong and multifaceted interactions.

Discussion and Conclusion

AD represents a significant public health issue, with its precise mechanisms and treatments remaining unidentified (25). The World Health Organization (WHO) predicts roughly 140 million cases of AD globally in 25 years (26). As the baby boom generation ages, an anticipated 10 million new diagnoses of AD are projected annually, which corresponds to almost 20 new people per minute (27). Since its identification, many hypotheses have been established for AD that involve impaired cholinergic system, Aβ accumulation, tau hyperphosphorylation, neuroinflammation, and various other pathways associated with the pathogenesis of AD (28). The association between these hypotheses and AD-related cognitive dysfunction has been well established. The cholinergic theory posits that as AD advances, ChE activity increases, hence limiting acetylcholine levels in the brain. Since cholinergic transmission is effective in both long-term memory and learning, any disruption in this system can have profound consequences (29, 30).

Therefore, cholinesterase inhibitors that will stabilize acetylcholine levels are in a critical position in the treatment of this pathology. Although ChE inhibitors cannot completely fully remediate AD, they can help patients manage symptoms and prolong the time to more intensive care (30, 31). The fact that AChE and BChE appear to have comparable functions in the pathophysiology of AD does not mean that they are equivalent targets for therapies against AD. Clinical results show that as AD progresses dramatically, AChE activity levels drop by up to 85-90%, and BChE, which is found in trace amounts in healthy individuals, increases due to plaques and tangles formed as the AD progresses. As a result, the BChE:AChE ratio could fluctuate from 0.2 to 11, representing a 22-fold increase. This alteration in the activity levels of AChE and BChE enzymes can be interpreted as an important target and strategy in drug designs to increase ACh levels, not only AChE inhibition but also BChE inhibition (32, 33).

Guillozet et al. suggested that BChE may be important in the conversion of Aβ from its non-pathogenic form to its pathogenic form related to neuritic tissue degeneration and AD (34). An *in vivo* study by Greig et al. presented the beneficial effects of BChE inhibition on learning and memory due to increased ACh levels and decreased Aβ levels (32). Their effect on cholinergic networks and amyloid plaques causes BChE inhibitors to be deserving of investigation in AD-related drug designs. Cationic phenothiazine derivative compounds, which have various pharmacological properties and clinical uses, are also of interest in AD-targeted drug research (35).

Since its discovery, numerous natural and modified synthetic phenazine ring compounds have been identified in all shades of the rainbow, and as mentioned in the introduction, a wide range of pharmacological activities has been recognized for phenazine compounds. Many studies have been presented for phenazine compounds and their pyrazine rings, which are of therapeutic importance for many diseases (17). The WHO 2019 Model List of Essential Medicines at *list.essentialmeds.org* includes four pyrazines (amiloride, bortezomib, paritaprevir, and pyrazinamide) and one phenazine (clofazimine). Common drug-target interactions for biologically active pyrazines have been demonstrated in computational studies (36). In the studies we conducted in our laboratory, we targeted the 'cholinergic hypothesis' and focused on the effects of phenazine-based compounds on cholinesterases. In our recent studies, we characterized the inhibition kinetics of methylene violet 3RAX (18) and Safranin-O (19) on cholinesterases. In this current study, the interactions of four phenazine-based dyes-Safranin-O, Phenosafranine, Pyocyanine, and Janus Green B with, two key cholinesterase enzymes, AChE and BChE enzymes were investigated via their binding energies and the potential inhibitory effects of these molecules were evaluated. The molecular docking data indicated that all four drugs revealed significant binding energies, confirming their potential as cholinesterase inhibitors. Janus Green B showed the highest affinity for AChE among the tested compounds, with a docking score of-9.2 kcal/mol. This implies that the compound's extended aromaticity and capacity to establish a variety of interactions, such as multiple hydrogen bonds and -alkyl contacts within the catalytic gorge of AChE, may contribute to a strong and stable binding. After the reference molecule Safranin-O, Phenosafranine showed

the best binding score with BChE (-8.9 kcal/mol), supported by a complex interaction network including hydrogen bonding with catalytically critical residues (e.g. THR120, SER79, and PRO285), hydrophobic -alkyl interactions and a significant electrostatic attraction with TYR332, PHE329, and ALA328. Particularly, TRP286 and TYR341 in AChE and TRP82 and PHE329 in BChE were consistently engaged in -interactions across all ligands, underlining their central role in stabilizing the ligand within the active site. This is consistent with prior structural analyses showing the significance of these aromatic residues in substrate accommodation and inhibitor binding. However, the binding affinity and interaction patterns of the ligands were observed to be influenced by subtle differences in the substituents of the ligands, despite the same central structures. In the active compartment, Pyocyanine, which showed moderate scores for both enzymes, formed fewer hydrogen bonds, potentially indicating a trade-off between steric compatibility and electronic distribution. From a therapeutic perspective, the strong binding profiles of Safranin-O and Janus Green B indicate their potential as lead compounds for the further design and optimization of dual AChE/BChE inhibitors.

Although the phenazine-based dyes examined in this study demonstrated promising binding affinities *in silico*, some of them (Pyocyanin, Janus Green B) are known to cytotoxic effects at higher concentrations. Although phenazine-based dyes demonstrate favorable binding affinities toward cholinesterase enzymes, it is crucial to emphasize that their biological behavior is highly dose-dependent. Janus Green B and other compounds are recognized as redox-active agents. Although low concentrations may produce beneficial inhibitory effects on target enzymes (37), higher doses have been linked to cytotoxicity, increased reactive oxygen species production, and mitochondrial dysfunction in neuronal and non-neuronal cell lines. Consequently, the therapeutic applicability of these molecules is contingent upon the identification of safe and effective concentration ranges, as they may function as a double-edged sword. In order to verify their potential as drug candidates, additional dose-response studies, such as IC_{50} and cytotoxicity analyses in pertinent neuronal models, are essential. Nevertheless, Phase II clinical trials for Alzheimer's disease have been initiated for certain redox-active dyes, including methylene blue (MethB), a phenothiazine derivative, as a result of their multitargeted effects, which include antiaggregatory activity on tau and Aβ and cholinesterase inhibition (38, 39). Research has demonstrated that various phenothiazine compounds, including thionine and toluidine blue, function as effective inhibitors of cholinesterases. Furthermore, these compounds have a beneficial impact on the phosphorylation of tau and the metabolism of APP (40-42). These precedents indicate that phenazine-based structures may continue to demonstrate potential as pharmacological leads when employed at optimized, non-toxic concentrations.

Considering the complex factors involved in Alzheimer's pathology, such as cholinergic dysfunction and oxidative stress, repurposing these redox-active dyes may provide a dual benefit in regulating enzyme activity and reducing oxidative damage.

In conclusion, this study highlights the cholinesterase inhibitory potential of various novel phenazine-based dyes, with Janus Green B and Phenosafranine standing out as a notably promising candidate. The results establish the groundwork for future studies focused on identifying and altering these scaffolds for the progress of neuroprotective drug development.

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Consent of Patients: The participants were informed in detail, and informed consent was obtained.

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Social Desirability, Mediterranean Diet, and Body Appreciation: Exploring Relationships Through Mediation Analysis

Sosyal Arzu Edilebilirlik, Akdeniz Diyeti ve Beden Beğenisi: Aracılık Analizi Yoluyla İlişkilerin Araştırılması

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ABSTRACT

Introduction: This study examines the relationships between social desirability, body appreciation, and adherence to the Mediterranean diet across different Body Mass Index (BMI) categories.

Material and Methods: A cross-sectional study was conducted with 254 randomly selected individuals aged 18–40 at a foundation university. Those with problematic eating behaviors and pregnant or lactating women were excluded. Participation was voluntary, and ethical approval was obtained. Data were collected via face-to-face interviews using a sociodemographic form, adherence to the Mediterranean diet, Body Appreciation, and the Social Desirability Scale. Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program version 23 and AMOS version 24, employing Pearson correlation and bootstrap methods (5000 resamples, $p<0.050$).

Results: Among underweight individuals, higher social desirability is linked to lower adherence to the Mediterranean diet and decreased body appreciation. Similarly, in normal-weight individuals, increased social desirability correlates with reduced adherence to the Mediterranean diet scores and lower positive body appreciation. However, in overweight and obesity categories, the direct effects of social desirability on adherence to the Mediterranean diet and Body Appreciation are not statistically significant. Additionally, social desirability (SD) indirectly influences adherence to the Mediterranean diet, suggesting that body appreciation is partly mediated by dietary adherence, particularly in underweight individuals.

Conclusion: These findings highlight the complex interactions between social desirability, body appreciation, and dietary adherence across BMI categories. Understanding these relationships emphasizes the importance of social and dietary factors in shaping body image and health behaviors. The results can inform future interventions and health programs to promote positive body image and healthy eating habits in individuals with different BMI statuses.

Keywords: Body image, psychological well-being, mediterranean diet, social behavior

ÖZ

Giriş: Bu çalışma, farklı Beden Kitle İndeksi (BKİ) kategorilerinde sosyal beğenirlik, beden beğenisi ve Akdeniz diyetine uyum arasındaki ilişkileri incelemektedir.

Materyal ve Metodlar: Kesitsel çalışma, bir vakıf üniversitesinde 18–40 yaş arası rastgele seçilen 254 birey ile gerçekleştirilmiştir. Problematik yeme davranışları olan bireyler ile hamile veya emziren kadınlar çalışmaya dâhil edilmemiştir. Katılım gönüllülük esasına dayalı olup etik onay alınmıştır. Veriler, sosyodemografik form, Akdeniz Diyetine Uyum, Beden Takdiri ve Sosyal Beğenirlik Ölçeği kullanılarak yüz yüze görüşmeler yoluyla toplanmıştır. İstatistiksel analizler IBM Sosyal Bilimlerde İstatistik Paket Programı (SPSS) sürüm 23 ve AMOS sürüm 24 programları ile Pearson korelasyonu ve "bootstrap" yöntemleri (5000 tekrar, $p<0,050$) kullanılarak yapılmıştır.

Bulgular: Zayıf bireylerde, sosyal beğenilirlik arttıkça Akdeniz diyetine uyum azalmakta ve beden beğenisi düşmektedir. Benzer şekilde, normal kilolu bireylerde de artan sosyal beğenilirlik, daha düşük Akdeniz diyetine uyum skorları ve azalan beden beğenisi ile ilişkilidir. Ancak, fazla kilolu ve obezite kategorilerindeki bireylerde, sosyal beğenilirliğin Akdeniz diyetine uyum ve beden beğenisi üzerindeki doğrudan etkileri istatistiksel olarak anlamlı bulunmamıştır. Ayrıca, sosyal beğenilirliğin Akdeniz diyetine uyum üzerindeki dolaylı etkileri, özellikle zayıf bireylerde beden beğenisinin kısmen diyet uyumu aracılığıyla etkilendiğini göstermektedir.

Sonuç: Bu bulgular, sosyal beğenilirlik, beden beğenisi ve diyet uyumu arasındaki karmaşık ilişkileri ortaya koymaktadır. Bu ilişkilerin anlaşılması, beden imajı ve sağlıkla ilgili davranışları şekillendirmede sosyal ve beslenme faktörlerinin önemini vurgulamaktadır. Sonuçlar, farklı BKİ gruplarındaki bireyler için olumlu beden imajı ve sağlıklı beslenme alışkanlıklarını teşvik eden müdahaleler ve sağlık programlarının tasarımına rehberlik edebilir.

Anahtar Sözcükler: Beden imajı, psikolojik iyilik hali, akdeniz diyeti, sosyal davranış

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Introduction

The complex etiology of obesity cannot be solely explained by physical health factors; social and psychological factors also play crucial roles in its development (1). Body image is a complex concept encompassing individuals' feelings, thoughts, and attitudes towards their own bodies, including aspects related to appearance, functionality, and performance (2). Developing a positive body image involves not only the absence of body dissatisfaction but also includes valuing one's body, paying attention to its needs, and processing body-related information in a self-protective manner (3). This construct goes beyond the absence of negative body image and represents a separate structure that includes acceptance, respect, and a positive outlook towards one's own body (4). The development of a positive body image has been associated with increased psychological well-being and establishing a healthier relationship with one's body (5). This positive link indicates that body image plays a significant role not only at a physical level but also at emotional and psychological levels. A positive view of one's body enhances psychological well-being, elevates life quality, and facilitates the establishment of a more positive and harmonious relationship with the body (6). Similarly, adherence to the Mediterranean Diet has been linked to various health benefits, including reducing the risk of cardiovascular diseases, certain cancer types, and cognitive disorders like Alzheimer's disease. Compliance with this dietary pattern has many positive effects on health and contributes to an increased life expectancy (7). The Mediterranean Diet provides essential nutrients for the body's well-being while also being recognized for its protective properties against various illnesses. A significant parallelism is observed between these two associations. Developing a positive body image and adhering to the Mediterranean Diet both contribute positively to individuals' physical and psychological health. The combination of positive feelings towards one's body and healthy eating habits represents an important synergy for overall health and well-being. Therefore, fostering a positive body image and adopting healthy eating habits are crucial steps towards achieving health goals and maintaining a healthy life. However, recent trends show a decline in adherence to the Mediterranean Diet among children and adolescents, raising concerns about future health issues (8). Hence, understanding the factors influencing dietary compliance is of utmost importance. Factors such as age, nationality, gender, preferences, nutrition knowledge, physiological status, and psychological factors play a role in determining individuals' dietary choices (9). Social desirability, body image and eating attitudes are closely interrelated psychosocial factors that significantly influence health-related behaviors. Research suggests that individuals often conform their self-reported eating habits to societal norms, which can make it difficult to assess actual eating behaviors. Positive body image is associated with healthier eating attitudes, while body dissatisfaction is associated with dysfunctional eating behaviors (10). A systematic review conducted by Bonfanti et al. shows that social comparisons caused by social media increase body image concerns and as a result, disordered eating behaviors may occur (11). This study aims to examine the relationships between obesity and body image by considering Body Mass Index (BMI) categories, and explore the associations between social desirability, adherence to the Mediterranean Diet, and body appreciation.

Material and Methods

Participants

This observational cross-sectional study is carried out with procedures in the age range of 18–40, with observations collected at the Faculty of Health Sciences, a foundation university organization, between April and September 2022. The sample size required for the study was determined through power analysis using the G*Power software. Accordingly, the required sample size for the F test interval with 90% power to reveal an effect of medium effect size (d=0.25) was calculated as 254. The study group was selected from undergraduate students studying in different faculties of a university by simple random sampling method. Inclusion criteria included being between the ages of 18–65, voluntarily agreeing to participate in the study and signing the informed consent form. Exclusion criteria were as follows: not having a psychiatric diagnosis and/or not receiving active psychiatric treatment, not applying a special nutritional treatment due to a chronic disease, and filling out the questionnaire forms incompletely or incorrectly. The classification of BMI was conducted according to the criteria set by the World Health Organization. Based on these guidelines, participants were categorized as follows: underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥30.0 kg/m²). This study was conducted in accordance with the 2018 Declaration of Helsinki. Informed consent was obtained from all participants. The scheme of this program was approved by the Non-Interventional Clinical Research Ethics Committee of Yüksek İhtisas University with the decision dated 10.03.2022 and numbered 2022/04/02.

Data collection tools

For the purpose of determining the demographic data of the participate, the researchers developed a sociodemographic data form. This form was tailored specifically to align with the objectives of the research. Face-to-face interviews were conducted with the participants, during which the sociodemographic data form was administered along with relevant scales. The researchers employed this comprehensive approach to ensure the accurate and reliable collection of essential information from the participants. By utilizing face-to-face interactions and incorporating standardized scales, the data collection process aimed to capture a comprehensive overview of the sociodemographic characteristics of the participants involved in the study.

Mediterranean Diet Adherence Screener (MEDAS): The scale is a questionnaire consisting of 14 questions. The Turkish adaptation and validity-reliability of the MEDAS were performed by Pehlivanoğlu, et al. in 2020. In the questionnaire, the type of basic oil used by the patients in meals, the amount of olive oil consumed daily, fruit and vegetable portions, margarine/butter and red meat consumption, weekly consumption of wine, pulses, fish-seafood, snacks, shellfish, consumption of nuts, cakes, tomato sauce with olive oil and whether white meat is preferred more than red meat. 1 or 0 points are taken for each question asked according to the amount of consumption, and the total score is calculated. A total score of 7 and above indicates that the individual has an acceptable degree of adherence to the Mediterranean diet, and a score of 9 and above indicates that the individual has a strict adherence to the Mediterranean diet. As a result of the questionnaire, it is learned that the patient has or does not have a Mediterranean type diet (12).

Body Appreciation Scale-2 (BAS): In order to assess the body appreciation status of the participants, the researchers employed the Turkish version of the BAS, which was developed by Tylka and Wood-Barcalow in 2015 to measure individuals' positive thoughts about their own bodies and the level of respect they have for these thoughts (13). The BAS is a 5-point Likert-type measurement tool, consisting of 10 items. Unlike the original version, BAS does not include any reverse items. Participants rate each item on a scale from 1 to 5, with a minimum total score of 10 and a maximum of 50 points achievable on the scale. By summing the scores of all items, a total score is obtained for each participant. A lower score on the BAS indicates that individuals have a more negative body appreciation, while a higher score reflects a more positive body appreciation. In other words, higher scores on the scale suggest that individuals possess a greater level of positive thoughts and respect towards their bodies (13).

Social Desirability Scale (SDS): To investigate the role of social desirability in our study, the researchers utilized the Turkish version of the SDS, which was developed by Erzen et al. in 2021. The SDS is designed to assess the social desirability levels of individuals and comprises a total of 15 items, presented in a 5-point Likert format. In the final form of the SDS, there are no reverse-scored items, meaning that all items are positively oriented. Consequently, participants are asked to rate each item on a scale ranging from 1 to 5, without any negatively phrased questions. The absence of sub-dimensions with negative content within the scale allows for the computation of a total score, which determines the overall level of social desirability exhibited by each individual (14).

Data Analyses

The data were analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 23 and IBM AMOS version 24 software. Pearson correlation coefficient was used to examine the relationship between normally distributed continuous variables. To test the hypothesized mediation models, bootstrap-based mediation analyses were conducted using the Maximum Likelihood estimation method in AMOS. In these analyses, 5.000 bootstrap resamples were used to estimate 95% bias-corrected confidence intervals (CI) for the direct, indirect, and total effects. Mediation was considered statistically significant when the 95% CI did not include zero. The significance level for all statistical tests was set at $p < 0.050$. These analyses were performed to evaluate the presence and strength of mediation effects of body appreciation and adherence to the Mediterranean diet in the relationship between social desirability and the outcome variables, across different BMI classifications.

Results

Table 1 presents the demographic characteristics of the participants in the study. Out of the total participants, 87.3% were women and 12.7% were men. The mean weight of the participants was 61.2 (±12.6) kg, while the mean height was 166.3 (±12.2) cm. The participants had an mean BMI of 21.9 (±3.7) kg/m². Regarding BMI classification, 70.8% of the participants were categorized as having a normal BMI, indicating a healthy weight range for their height. In contrast, 15.7% were classified as underweight, 10.1% as overweight, and 3.4% as obese. In terms of health behaviors, 19.9% of the participants reported consuming alcohol, and an equal percentage (19.9%) identified as smokers. Concerning meal habits, the majority of the participants (81.6%) reported consuming between 1 to 3 meals per day. Among those who skipped meals, 34.5% indicated that they did not have a habit of skipping meals

Table 2 presents the descriptive statistics of the scales used in the study. The mean MEDAS score was 5.8±1.9, with a median of 6.0, indicating that participants, on average, demonstrated low adherence to the Mediterranean diet. This score is below the threshold of 7 for acceptable adherence and significantly lower than the 9-point cut-off indicating strict adherence (12). The mean score on the Body Appreciation Scale-2 (BAS-2) was 37.3±8.1. While the scale does not have a defined cut-off value, higher scores indicate more positive body image. The mean Social Desirability Scale (SDS) score was 33.1±8.2. Similar to BAS-2, this scale does not have a cut-off point; however, higher scores are indicative of greater tendencies toward socially desirable responding.

Table 3 presents the results of the examination of the relationship between the scales used in the study Regarding the relationship between the MEDAS and the BAS, a positive correlation coefficient of 0.160 was observed, indicating a weak positive relationship between the two scales. The p-value of 0.009 suggests that this correlation is statistically significant at the 0.05 significance level, indicating that the relationship is not likely due to random chance. Similarly, when examining

Table 1. Demographic characteristics of the participants

	Frequency (n) / mean ± standard deviation
Gender	
Woman	87.3%
Man	12.7%
Weight	61.2±12.6
Height	166.3±12.2
BMI mean	21.9±3.7
BMI	
Underweight	15.7%
Normal weight	70.8%
Overweight	10.1%
Obese	3.4%
Age year	26.4±3.1
Smoking situation	
No	80.1%
Yes	19.9%
Alcohol consumption	
No	80.1%
Yes	19.9%
How many meals do you eat per day?	
1–3	81.6%
>3	18.4%
Reason for skipping meals*	
I eat two meals	0.4%
I have no habit	34.5%
I don't skip	0.4%
I don't want	26.6%
I have no appetite	26.6%
I don't skip meals	1.5%
Because I forgot	10.1%
Lack of time	24.0%
I want to lose weight	19.9%

* Multiple response.

Table 2. Descriptive statistics of the scales used in the study

Scale	Score range	Mean ± SD	Median (min–max)
MEDAS	0–14	5.8±1.9	6.0 (1.0 – 12.0)
Body appreciation (BAS-2)	10–50	37.3±8.1	38.0 (14.0 – 50.0)
Social desirability (SDS)	15–75	33.1±8.2	33.0 (16.0 – 64.0)

Table 3. The relationship between the scales

		MEDAS	BAS-2
MEDAS	r	-	
	p	-	
BAS-2	r	0.160	-
	p	0.009	-
SDS	r	-0.196	-0.250
	p	0.001	<0.001

r: Pearson correlation coefficient.

the relationship between MEDAS and the SDS, a negative correlation coefficient of -0.196 was found. This indicates a weak negative relationship between adherence to the Mediterranean diet and social desirability. The p-value of 0.001 suggests that this correlation is statistically significant at the 0.05 significance level. Furthermore, the relationship between BAS-2 and SDS was also investigated. A negative correlation coefficient of -0.250 was obtained, indicating a weak negative relationship between body appreciation and social desirability. The p-value for this correlation was found to be less than 0.001, which indicates that this relationship is statistically significant at the 0.05 significance level.

The results of Table 4 show the examination of total, direct, and indirect effects between SDS, BAS, and MEDAS for participants with different body mass indexes. Regarding the total effects, significant negative relationships were observed between Social Desirability and MEDAS for participants with underweight, normal, and obese body mass indexes (total effects: -0.467, -0.692, and -0.375, respectively; $p<0.050$). However, for those with overweight body mass index, the total effect of Social Desirability on MEDAS was not statistically significant (total effect: -0.101; $p>0.050$). This indicates that higher levels of Social Desirability are associated with lower adherence to the Mediterranean diet in individuals with underweight, normal, and obese body mass indexes. Regarding the direct effects, a significant negative relationship was found between Social Desirability and Body Appreciation for participants with underweight body mass index (direct effect: -0.46; $p<0.050$). However, for those with normal and overweight body mass indexes, the direct effect of Social Desirability on Body Appreciation was not statistically significant (direct effects: 0.305 and -0.104, respectively; $p>0.050$). This suggests that higher levels of Social Desirability are associated with lower body appreciation in underweight individuals. Moreover, a significant negative relationship was observed between Social Desirability and MEDAS for participants with normal and obese body mass indexes (direct effects: -0.653 and -0.309, respectively; $p<0.050$). However, for those with underweight and overweight body mass indexes, the direct effect of Social Desirability on MEDAS was not statistically significant (direct effects: -0.289 and -0.096, respectively; $p>0.050$). This indicates that higher levels of Social Desirability are associated with lower adherence to the Mediterranean diet in individuals with normal and obese body mass indexes. Regarding the indirect effects, for participants with underweight body mass index, the indirect effect of Social Desirability on MEDAS was statistically significant (indirect effect: -0.178; $p<0.050$). However, for those with normal, slightly obese, and obese body mass indexes, the indirect effects of Social Desirability on MEDAS were not statistically significant (indirect effects: -0.039, -0.004, and -0.066, respectively; $p>0.050$). This suggests that the indirect effects of Social Desirability on adherence to the Mediterranean diet were only significant for individuals with underweight body mass index.

Table 4. Examination of intermediary model results according to BMI classes

BMI classification	Independent variable	Total effect		Direct effect		Indirect effect	
		BAS	MEDAS	BAS	MEDAS	BAS	MEDAS
Underweight	SDS	—	-0.467 (-0.697; -0.178) a*	-0.46 (-0.715; -0.13) c*	-0.289 (-0.601; 0.01) ab**	—	-0.178 (-0.332; -0.016)*
	BAS	—	—	—	0.387 (0.068; 0.619) a*	—	
	R2	0.218		0.212	0.336		
Normal weight	SDS	—	-0.692 (-0.92; -0.283) a*	0.305 (-0.308; 0.768) a**	-0.653 (-1.089; -0.207) a*	—	-0.039 (-0.199; 0.375)**
	BAS	—	—	—	-0.128 (-0.646; 0.559) b**	—	
	R2	0.478		0.093	0.493		
Overweight	SDS	—	-0.101 (-0.379; 0.2) b**	-0.104 (-0.329; 0.14) ab**	-0.096 (-0.375; 0.208) b**	—	-0.004 (-0.051; 0.029)**
	BAS	—	—	—	0.042 (-0.176; 0.255) b**	—	
	R2	0.010		0.011	0.012		
Obese	SDS	—	-0.375 (-0.536; -0.186) a*	-0.38 (-0.605; -0.11) bc*	-0.309 (-0.508; -0.07) ab*	—	-0.066 (-0.199; 0.025)**
	BAS	—	—	—	0.174 (-0.071; 0.419) ab**	—	
	R2	0.14		0.144	0.166		

BAS: body appreciation; SDS: social desirability; a-c: no difference between effects with the same letter; different letters indicate a statistically significant difference; *p<0.050; **p>0.01; β (95% CI): standardized effect (Bootstrap 95% confidence interval).

Discussion

In this study, the interactions between obesity, body image, and the Mediterranean diet were examined by considering BMI classifications and the levels of social desirability, MEDAS, and body appreciation. Our findings provide important insights and contribute to the development of health policies and interventions. However, this study also demonstrates the significant impact of psychosocial factors, such as body image and social desirability on obesity. Body image is a complex concept that encompasses individuals' feelings and evaluations of their own bodies. Our results show a negative relationship between obesity and positive body image. Individuals in the underweight had higher body appreciation compared to those in the obese. This suggests that positive body image may play a role in reducing the risk of obesity. Accordingly, the first hypothesis of the study suggested that the indirect effect of social desirability on MEDAS adherence would be more effective only in individuals with underweight. The findings supported this hypothesis, revealing that greater adherence to MEDAS was associated with decreased social desirability, and this effect was particularly evident in underweight participants. Although previous research has not directly examined this conditional indirect effect, it was not unexpected. Earlier studies have established a relationship between body appreciation and eating behaviors (15). Our results indicate a protective role of body appreciation specifically for underweight individuals. These findings are in line with the concept of positive body image research, indicating that body appreciation is associated with higher resistance to sociocultural pressures towards appearance, less internalization of beauty ideals, and more positive adherence to MEDAS (16). The results of this study contribute new empirical data suggesting that positive body image may protect underweight individuals from the detrimental effects of internalizing stereotyped underweight body ideals in social desirability and increase adherence to MEDAS in the presence of such internalization.

The second hypothesis proposed that the relationship between MEDAS adherence and social desirability would be negatively moderated only in individuals with weak body appreciation. This hypothesis was also supported. Social desirability level played a significant moderating role in the relationship between obesity and body image. Individuals with high social desirability were more prone to negative body image and obesity. These consistent findings support the idea that individuals with social desirability sensitivity may experience a decrease in diet adherence. Moreover, the nonsignificant direct effects observed in the overweight and obese groups may reflect the tendency of individuals in these categories to report their health behaviors differently due to social approval concerns, as discussed by Puhl and Heuer (17). Thus, the differential influence of social desirability on eating attitudes and body image across BMI categories is a phenomenon supported by the literature and represents a novel contribution of the present study. Our findings are consistent with the significant results regarding the negative relationship between social desirability and MEDAS, as well as the tendency towards bias, which is an important limitation in diet therapy research, as mentioned in Lorgeril et al.'s study. This result indicates that social norms and expectations can influence body image and obesity risk. Therefore, measures and policies aimed at reducing negative body image caused by societal norms and social expectations are necessary. Additionally, in our study, a positive relationship between adherence to the Mediterranean diet and body image was found. It is suggested that the Mediterranean diet may positively influence body image, leading individuals to have a more positive perception of their bodies. The Mediterranean diet has emerged as a comprehensive lifestyle that includes not only specific foods and meal composition but also behavioral and social aspects, such as the production of specific foods, social exchange, and communication (18). The results of this study support the notion that adherence to the Mediterranean diet includes some social behaviors (19). Overall, this study

provides important insights into the complex relationships between obesity, body image, and the Mediterranean diet, taking into account BMI classes and social desirability. These findings highlight the relevance of psychosocial factors in obesity and body image, and emphasize the importance of considering social desirability and body appreciation in dietary interventions, particularly for underweight individuals. Moreover, the positive association between adherence to the Mediterranean diet and body image suggests that promoting the Mediterranean diet may contribute to fostering positive body image in individuals.

In this study, there are some limitations. Firstly, the participants of this study were selected from a specific geographical region, which may limit the generalizability of the findings. Including participants from different geographical regions and cultural backgrounds could enhance the applicability of the results to a wider population. Secondly, this study has an observational design, which does not allow for establishing causal relationships between the variables. Therefore, to fully understand the directional and causal nature of the relationships between social desirability, adherence to the Mediterranean diet, and body appreciation, future prospective experimental studies are needed. Thirdly, the data collection tools used in this study rely on self-reporting by the participants regarding their social desirability, dietary habits, and body appreciation. Self-report responses may be influenced by participants' personal perceptions and memory, which could introduce accuracy and recall biases. Lastly, this study only examined the relationships between social desirability, adherence to the Mediterranean diet, and body appreciation. Not considering the effects of other potential factors (e.g., age, gender, education level, psychological status, etc.) may result in incomplete explanations of the findings, especially in terms of interactive effects. Despite these limitations, this study contributes to the understanding of the complex interactions between social desirability, adherence to the Mediterranean diet, and body appreciation across different BMI classes. Future research, taking these limitations into account, can utilize data from a broader and more diverse range of participants to achieve more comprehensive results.

Specifically, it aims to evaluate different interactions among underweight, normal weight, overweight, and obese individuals, providing valuable insights to guide the development of health policies and interventions related to obesity and body image. The knowledge gap missing from previous literature and targeted by this study is that it has not been clarified how physical and psychological health problems caused by obesity or risk factors can be addressed with effective interventions. The findings of this research may contribute to the design of appropriate and effective interventions in the healthcare field and help improve individuals' physical and psychological health, thereby preventing future health issues.

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Ethical Considerations: This study was approved by the Non-Interventional Clinical Research Ethics Committee of Yüksek İhtisas University with the decision dated 10.03.2022 and numbered 2022/04/02.

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Consent of Patients: The participants were informed in detail, and informed consent was obtained.

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Can Computer-Aided CT Analysis Redefine Mediastinal Lymph Node Diagnosis?

Bilgisayar Destekli BT Analizi Mediastinal Lenf Nodu Tanısını Yeniden Tanımlayabilir mi?

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ABSTRACT

Introduction: Accurate mediastinal lymph node evaluation is essential in the diagnosis and staging of malignant tumors. Traditional size-based criteria pose challenges, particularly for smaller nodes, necessitating alternative approaches. To investigate the diagnostic value of volume, calculated diameter, and HU values obtained using computer-aided software in distinguishing between benign and malignant mediastinal lymph nodes on contrast-enhanced and non-contrast thoracic computed tomography.

Material and Methods: A retrospective analysis of 103 patients with 172 lymph nodes. Quantitative metrics were derived using the "Vitrea Lung Nodule Analysis" software. Diagnostic performance was assessed using ROC analysis, and statistical associations were examined through univariate and multivariate logistic regression models.

Results: Age and male gender were significant predictors of malignancy ($p<0.001$). While HU values and calculated parameters showed limited diagnostic performance, multivariate analysis revealed significant effects of lymph node diameter and multiple nodes on malignancy classification ($p<0.05$). The model achieved an AUC of 0.804, with sensitivity and specificity of 0.815 and 0.684, respectively.

Conclusion: Despite incorporating entire lymph nodes in quantitative assessments, HU values and volumes demonstrated limited clinical utility. However, advanced imaging and AI-driven three-dimensional analyses may enhance diagnostic accuracy.

Keywords: Mediastinal lymph nodes, computed tomography, lung cancer, artificial intelligence, lymph node metastasis, computer-aided diagnosis

ÖZ

Giriş: Malign tümörlerin tanı ve evrelemesinde mediastinal lenf nodlarının doğru değerlendirilmesi kritik öneme sahiptir. Geleneksel boyut temelli kriterler, özellikle küçük lenf nodları için zorluklar yaratmakta ve alternatif yaklaşımların gerekliliğini ortaya koymaktadır. Bu çalışmada kontrastlı ve kontrastsız toraks bilgisayarlı tomografide bilgisayar destekli yazılım kullanılarak elde edilen hacim, hesaplanan çap ve HU değerlerinin, benign ve malign mediastinal lenf nodlarının ayırt edilmesindeki tanısal değerini araştırmak amaçlanmıştır.

Materyal ve Metodlar: 172 lenf nodu bulunan 103 hastanın retrospektif analizi yapıldı. Kantitatif ölçümler "Vitrea Lung Nodule Analysis" yazılımı ile elde edildi. Tanısal performans ROC analizi ile değerlendirildi; istatistiksel ilişkiler ise tek değişkenli ve çok değişkenli lojistik regresyon modelleri kullanılarak incelendi.

Bulgular: Yaş ve erkek cinsiyet malignite için anlamlı öngördürücülerdi ($p<0.001$). HU değerleri ve hesaplanan parametreler sınırlı tanısal performans gösterirken, çok değişkenli analizde lenf nodu çapı ve çoklu nod varlığı malignite sınıflamasında anlamlı etkiler gösterdi ($p<0.05$). Modelin AUC değeri 0.804 olup, duyarlılık 0.815 ve özgüllük 0.684 olarak bulundu.

Sonuç: Lenf nodlarının tamamını içeren kantitatif değerlendirmelere rağmen HU değerleri ve hacimlerin klinik faydası sınırlı kalmıştır. Bununla birlikte, ileri görüntüleme yöntemleri ve yapay zekâ destekli üç boyutlu analizler tanısal doğruluğu artırabilir.

Anahtar Sözcükler: Mediastinal lenf nodları, bilgisayarlı tomografi, akciğer kanseri, yapay zekâ, lenf nodu metastazı, bilgisayar destekli tanı

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Introduction

Despite considerable advances in medical science, lung cancer continues to be the most prevalent malignancy worldwide and remains the leading cause of cancer-related mortality (1,2).

While the majority of lung cancer cases are identified at an advanced stage, curative treatment remains possible for those detected earlier. This underscores the critical role of timely diagnosis and precise radiological staging. Establishing a histopathological diagnosis is fundamental not only for early detection but also for determining prognosis, guiding therapeutic decisions, and estimating the likelihood of favorable outcomes (1,3).

Assessment of mediastinal lymph nodes is essential in the diagnosis, management, and surveillance of lung cancer, given the frequent involvement of mediastinal and hilar nodes in disease progression. Importantly, lymphoscintigraphy studies have demonstrated that bilateral paratracheal regions serve as primary lymphatic drainage routes. Consequently, accurate detection of paratracheal lymph nodes holds particular significance for proper tumor staging. Identification of nodal involvement can alter the staging outcome and directly affect therapeutic planning (4,5).

A short-axis diameter greater than 1.0 cm is commonly used as a radiological threshold for identifying pathological lymph nodes. Nevertheless, emerging evidence suggests that nodes smaller than this threshold may also harbor metastatic disease. Early detection of such metastatic involvement is critical for determining prognosis. Moreover, potentially malignant lymph nodes should not be underestimated during surgical evaluation. While enlarged nodes are generally easier to detect on imaging and during operations, the identification of smaller nodes poses a notable diagnostic challenge. Precise recognition of these smaller lymph nodes may influence staging accuracy and subsequently impact surgical planning, therapeutic strategies, and patient outcomes (6,7).

A range of imaging techniques is employed to detect, stage, and monitor mediastinal lymph nodes, including computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI). Despite their widespread use, these modalities may have limited sensitivity in identifying small-sized lymph nodes, which can compromise diagnostic accuracy (8,9).

In this study, we applied the "Vitrea Lung Nodule Analysis" auxiliary software, available at our clinic's workstation, to mediastinal lymph nodes. Unlike previous similar studies, we aimed to evaluate the diagnostic value of attenuation, lymph node volume, and the diameter calculated by the software during volumetric measurements of all lymph nodes in contrast-enhanced and non-contrast thoracic CT scans.

Material and Methods

Participants

The study received approval from the Local Non-invasive Investigation Ethics Committee (Approval No: 2025-04-299, dated April 14, 2025). Diagnostic procedures were conducted in alignment with the approved protocols. Written informed consent was obtained from all participants. Histopathological assessments were performed by a certified pathologist following internationally accepted guidelines. All procedures adhered to national ethical standards and conformed to the principles of the 1964 Helsinki Declaration and its subsequent revisions. The study included 103 patients with a prior diagnosis of malignancy and evaluated a total of 172 lymph nodes between January 1, 2018, and December 31, 2023. Inclusion criteria encompassed lymph nodes that were either deemed suspicious in standard CT evaluations or exhibited hypermetabolic activity (SUVmax ≥2.5) on PET/CT imaging.

To confirm the diagnosis of suspiciously enlarged lymph nodes, all patients underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Histopathological evaluation of the EBUS-TBNA samples served as the basis for identifying nodal metastases. Prior to the procedure, the pulmonologist performing the endoscopy reviewed the anatomical location of target lymph nodes on CT scans, allowing for correlation between radiological findings and EBUS-TBNA results across matching lymph node stations and comparable sizes. Given the retrospective design of the study, the radiologist conducting the image-based measurements was already informed of the biopsy locations and corresponding pathological outcomes.

The radiologist marked the lymph nodes on contrast-enhanced and non-contrast thoracic CT images using the "Vitrea Lung Nodule Analysis" program. Since the software is designed for lung nodules, it was unable to delineate the boundaries of lymph nodes with complete accuracy. The radiologist used the "edit" mode to make necessary adjustments to the lymph node boundaries. After corrections, the volumetric measurements of the mediastinal lymph nodes, their diameters as calculated by the software, and their attenuation values on non-contrast and contrast-enhanced CT were recorded (Fig. 1). The edge characteristics and shapes of the lymph nodes were not evaluated. None of the lymph nodes included in the study showed calcification.

EBUS-TBNA Procedure

Endobronchial ultrasound-guided transbronchial needle aspiration (TBNA) was performed using a convex probe EBUS bronchoscope (EB-530US; Fujifilm, Tokyo, Japan) and a 22G needle (NA-201SX-4022; Olympus). All EBUS procedures were conducted under general anesthesia with the presence of an anesthesiologist. Each visualized station was systematically

sampled. If multiple lymph nodes were present in a single region, the largest lymph node was sampled. At least three samples were obtained from each lymph node. Rapid on-site evaluation (ROSE) for cytopathological examination was not utilized.

Statistical Analysis

Descriptive statistics were used to summarize the data obtained from the study. Numerical variables were presented as mean ± standard deviation or as median, minimum, and maximum, depending on the distribution, in a tabular format. Categorical variables were summarized as counts and percentages. The normality of numerical variables was assessed using appropriate tests and visual tools based on the sample size and data characteristics. For comparisons involving larger samples (n ≥50), the Kolmogorov-Smirnov and Anderson-Darling tests were employed. Additionally, visual tools such as histograms and Q-Q (quantile-quantile) plots were used to evaluate the assumption of normality.

To compare differences in categorical variables between groups, the Pearson Chi-Square test was used for larger sample sizes, as it provides more reliable results in such cases. For smaller sample sizes, Fisher's Exact Test was preferred due to its greater sensitivity. In RxC tables where the expected frequency was less than 5, the Fisher-Freeman-Halton test was employed, as it is more suitable for smaller samples.

For comparisons between two independent groups, the Mann-Whitney U test was preferred when numerical variables did not follow a normal distribution.

To evaluate the capacity of lymph nodes to predict malignancy, Receiver Operating Characteristic (ROC) analysis was performed. The analysis included the Area under the Curve (AUC), sensitivity, specificity, and optimal cutoff values for each parameter (Minimum HU Value, Maximum HU Value, Mean HU Value, Volume, and Diameter) to assess their ability to distinguish malignancy. AUC, sensitivity, specificity, cutoff values, and 95% confidence intervals were calculated and presented. P-values were reported to determine the statistical significance of the analysis results.

Statistical analyses were conducted using the Jamovi software package (Version 2.3.28, Jamovi Project, 2023, University of Sydney, Sydney, Australia, https://www.jamovi.org) and JASP (Version 0.18.3, Jeffreys' Amazing Statistics Program, 2024, University of Amsterdam, Amsterdam, The Netherlands, https://jasp-stats.org). A p-value of ≤0.05 was considered the threshold for statistical significance.

Results

A total of 103 patients and 172 lymph nodes were included in this study. The median age of participants was 58 years, with 32% (n=55) being female and 68% (n=117) male. The proportion of patients with one lymph node was 29.1% (n=50), with two lymph nodes was 45.3% (n=78), with three lymph nodes was 20.9% (n=36), and with four lymph nodes was 4.7% (n=8). The proportion of patients with a single lymph node was 29.1% (n=50), while those with multiple lymph nodes accounted for 70.9% (n=122). The median lymph node volume was measured at 6543.7 mm^3, and the median diameter of the lymph nodes was 17.0 mm.

Comparative analyses revealed that patients with malignant lesions were significantly older than those with benign lesions ($p<0.001$). Additionally, a higher proportion of male patients was observed in the malignant lesion group ($p<0.001$).

From a localization perspective, more lymph nodes were observed in the 4L location in malignant patients, while the 2R location was more common in benign patients ($p=0.031$). No significant differences were found between the groups in terms of the number of lymph nodes, lymph node volume, or the diameter of the lymph nodes ($p>0.05$ for all) (Table 1).

When HU values were analyzed based on contrast-enhanced and non-contrast imaging methods, it was observed that patients with benign and malignant lymph nodes had similar values ($p>0.05$ for all) (Table 2).

ROC analysis showed that HU-based measurements from both contrast-enhanced and non-contrast CT images yielded low AUC values and did not demonstrate statistically significant discriminatory power for predicting malignancy. Similarly, lesion volume and diameter exhibited limited diagnostic performance, with AUC values below 0.60. These detailed results are summarized in Table 3.

According to univariate analyses, age and sex were found to have significant effects ($p<0.001$ for both) on the classification of lesions as benign or malignant based on imaging findings. Specifically, a one-unit increase in patient age was associated with a 6% increase in the likelihood of the lesion being classified as malignant. Male patients were 3.99 times more likely than female patients to have lesions classified as malignant. The number of lymph nodes (single or multiple), the diameter, and the volume of lymph nodes did not show significant effects in the univariate analyses ($p>0.05$ for each).

In multivariate analyses, age, sex, the number of lymph nodes, and the calculated diameter of the lymph nodes were found to have significant effects on the classification of lesions as malignant or benign ($p<0.05$ for each). Specifically, a one-unit increase in age and the diameter of lymph nodes increased the likelihood of malignancy by 7% and 7%, respectively. Male patients and those with multiple lymph nodes were 3.68 and 2.29 times more likely, respectively, to have lymph nodes classified as malignant. Lymph node volume did not show a significant effect

Table 1. The demographic and clinical characteristics of the patients, as well as the binary comparisons regarding the malignant/benign status of the lymph nodes

		Lymph Node Status		
	Overall (n=172)	Benign (n=80)	Malignant (n=92)	p-value
Age	58.0 [26.0 – 85.0]	48.0 [26.0 – 85.0]	63.0 [30.0 – 85.0]	<0.001**
Gender				
Female	55 (32.0)	38 (47.5)	17 (18.5)	<0.001*
Male	117 (68.0)	42 (52.5)	75 (81.5)	
Number of Lymph Nodes				
1	50 (29.1)	28 (35.0)	22 (23.9)	0.228*
2	78 (45.3)	30 (37.5)	48 (52.2)	
3	36 (20.9)	18 (22.5)	18 (19.6)	
4	8 (4.7)	4 (5.0)	4 (4.3)	
Number of Lymph Nodes				
Single	50 (29.1)	28 (35.0)	22 (23.9)	0.153*
Multiple	122 (70.9)	52 (65.0)	70 (76.1)	
Volume (mm^3)	6543.7 [93.2 – 476007.8]	5000.0 [93.2 – 321868.8]	7202.0 [300.0 – 476007.8]	0.283**
Calculated Diameter (mm)	17.0 [5.6 – 64.4]	16.3 [5.6 – 64.4]	18.4 [7.4 – 53.6]	0.067**
Location (%)				
1	2 (1.2)	0 (0.0) a	2 (2.2) a	0.031*
10L	7 (4.1)	4 (5.0) a	3 (3.3) a	
10R	6 (3.5)	5 (6.2) a	1 (1.1) a	
11–14L	1 (0.6)	0 (0.0) a	1 (1.1) a	
11L	7 (4.1)	5 (6.2) a	2 (2.2) a	
11R	5 (2.9)	3 (3.8) a	2 (2.2) a	
2L	2 (1.2)	0 (0.0) a	2 (2.2) a	
2R	3 (1.7)	2 (2.5) a	1 (1.1) b	
4L	12 (7.0)	1 (1.2) a	11 (12.0) b	
4R	55 (32.0)	26 (32.5) a	29 (31.5) a	
7	71 (41.3)	34 (42.5) a	37 (40.2) a	
8	1 (0.6)	0 (0.0) a	1 (1.1) a	

‡: n (%), §: Median [Min. –Max.]
a, b: Different superscripts indicate statistically significant differences between groups in each row. Groups sharing the same superscripts do not exhibit statistical differences.
*: Pearson Chi-Square veya Fisher Freeman Halton test.
**: Mann-Whitney U test.

Table 2. Binary comparisons of HU measurements and malignant/ benign status based on contrast-enhanced and non-contrast imaging methods

		Benign (n=80)	**Malignant (n=92)**	**p-value***
Minimum HU value	non-contrast	-37 [-102 – 85]	-34.5 [-185 – 46]	0.907
	contrast-enhanced	-31 [-165 – 36]	-24.5 [-155 – 74]	0.561
Maximum HU value	non-contrast	97.5 [32 – 343]	92 [32 – 718]	0.588
	contrast-enhanced	147 [57 – 449]	147.5 [64 – 822]	0.617
Mean HU value	non-contrast	34.4 [2.2 – 104.5]	36.1 [-8 – 105]	0.569
	contrast-enhanced	63 [7.4 – 86.9]	60.4 [18 – 201]	0.572

§: Median [Min. –Max.]; *: Mann-Whitney U test.

Table 3. The diagnostic performance of relevant parameters in distinguishing between benign and malignant lesions

Lesion Status (Malignant)	**AUC**	**Sensitivity**	**Specificity**	**Cut-off value**	**95% CI**	**p-value**
Contrast-enhanced (n=87)						
Minimum HU value	0.537	47.37	71.43	>-17	0.427 – 0.644	0.571
Maximum HU value	0.532	36.84	81.63	>174	0.422 – 0.640	0.631
Mean HU value	0.536	26.32	89.80	≤39	0.426 – 0.643	0.581
Non-contrast (n=85)						
Minimum HU value	0.508	20.37	96.67	≤-85	0.397 – 0.619	0.900
Maximum HU value	0.536	40.74	73.33	≤85	0.424 – 0.646	0.591
Mean HU value	0.538	79.63	36.67	≤41.7	0.426 – 0.647	0.538
Volume (mm^3)	0.548	23.91	88.61	>36944	0.470 – 0.624	0.280
Calculated diameter (mm)	0.581	61.96	55.70	>16.6	0.504 – 0.656	0.065

AUC: area under the curve.

Table 4. The predictive effects of patient– and lesion-related variables in distinguishing between benign and malignant lesions and model performance metrics for logistic regression analysis

	Univariate logistic regression model		Multivariate logistic regression model	
	OR [%95 CL]	**p-value**	**OR [%95 CI]**	**p-value**
Age	1.06 [1.04 – 1.09]	<0.001	1.07 [1.04 – 1.1]	<0.001
Gender Male vs. female	3.99 [2.01 – 7.92]	<0.001	3.68 [1.64 – 8.25]	0.002
Number of lymph nodes Multiple vs. single	1.71 [0.88 – 3.33]	0.112	2.29 [1.02 – 5.14]	0.045
Volume (mm^3)	1.01 [1.01 – 1.02]	0.087	1.01 [1.01 – 1.02]	0.538
Calculated diameter (mm)	1.03 [0.99 – 1.06]	0.122	1.07 [1.01 – 1.13]	0.019
	Accuracy	**Specificity**	**Sensitivity (recall)**	**Area under the curve (AUC)**
	0.754	0.684	0.815	0.804

(p=0.538). When examining model performance metrics, the model's accuracy was 0.754, sensitivity was 0.815, specificity was 0.684, and the area under the curve (AUC) was 0.804 (Table 4).

Discussion

The presence of mediastinal lymph node metastases is critically important for the initial staging of malignant tumors and serves as a significant prognostic indicator. Additionally, the emergence of mediastinal lymphadenopathy during the course of therapy requires careful evaluation, as confirming nodal metastasis can substantially influence the direction of subsequent treatment planning (10). Determining the nodal (N) stage within the TNM classification system is notably more difficult than assessing the primary tumor (T) stage. Studies have shown that the agreement between preoperative clinical staging and postoperative pathological staging in lung cancer patients is as low as 39%. This gap is primarily due to the limited diagnostic reliability in detecting mediastinal lymph node metastases (11,12).

Non-invasive methods such as PET/CT and conventional CT are widely used for diagnosing metastatic lymph nodes to determine mediastinal involvement; however, they do not provide a definitive diagnosis. To confirm mediastinal metastases, a range of invasive techniques for tissue sampling is available. Invasive diagnostic methods, including mediastinoscopy, EBUS-TBNA, and intraoperative sampling, can accurately diagnose mediastinal lymph node metastases (13).

In clinical practice, metastatic lymph nodes are often diagnosed based on size-dependent criteria using imaging methods. However, detecting small metastatic lymph nodes based on CT characteristics poses a diagnostic challenge. For years, a short-axis diameter of 1.0 cm has been recommended as the threshold for normal lymph nodes and is still widely used today. However, recent findings have provided more insights into the normal size of lymph nodes. Specifically, when a short-axis diameter of 1.0 cm is used as the threshold, the presence of false positives and false negatives becomes a major concern, particularly given the correlation between lymph node size and survival (11,14).

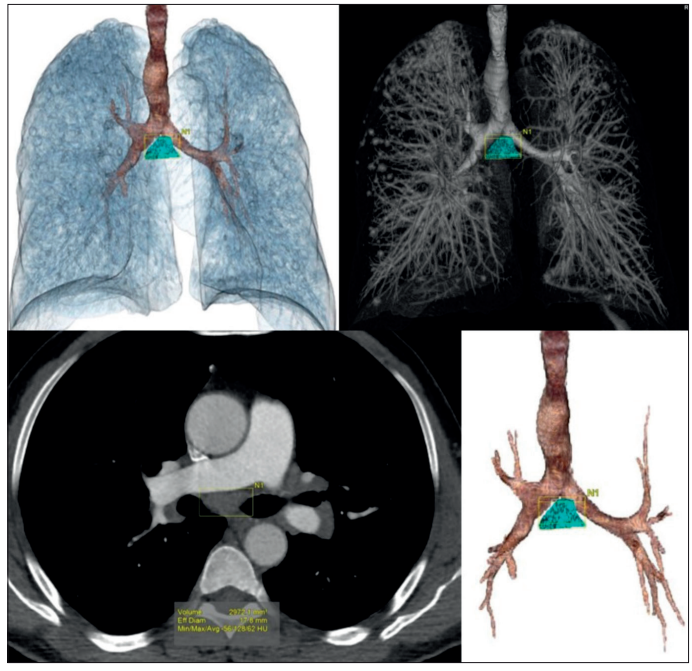

Figure 1. The image presents an example case where volume, calculated diameter, and minimum/mean/maximum HU values were measured with the assistance of computer-aided software.

For this reason, in our study, we hypothesized that volume measurements obtained by selecting the entire lymph node using computer-aided software, along with the diameter calculated based on volume through the software, could contribute to the evaluation of metastatic lymph nodes (Fig. 1). Another notable observation from our study was that assessing CT attenuation by evaluating the entire lymph node—rather than relying on region of interest (ROI) selection –may offer diagnostic value in identifying metastatic involvement (Fig. 1).

The results of our study, despite including the entire lymph node in the measurements using computer-aided software, were largely consistent with similar studies in the literature. Including the entire lymph node in volume, calculated diameter, and HU measurements did not demonstrate superior diagnostic performance compared to HU measurements using ROIs or short-axis diameter measurements (15).

When evaluating the diagnostic performance of HU values, it was found that HU values demonstrated low diagnostic performance in distinguishing between malignant and benign lesions. This finding aligns with other studies indicating that HU values have limited diagnostic value, even when the entire lymph node is assessed using software without ROIs. The low diagnostic performance of HU values underscores the necessity for advanced imaging and biopsy techniques, reaffirming that histopathological diagnosis remains the gold standard (16,17).

Given that lymph node volume and calculated diameter may serve as stronger predictors for distinguishing malignancy, the necessity for more detailed investigation of these parameters through three-dimensional analyses becomes apparent. The application of artificial intelligence-based models in lymph node detection and malignancy differentiation holds promising potential. Specifically, AI and machine learning algorithms could identify patterns in three-dimensional analyses that were not detected in our study, potentially leading to higher diagnostic accuracy (18).

In our study, it was found that patients with malignant lesions were significantly older than those with benign lesions, and male patients were more prevalent in the malignant lesion group. Age and sex have been reported as important predictors of lymph node malignancy. These findings suggest that older and male patients require closer monitoring (19).

In terms of lymph node localization, more lymph nodes were observed in the 4L location in malignant patients, while the 2R location was more common in benign patients. These findings support the hypothesis that pathological lymph nodes may be more prevalent in certain anatomical regions, aligning with similar observations reported in the literature (20,21).

This study has several limitations. The primary limitation is the limited sample size, which necessitates validation in larger populations. The restricted sample size reduces the generalizability of the results. Secondly, the study has a retrospective design, which may introduce certain biases compared to prospective studies. The retrospective nature of the study makes it challenging to control for variability in the data collection process. To validate our findings and assess their applicability in clinical practice, larger prospective and randomized controlled studies are needed. Thirdly, we did not account for potential clustering effects among the multiple lymph nodes evaluated within individuals. To mitigate this effect, we reported the number of lymph nodes in the analysis and included single– and multiple-lymph-node columns in the tables. Fourthly, the images were obtained from different institutions, leading to variations in imaging protocols. Despite these differences, all images were loaded onto a single workstation for objective measurements, disregarding variations in imaging protocols.

Conclusion

This study evaluated the diagnostic value of volume, calculated diameter, and HU measurements obtained from contrast-enhanced/non-contrast thoracic CT and PET CT images using the “Vitrea Lung Nodule Analysis” software. Although all lymph nodes were analyzed volumetrically, these quantitative parameters showed limited performance in distinguishing malignant from benign nodes.

Age and sex emerged as significant predictors, with older age and male sex being associated with malignancy. Additionally, lymph node localization patterns differed by malignancy status.

Our findings reaffirm that histopathological evaluation remains essential for definitive diagnosis. Future studies incorporating 3D analysis of lymph node morphology—including edge characteristics and shape—and integrating AI-based pattern recognition may enhance diagnostic accuracy.

AI-Assisted Technologies Statement

The authors affirm that no artificial-intelligence tools (including large language models, chatbots, or image generators) were used at any stage of the conception, execution, analysis, or writing of this manuscript.

Ethical Considerations: This study was approved by the Yüksek İhtisas Universityh Ethics Committee of Yüksek İhtisas University with the decision dated 14.04.2025 and numbered 2025-04-299.

Peer-review: Externally peer-reviewed.

Consent of Patients: The participants were informed in detail, and informed consent was obtained.

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Declaration of Interest Statement: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data Availability Statement: All relevant data are within the paper and they are available from the corresponding author on reasonable request.

Author Contributions: Concept - Ş.B.A.; Design - Ş.B.A; Supervision - K.C.; Literature Search - Ş.B.A.; Analysis or Interpretation - Ş.B.A.; Writing - Ş.B.A.; Critical Review - K.C.

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Left Azygos Lobe and Its Vein: A Rare Anatomical Variant with Clinical Implications

Sol Azigos Lobu ve Veni: Klinik Etkileri Olan Nadir Bir Anatomik Varyant

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ABSTRACT

Introduction: Although anatomical variations of the azygos system are uncommon, they hold clinical significance, particularly when misinterpreted as pathological findings on imaging. Among these variations, the presence of a left azygos lobe and its associated venous anomaly are especially rare and often under-recognized.This study aims to raise awareness of the left azygos lobe and its associated vein as an uncommon venous variation, and to highlight its anatomical, embryological, and clinical relevance through radiological illustrations and literature review.

Case: This descriptive study presents cases illustrating medial entrapment of the left upper lobe by an aberrant left superior posterior intercostal vein, forming a rare left azygos lobe configuration. Multidetector computed tomography with multiplanar reconstructions was used to visualize vascular and parenchymal anatomy. Embryological correlations and potential clinical implications were also examined through a review of relevant radiological and anatomical literature.

Results: Imagings revealed left azygos lobe variant with a medially displaced left upper lobe, entrapped by a dilated vein coursing between the aortic arch and the lung apex. The vein was identified as left superior posterior intercostal vein, forming a pseudo-fissure without bronchovascular separation. This variation mimicked a soft tissue mass on chest radiography and was clarified by cross-sectional computed tomography. Recognition of this anomaly prevented unnecessary diagnostic procedures.

Conclusion: The awareness of rare venous anomalies, such as the left azygos lobe and its associated vein, is essential for radiologists to avoid misdiagnosis. Computed tomography imaging offers reliable identification of such variations and enhances understanding of thoracic venous anatomy, aiding in surgical and interventional planning. Improved awareness of these variations can prevent misdiagnosis and guide future prevalence-based studies.

Keywords: Azygos lobe, left superior intercostal vein, anatomical variation, thoracic CT, venous anomaly, embryology

ÖZ

Giriş: Azygos sistemin anatomik varyasyonları nadirdir ancak özellikle görüntülemede patolojik bulgularla karıştırıldığında klinik açıdan önemlidir. Bu varyasyonlar arasında, sol azygos lobu ve ona eşlik eden venöz anomali oldukça nadir olup genellikle fark edilmez. Bu vaka temelli radyolojik analiz aracılığıyla, sol azygos lobu ve ona eşlik eden venin anatomik, embriyolojik ve klinik önemini tanımlamak amaçlanmıştır.

Olgu: Bu tanımlayıcı çalışma, nadir görülen bir sol azygos lob konfigürasyonu oluşturan aberan sol superior posterior interkostal ven tarafından sol üst lobun mediyal tuzağa düşmesini gösteren bir vakayı sunmaktadır. Vasküler ve parankimal anatomiyi görüntülemek için çok dedektörlü bilgisayarlı tomografi ve multiplanar rekonstrüksiyonlar kullanılmıştır. Radyolojik ve anatomik literatür temelinde embriyolojik ilişkiler ve olası klinik sonuçlar da gözden geçirilmiştir.

Bulgular: Görüntüleme, aort kavsi ile akciğer tepesi arasında seyreden dilate bir ven tarafından mediyal olarak yer değiştirmiş sol üst lob ile birlikte bir sol azygos lob varyantını ortaya koymuştur. Bu ven, bronkovasküler ayrım olmaksızın yalancı bir fissür oluşturan sol superior posterior interkostal ven olarak tanımlanmıştır. Bu varyasyon, akciğer grafisinde yumuşak doku kitlesi olarak taklit edilmiş, kesitsel bilgisayarlı tomografi ile açıklığa kavuşturulmuştur. Bu anomalinin tanınması gereksiz tanısal girişimlerin önüne geçmiştir.

Sonuç: Sol azygos lobu ve ona eşlik eden ven gibi nadir venöz anomalilerin farkında olmak, radyologlar için yanlış tanıların önlenmesi açısından çok önemlidir. BT görüntüleme, bu tür varyasyonların güvenilir şekilde tanımlanmasını sağlar ve torasik venöz anatomiyi anlamayı geliştirerek cerrahi ve girişimsel planlamaya katkıda bulunur.

Anahtar Sözcükler: Azygos lob, sol superior interkostal ven, anatomik varyasyon, torasik BT, venöz anomali, embriyoloji

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Introduction

The azygos system is a paravertebral venous tract in the posterior thorax that includes the azygos, hemiazygos, and accessory hemiazygos veins (1). It connects the superior and inferior venae cavae. Actually, the azygos systems generate essential collateral routes that serve as a critical shunt when the principal pathways are blocked (2).

Abnormalities in embryonic development can lead to a range of venous system anomalies. Variations in the azygos venous system are radiologically well-known to be prevalent with a 0.5–1.2% incidence. Azygos system variations almost never result in symptoms (3). While the exact incidence is unknown, the left azygos lobe and its vein, which are seen significantly less frequently, have been documented in the literature (Table 1). However, it remains under-recognized in both radiological practice and anatomical literature (4).

This article aims to provide a comprehensive descriptive review of the left azygos lobe and its associated vein, with emphasis on embryological development, anatomical course, and clinical implications. By integrating radiological imaging with embryological and anatomical context, this manuscript seeks to increase awareness of this rare entity and to encourage future studies investigating its prevalence and diagnostic significance.

Anatomical and Embryological Background

To better understand the anatomical positioning, embryological development, and potential diagnostic implications of the left azygos lobe and its associated vein, it is essential to first review the relevant venous anatomy of the thorax. In this context, the structures of the superior and inferior vena cava and their developmental variations provide a foundational basis. These venous components not only contribute to normal systemic circulation but also exhibit several rare variants that can mimic pathological findings on imaging. The following sections outline the anatomy, embryology, and clinical significance of these major thoracic venous pathways, offering a framework to contextualize the rare presentation of the left azygos lobe.

Superior Vena Cava

Anatomy

The right and left brachiocephalic veins, collectively referred to as the innominate veins, converge to form the superior vena cava (SVC), which courses vertically downward behind the sternum. The azygos vein drains into the SVC through the azygos arch (Fig. 1). The azygos arch curves over the right lung hilum, passing from posterior to anterior, before draining into the SVC (3).

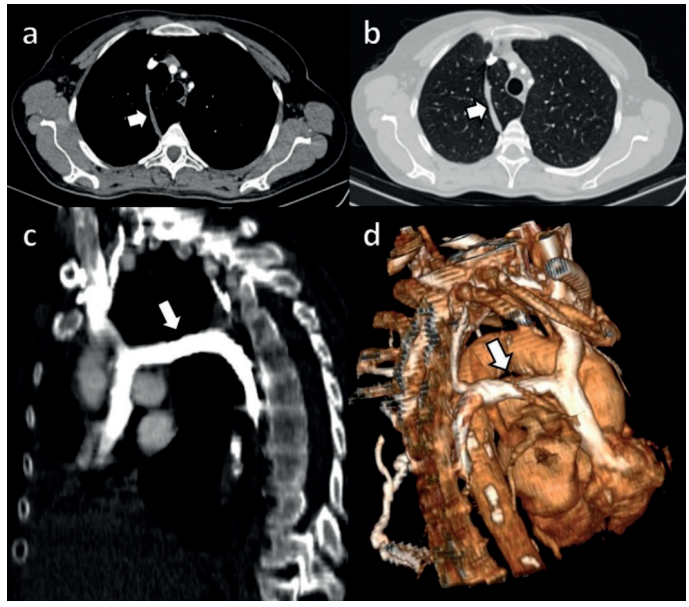

Figure 1. Axial contrast enhanced thorax CT mediastinal and parenchyma window images (a, b) of azygos vein (white arrows), azygos fissure and azygos lobe. MPR sagittal image (c) and 3D reformat image (d) show azygos arch (white arrow).

Table 1. Literature review of the left azygos lobe cases

Year	Author	Title
1954	Weston WJ	Left-sided Lobe of the Azygos Vein
1964	Lesser MB	Left Azygos Lobe. Report of A Case
1967	Hanke R	The Accessory Hemiazygos Vein in the x-ray Picture; Contribution to the Problem of the "Left Azygos Lobe"
1989	Takasugi JE, Godwin JD	Left Azygos Lobe
2003	Ishii A, Fuse S, Kubo N, Hatakeyama K, Takamuro M, Tomita H, Tsutsumi H	Improvement of Protein-losing Enteropathy by Coil Embolization of the Left Azygos Vein
2006	Hazirolan T, Ozkan E, Haliloglu M, Celiker A, Balkanci F	Complex Venous Anomalies: Magnetic Resonance Imaging Findings in a 5-year-old Boy
2009	Uemura M, Takemura A, Ehara D, Yasumitsu H, Ohnishi Y, Suwa F	Left Superior Vena Cava with Left Azygos Vein
2013	Keskin S, Keskin Z, Sekmenli N	The Independent Right and Left Azygos Veins with Hemiazygos Absence: A Rare Case Presentation
2020	Ayyildiz V, Aydin F, Ogul H	Unusual Coexistence In Situs Inversus Totalis; Right Arcus Aorta, Variant Left Azygos Lobe, and Aberrant Left Subclavian Artery
2020	Tang Z, Teng Y, Li J, Du X, Xiao J, Tang G	Left Upper Lung Cancer With Persistent Left Superior Vena Cava and Left Azygos Vein: A Case Report
2020	Notsu E, Ono K, Horie S, Morris JF, Toida K	Double Superior Venae Cavae with Absence of the Coronary Sinus and Anomalies of the Azygos Venous System
2020	Shiri E, Madadi S	An Abnormal Course of the Interazygos Vein: A Case Report

Embryology

Under normal development, the left anterior cardinal vein and the adjacent segment of the common cardinal vein regress. The SVC originates from the proximal portion of the right anterior cardinal vein and the right common cardinal vein. Failure of regression of the left anterior cardinal vein and the corresponding part of the common cardinal vein leads to the formation of a persistent left SVC (Fig. 2) (0.5–2% of population) (5).

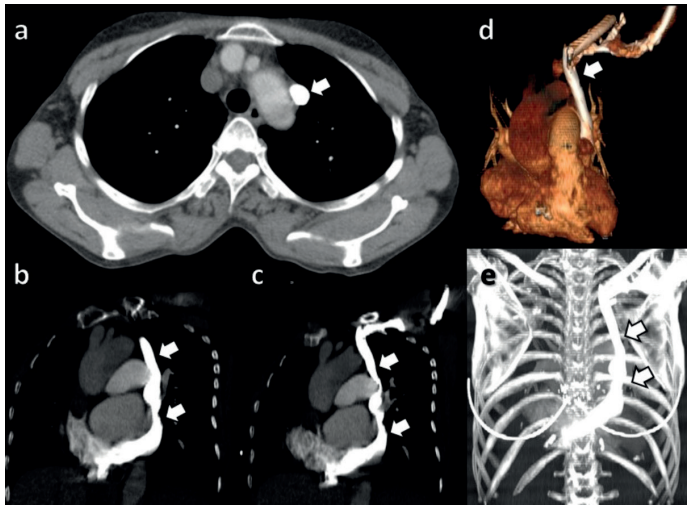

Figure 2. After left arm IV contrast administration, axial contrast enhanced thorax CT image (a), coronal MPR images (b, c), 3D reformat image (d) and MIP image (e) shows the persistent left vena cava superior vein (white arrows).

Clinical Significance

Superior vena cava syndrome may arise as a consequence of complete or partial obstruction of the SVC. This syndrome is most commonly seen secondary to malignancy (Fig. 3). The severity of symptoms depends on the development of rich collateral via azygos venous system network (6).

Many patients develop multiple collateral pathways. Most veins draining in SVC are connected to a rich network of venous plexus. These venous plexus networks are not normally used. If there is venous occlusion, they become visible and provide a clue for location of occlusion. The shunting by the help of the intercostal veins to azygos venous system and creating caval-caval anastomosis (Fig. 4) by the help of the superficial veins are the most important systems enabling anastomosis (7).

Inferior Vena Cava

Anatomy

The inferior vena cava (IVC) is formed by the union of the right and left common iliac veins, typically at the level of the L5 vertebra. The IVC is positioned along the right anterolateral side of the vertebral column. (8).

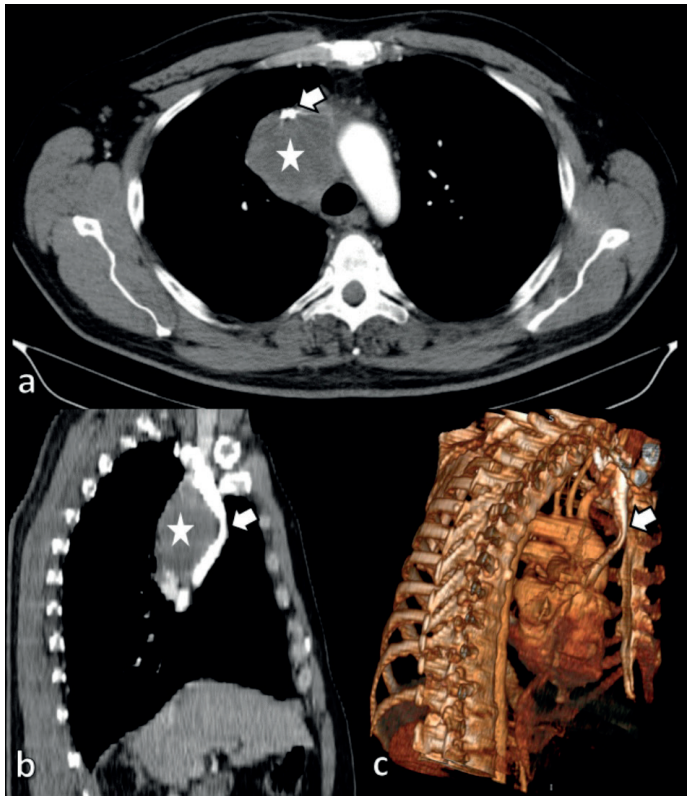

Figure 3. Axial and sagittal contrast enhanced thorax CT mediastinal window images (a, b) and 3D reformat image (c) shows mass lesion (white stars) and partial obstruction of superior vena cava (white arrows).

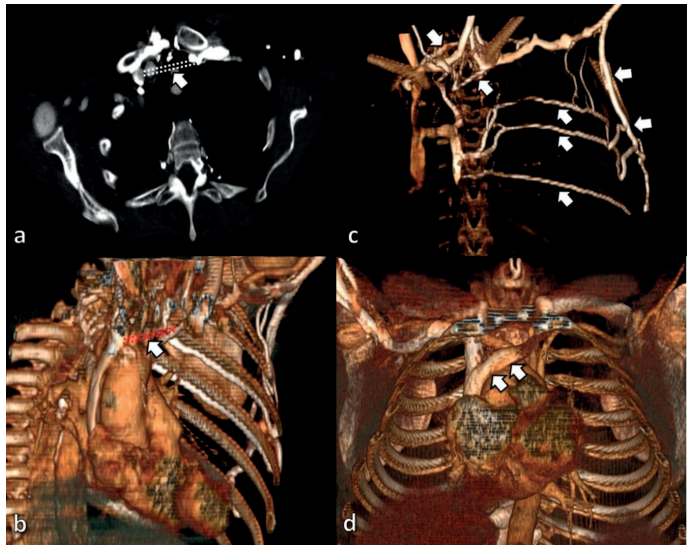

Figure 4. On axial contrast enhanced thorax CT and 3D reformat images (a, b) there is an interrupted course of left innominate vein (white and red dots). 3D reformat image (c) shows rich network of venous plexus (white arrows). The left subclavian vein continues as shunting by the help of the intercostal veins to azygos venous system and creating caval-caval anastomosis by the help of the superficial veins in same patient (c). 3D reformat image (d) shows normal left innominate vein (white arrows).

Embryology

The formation of the right-sided IVC involves the sequential development and remodeling of three paired embryonic venous systems: the posterior cardinal, subcardinal, and supracardinal veins. This formation occurs as certain segments of these venous

systems undergo anastomosis, while others regress. (9). Due to the complexity in its embryogenesis, there are numerous variations of IVC.

The most common anatomical variation of the IVC is a duplicated IVC (Fig. 5), occurring in 0.2–3% of cases. Duplication of the IVC occurs when both the right and left supracardinal veins persist. Anomalies involving the suprarenal segment of the IVC are comparatively less common (Fig. 6a), with an incidence of about 0.6%. A rare variant is an intrahepatic interruption of the IVC with azygos continuation (Fig. 6b), which occurs when the right subcardinal vein does not merge with the vitelline vein to form the intrahepatic segment of the IVC (10).

Another variation is circumaortic left renal vein (Fig. 7). The incidence of this anomaly is 1.5–16%. Anastomotic communications between subcardinal and supracardinal veins form a collar of veins encircling the aorta. A circumaortic vein forms when the dorsal venous collar fails to regress during embryonic development. If the dorsal collar persists and ventral collar regresses, it is called retroaortic left renal vein (Fig. 8). The incidence of this anomaly is 0.8–3.7% (9).

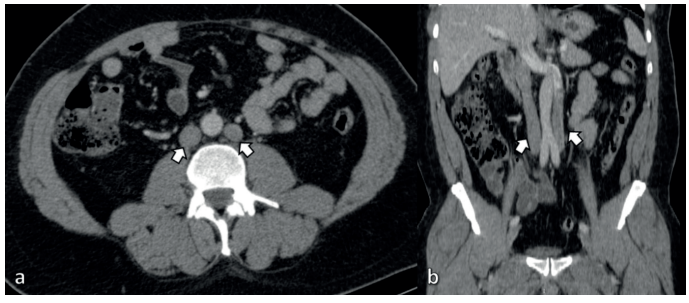

Figure 5. On axial and coronal contrast enhanced abdomen CT images (a, b) you can see duplicated inferior vena cava (white arrows).

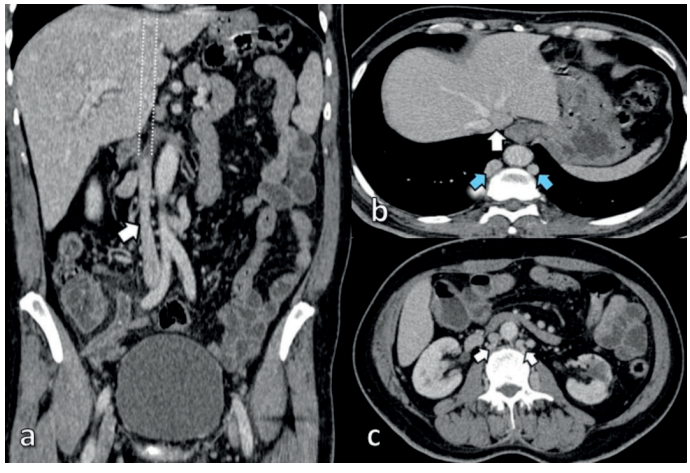

Figure 6a. On coronal CT image (a), infrarenal IVC is intact (white arrow), whereas the suprarenal portion of the IVC is absent (white dots). (b) The intrahepatic IVC is intact and the hepatic veins drain into the hepatic segment of the IVC (white arrow) on axial CT image. (c) The interrupted IVC continues by the help of lumber venous plexus (white arrows) on axial CT image and drains into the azygos and hemiazygos veinous system on axial CT image. You can see enlarged azygos and hemiazygos veins (blue arrows) on image b.

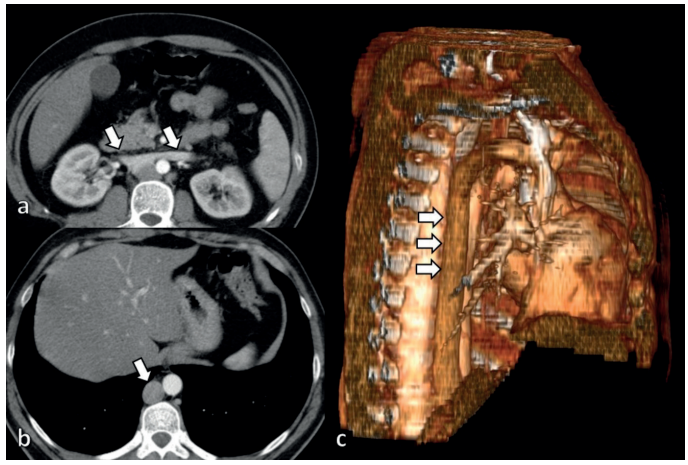

Figure 6b. In another case additionally absence of the intrahepatic IVC is present too. (a) On axial CT image, blood in renal veins return in the azygos system directly (white arrows). On axial CT image (b) and 3D reformat image (c) you can see enlarged azygos vein (white arrows).

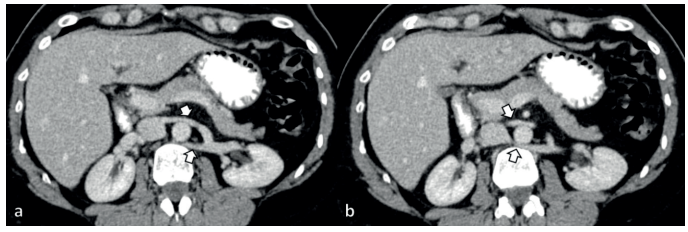

Figure 7. You can see circumaortic left renal vein (white arrows) of axial enhanced abdomen CT images (a, b).

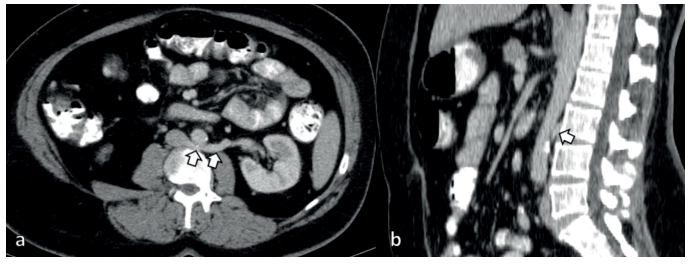

Figure 8. On axial MPR and sagittal contrast enhanced abdomen CT images (a, b) you can see retroaortic left renal vein (white arrows).

Clinical Significance

Retroaortic renal vein variation is usually asymptomatic, but may cause hematuria and abdominal/flank pain due to compression of left renal vein like nutcracker syndrome (11).

Complete or partial obstruction of the IVC can occur resulting in a condition like non-specific abdominal or back pain; may also include lower extremity cramping, swelling or pain. These occlusion conditions may be seen secondary to malignancies, which may alter staging and surgical management (Fig. 9) (12).

Recurrent deep venous thromboses and pulmonary emboli refractory to treatment with anticoagulation may require placement of an inferior vena cava filter. Congenital anomalies may cause difficulty in vascular access and IVC filter placement. Understanding variant IVC anatomy helps avoid problems in several situations during IVC filter placement (13).

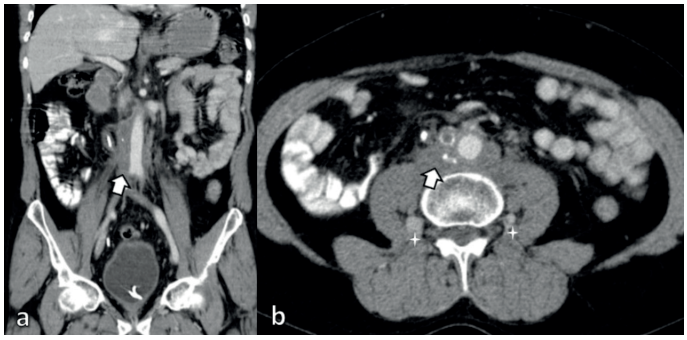

Figure 9. On coronal and axial contrast enhanced abdomen CT images (a, b) you can see complete obstruction of IVC because of malignancy (white arrows). (b) Be aware of enlarged lumber venous collateral pathways (white stars).

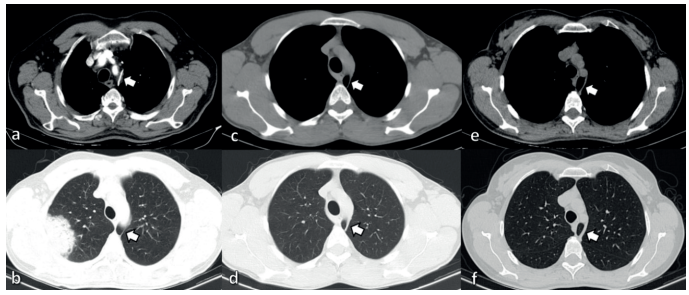

Figure 10. (a) You can see normal posterior superior intercostal vein course (white arrow) on axial enhanced thorax CT image. The other images (b-f) there are case examples of left upper lobe entrapped medially by an aberrant course of posterior superior intercostal vein, «left azygos lobe» can be seen (white arrows).

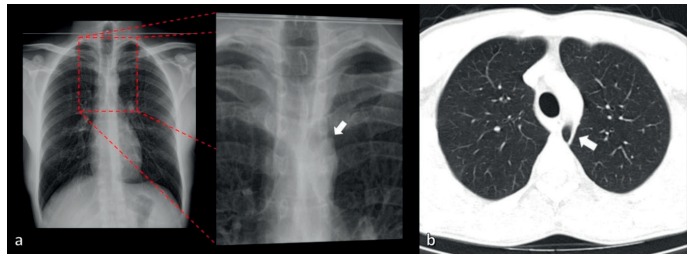

Figure 11. Posteroanterior (PA) chest radiograph (a) shows the "aortic nipple" sign due to a dilated left superior posterior intercostal vein (white arrow). Axial thoracic CT (b) demonstrates a left azygos lobe formed by medial entrapment of the left upper lobe.

Left Azygos Lobe and Its Vein

Anatomy

Although the azygos lobe and the left azygos lobe are termed accessory lobes, they do not represent true accessory lobes, as they lack a separate bronchus and arterial supply (14).

The azygos lob is a right lung variation that is seen 0.5–1.2% in population. The azygos lobe is located medially in upper lobe of right lung and usually diagnosed incidentally on imaging. It is separated from other segments of upper lobe by azygos fissure, which contains the azygos vein and four pleural layers (15). While the exact incidence is unknown, the left azygos lobe and its vein variation is located upper lobe in same way (4).

Embryology

Normally, the posterior cardinal vein passes through the apex of the right lung before settling into its typical anatomical location. An azygos lobe forms when, instead of following this usual migration path during embryonic development, the right posterior cardinal vein penetrates the lung apex. This lobe results from a failure of the azygos vein to shift medially toward the right tracheobronchial junction, staying above the lung apex instead (14).

Results

The aberrant vein described in this article corresponds to left superior posterior intercostal vein. The left superior posterior intercostal vein is an anatomical structure that we are familiar with in interventional radiology due to the frequently improper placing of central venous catheters when the SVC is obstructed (16). Under normal conditions, it courses adjacent to the aortic arch and drains into the left brachiocephalic vein.

The left azygos lobe may result from a medial movement-migration defect of the left superior posterior intercostal vein above the lung apex (Fig. 10) (4).

The clinical significance of the presence of the left superior posterior intercostal vein, which creates the appearance of "aortic nipple" on the chest X-ray, can be seen more clearly on the chest X-ray when it is dilated (Fig 11) (17). This dilatation is sometimes mistaken for a mediastinal tumor, lymphadenopathy, or aneurysm (18). Evaluation for inferior vena cava agenesis, Budd-Chiari Syndrome, superior or inferior vena cava obstruction is recommended in the presence of dilated left superior posterior intercostal vein in the cross-sectional examination (19).

Conclusion

In a 12-week-old fetus, the proximal portion of the left posterior cardinal vein persists, giving rise to the root of the left azygos vein. The right supracardinal vein differentiates into the right hemiazygos and accessory hemiazygos veins. Through an anastomotic connection, the right hemiazygos vein extends into the left azygos vein, which further continues into the left SVC. The left SVC drains into the right atrium via the coronary sinus (Fig. 12 and 13) (20).

Venous variations are often linked with various cardiovascular anomalies, including endocardial cushion defects, tetralogy of Fallot, and aortic coarctation. In patients with a left SVC, catheterization can lead to severe complications such as shock, cardiac arrest, or angina, likely due to catheter manipulation within the coronary sinus. Recognizing these venous variations is crucial in interventional radiology and cardiothoracic surgery to ensure that appropriate cannulation techniques are used, effectively diverting the substantial volume of systemic venous blood entering the heart through the coronary sinus (Fig. 14)

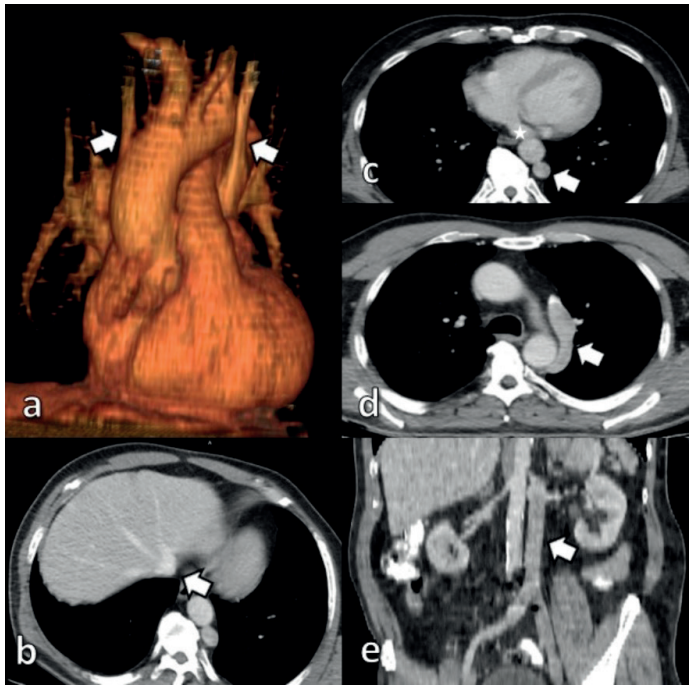

Figure 12. (a) 3D reformat image reveals double superior vena cava (white arrows). (b) The intrahepatic IVC is intact and the hepatic veins drain into the hepatic segment of the IVC (white arrow) on axial CT image. On coronal reformat CT image (e), infrarenal left IVC is intact (white arrow), whereas the suprarenal portion of the IVC is absent. (c, d) Left IVC continues by the help of left azygos vein (white arrows). There is anastomotic vein (white star) between the left superior vena cava and the right atrium through the coronary sinus.

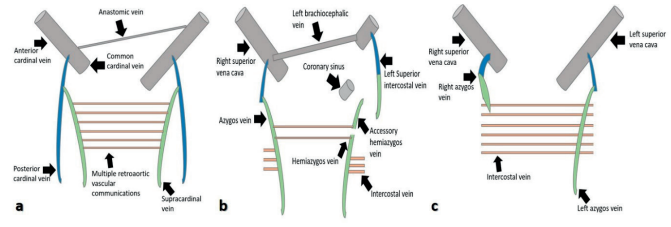

Figure 13. Schematic diagrams of SVC and the azygos venous system. (a) A schematic diagram of veins related to the SVC and azygos veins in the fetal period. (b) Usual morphology of the superior vena cava and the azygos system of veins. (c) The left azygos vein morphology.

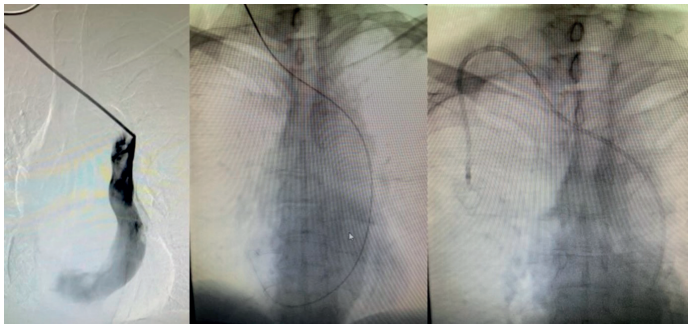

Figure 14. Digital subtraction angiography (DSA) image in a patient demonstrates careful placement of a central venous port catheter. Recognition of thoracic venous variations –particularly the presence of a persistent left superior vena cava and prominent coronary sinus– enabled successful and complication-free catheterization (Courtesy of Assoc. Prof. Dr. Mehmet Fatih İnecikli, used with permission).

(21). It is also known that being informed of the patient's variations and existing anatomy prior to any surgical operation boosts the likelihood of success. Radiologist should be aware of *left azygos lobe and its vein* to identify variations correctly.

In conclusion, CT plays a key role in diagnosing vascular anomalies, offering high spatial resolution with multiplanar reconstructions and volume-rendered imaging. Recent advances in CT technology, coupled with dose-reduction techniques, enable the acquisition of essential diagnostic information at lower radiation levels. Recognizing rare anatomical variants such as the left azygos lobe and its associated vein not only prevents potential diagnostic pitfalls but also deepens our understanding of thoracic vascular anatomy. By presenting and characterizing this unusual variation, this manuscript aims to raise awareness among radiologists and to encourage further research into its incidence and clinical implications.

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Consent of Patients: The participants were informed in detail, and informed consent was obtained.

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Data Availability Statement: All relevant data are within the paper and they are available from the corresponding author on reasonable request.

Author Contributions: Concept - Ş.B.A.; Design - Ş.B.A.; Supervision - Ş.B.A.; Data Collection and/ or Processing - Ş.B.A.; Analysis and/or Interpretation - Ş.B.A.; Literature Search - Ş.B.A.; Writing - Ş.B.A.; Critical Reviews - Ş.B.A.

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DERLEME / REVIEW

Mad Honey and Its Possible Biological Mechanisms in Alleviating Chronic Obstructive Pulmonary Disease

Deli Bal ve Kronik Obstrüktif Akciğer Hastalığını Yatıştırmada Yardımcı Olabilecek Potansiyel Mekanizmaları

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ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease is a progressive respiratory condition characterized by airflow limitation, chronic inflammation, and structural damage in the lungs The disease is primarily caused by long-term exposure to irritants, particularly cigarette smoke and, leading to airway remodeling, fibrosis, and oxidative stress. Although, current treatments help manage symptoms, they do not offer a definitive cure, and the morbidity and mortality rates are still high with very significant healthcare costs. Therefore, there is growing interest in alternative and natural remedies that may complement conventional therapies. One such substance is mad honey a rare and potent type of honey derived from the nectar of Rhododendron species, particularly Rhododendron ponticum and Rhododendron luteum.

Conclusion: In this commentary, we explore the possible mechanisms, by which mad honey could alleviate Chronic Obstructive Pulmonary Disease symptoms and improve lung function,considering different molecular and biological aspects.

Keywords: Chronic obstructive pulmonary disease, mad honey, rhododendron, inflammation

ÖZ

Giriş: Kronik Obstrüktif Akciğer Hastalığı nefes darlığı, kronik enflamasyon ve akciğerlerde yapısal hasar ile kendini gösteren ilerleyici bir hastalıktır. Hastalığa, hava yolu yeniden şekillenmesi, fibröz ve oksidatif strese yol açan, özellikle sigara dumanı ve çevresel kirleticiler gibi irritan maddelere uzun-süreli maruziyet sebep olmaktadır. Güncel tedaviler semptomları yönetmeye yardımcı olsa da kesin bir tedavi sağlamamakta ve çok ciddi sağlık masraflarıyla birlikte, morbidite ve mortalite oranları hâlâ oldukça yüksek seyretmektedir. Bu sebepten, güncel tedavilere eşlik eden alternatif ve doğal tedavilere olan ilgi her geçen gün artmaktadır. Bunlara örnek olarak ender bulunan ve Rhododendron türlerinden, özellikle Rhododendron ponticum ve Rhododendron luteum, elde edilen 'Deli Bal' verilebilir.

Sonuç: Bu tartışmada, Deli Bal'ın Kronik Obstrüktif Akciğer Hastalığı semptomlarını yatıştırma ve akciğer fonksiyonlarını geliştirmede yardımcı olma potansiyeli taşıyan mekanizmalar, farklı moleküler ve biyolojik mekanizmalar göz önünde bulundurularak incelenmiştir.

Anahtar Sözcükler: Kronik obstrüktif akciğer hastalığı, deli bal, rhododendron, inflamasyon

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory condition characterized by airflow limitation, chronic inflammation, and structural damage in the lungs (1–5). It includes chronic bronchitis and emphysema, with symptoms such as persistent cough, excessive mucus production, wheezing, and shortness of breath. The disease is primarily caused by long-term exposure to irritants, particularly cigarette smoke and environmental pollutants, leading to airway remodeling, fibrosis, and oxidative stress (2–4).

While current treatments, including bronchodilators, corticosteroids, and mucolytic agents, help manage symptoms, they do not offer a definitive cure. As a result, there is growing interest in alternative and natural remedies that may complement conventional therapies. One such substance is mad honey, a rare and potent type of honey derived from the nectar of

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Rhododendron species, particularly Rhododendron ponticum and Rhododendron luteum (6–8). This unique honey contains grayanotoxins, which interact with ion channels in the body, producing physiological effects that range from mild euphoria to serious neurotoxicity (6–9).

Despite its toxicity at high doses, mad honey has been traditionally used for its medicinal properties, including its anti-inflammatory, bronchodilatory, and analgesic effects. Recent studies suggest that mad honey's bioactive compounds might offer potential benefits for COPD patients by reducing inflammation, relaxing airway muscles, and modulating immune responses. This commentary explores the possible biological mechanisms by which mad honey could alleviate COPD symptoms and improve lung function.

Anti-Inflammatory Effects in Copd Management

Chronic Obstructive Pulmonary Disease and Chronic Inflammation

Chronic obstructive pulmonary disease is characterized by chronic airway inflammation, primarily driven by the overactivation of immune cells such as neutrophils, macrophages, and T-lymphocytes (2–4). This results in excessive production of inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8), which perpetuate tissue damage and airway remodeling (2–5).

Mad Honey's Anti-Inflammatory Properties

Mad honey contains polyphenols, flavonoids (e.g., quercetin, kaempferol), and diterpenes, which have been shown to exhibit potent anti-inflammatory effects (9,10).

Inhibit Pro-Inflammatory Cytokines: Studies suggest that flavonoids can suppress the activation of NF-κB, a transcription factor that regulates inflammatory cytokine production in COPD (10,11). By inhibiting NF-κB, mad honey may help reduce airway inflammation and tissue damage (9–11).

Modulate Oxidative Stress: COPD is associated with increased oxidative stress (2), which exacerbates lung injury. Polyphenols in mad honey act as antioxidants, scavenging reactive oxygen species (ROS) and protecting lung cells from oxidative damage (9,10).

Reduce Airway Hyperresponsiveness: Chronic inflammation in COPD leads to excessive airway narrowing and bronchial hyperreactivity (2–4). The anti-inflammatory properties of mad honey may help reduce airway sensitivity, leading to improved breathing (10,11).

Bronchodilatory and Smooth Muscle Relaxation Effects

Chronic Obstructive Pulmonary Disease and Airway Constriction

Airway narrowing due to bronchoconstriction, mucus hypersecretion, and structural remodeling is a major problem in COPD, leading to persistent breathing difficulties (1–5). Conventional bronchodilators, such as β2-agonists and anticholinergics, help relax airway smooth muscles, but they often have side effects, including increased heart rate and tremors (12).

Mad Honey's Effects on Smooth Muscle Relaxation

One of the most intriguing aspects of mad honey is its neuromodulatory effects via grayanotoxins. These toxins interact with voltage-gated sodium channels (VGSCs) in excitable tissues, leading to altered neuronal signaling and muscle relaxation (9,13).

Bronchodilation mechanism

Grayanotoxins cause sustained depolarization of airway smooth muscle cells (9,13), which may lead to calcium channel modulation and relaxation of bronchial muscles.

This mechanism is similar to how some bronchodilators work by reducing muscle contractility and improving airflow (14).

As a result, mad honey could act as a natural bronchodilator, helping COPD patients breathe more easily.

Reduced cough sensitivity

Persistent coughing in COPD results from airway irritation and hyperresponsiveness (1,2).

The neural desensitization effects of grayanotoxins might modulate vagal nerve activity, reducing cough frequency and severity.

These effects suggest that mad honey could be useful as a natural adjunct therapy for COPD patients struggling with airway constriction and persistent coughing.

Mucolytic And Expectorant Properties

Excess Mucus Production in COPD

One of the defining characteristics of chronic bronchitis, a major subtype of COPD, is excessive mucus secretion due to goblet cell hyperplasia. This leads to airway obstruction, bacterial infections, and increased disease exacerbations (5,15).

Mad Honey's Potential Role in Mucus Clearance

Hydration and enzymatic activity

Like regular honey, mad honey has hygroscopic properties (attracting water), which may help loosen thick mucus.

Honey contains enzymes such as glucose oxidase, which generate small amounts of hydrogen peroxide (11), exhibiting mild mucolytic effects.

Ciliary function enhancement

Proper ciliary movement is essential for clearing mucus from the airways (5).

Polyphenols in mad honey may stimulate ciliary motility, aiding in mucus clearance and preventing bacterial accumulation.

These mucolytic and expectorant properties suggest that mad honey could help COPD patients manage excessive mucus production, reducing airway obstruction and infection risk.

Immunomodulatory Effects: Balancing the Immune Response

Immune Dysregulation in COPD

Chronic obstructive pulmonary disease patients experience chronic immune activation, often leading to excessive neutrophilic inflammation and a weakened antiviral response. This imbalance increases susceptibility to respiratory infections, which worsen COPD symptoms (1,3).

Immunomodulatory Mechanisms of Mad Honey

Neutrophil regulation

Flavonoids in mad honey have been shown to reduce neutrophil infiltration into the airways, decreasing excessive inflammation (16).

This could help prevent further lung tissue damage.

Antimicrobial properties

Mad honey exhibits broad-spectrum antimicrobial effects, potentially reducing secondary bacterial infections in COPD patients.

The presence of hydrogen peroxide and other bioactive compounds may inhibit bacterial growth, particularly pathogens like Haemophilus influenzae and Pseudomonas aeruginosa, which commonly infect COPD patients.

Modulation of adaptive immunity

By influencing the balance of Th1 and Th2 responses, mad honey may help control excessive immune reactions while preserving the body's ability to fight infections (17).

These findings suggest that mad honey could support COPD patients by reducing excessive inflammation while enhancing antimicrobial defenses.

Neurophysiological and Analgesic Effects

COPD-Associated Pain and Discomfort

Many COPD patients suffer from chronic chest discomfort, muscle fatigue, and anxiety due to breathing difficulties (18,19). Traditional painkillers may not always be suitable due to their side effects.

Mad Honey's Role in Pain Relief

Neural modulation

Grayanotoxins interact with the nervous system, leading to temporary neural desensitization (9,13).

This could help alleviate chest tightness and respiratory discomfort associated with COPD.

Mild sedation and anxiety reduction

Many COPD patients experience anxiety and breathlessness-related panic episodes (19).

The psychoactive properties of mad honey may promote mild euphoria and relaxation, reducing anxiety and improving sleep quality.

Safety Considerations and Risks

Despite its potential benefits, mad honey comes with toxicity risks. Excessive consumption can cause nausea, vomiting, dizziness, hypotension, and even cardiac arrhythmias (6–8).

Safe dosage: Low and controlled doses are essential.

Contraindications: Individuals with heart disease, hypotension, or neurological disorders should avoid mad honey.

Medical supervision: COPD patients should consult healthcare professionals before using mad honey as a complementary therapy.

Conclusion

Mad honey holds promise as a natural adjunct therapy for COPD, thanks to its anti-inflammatory, bronchodilatory, mucolytic, immune-modulating, and analgesic properties. While preliminary evidence suggests potential benefits, clinical studies are needed to determine safe dosages and efficacy. If used correctly, mad honey could provide symptomatic relief and improved lung function, offering a complementary approach to COPD management.

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