International Archives of Medical Research

Cilt/Volume: 17, Sayı/Issue: 1 – 2025
ISSN : 2146-6033

İçindekiler / Table of Contents

Adress : Dicle Universty,Faculty of Medicine.Department of Microbiology / Diyarbakır
Post Code : 21280
Mail : nakpolat21@gmail.com
web : https://dergipark.org.tr/tr/pub/iamr
Online ISSN : 2146-6033

International Archives of Medical Research 17:1 (2025) 1-12

ORIGINAL RESEARCH

Effect of Coumarin and Its Derivatives on the Protein Profiles in CCl_4-Treated Rats

Received Date: 13.03.2025, Accepted Date: 15.04.2025 **DOI: 10.56484/iamr.1656926**

Cemre UÇAR EKİN[1a*], Mukadder BAYLAN[1b]

[1] Dicle University, Medicine Faculty, Department of Physiology, Diyarbakır, Turkiye

[a]*ORCID: 0000-0002-3085-589X*, [b]*ORCID: 0000-0002-4461-6822*

Abstract

Objective:

This study aimed to evaluate the effects of coumarin and its derivatives esculetin, scoparone, and 4-methylumbelliferone on serum protein profiles in male Sprague-Dawley rats with carbon tetrachloride (CCl_4)-induced hepatic injury. As the liver is essential for the synthesis of major plasma proteins such as albumin and globulin, disruptions in liver function can significantly alter these parameters. CCl_4, a commonly used industrial chemical, is known for its pronounced hepatotoxic and nephrotoxic effects.

Method:

Male Sprague-Dawley rats weighing between 150–200 grams were randomly assigned to six groups: a control group, a group receiving CCl_4 to induce hepatotoxicity, and four treatment groups that received oral doses of coumarin (30 mg/kg), esculetin (31.15 mg/kg), scoparone (35 mg/kg), or 4-methylumbelliferone (35 mg/kg). Hepatic injury was induced by administering CCl_4 (1.25 mL/kg) diluted in corn oil. Serum levels of total protein, albumin, and globulin were measured using standard biochemical techniques. Statistical analyses were performed using SPSS software, with p-values less than 0.05 considered statistically significant.

Results:

Oral administration of CCl_4 (1.25 mL/kg) resulted in a marked decrease in serum total protein and albumin concentrations, accompanied by a lowered albumin/globulin (A/G) ratio and elevated globulin levels. Conversely, treatment with coumarin and its derivatives significantly reversed the CCl_4-induced reductions in albumin and the A/G ratio. These compounds also effectively reduced the elevated globulin levels observed following CCl_4 exposure.

Conclusion:

The results suggest that the hepatoprotective effects of coumarin derivatives are closely related to their molecular structures, which appear to influence the regulation of hepatic protein synthesis. By modulating key enzymes involved in protein metabolism, these compounds may help preserve liver function and support the synthesis of essential proteins required for cellular regeneration and physiological balance. Coumarin based compounds hold potential as therapeutic agents for the prevention or mitigation of liver damage.

Keywords: *Hepatotoxicity, protein levels, carbon tetrachloride (**CCl_4**), coumarin, antioxidant*

Corresponding author: E-mail: cemre.ucar.ekin@gmail.com

Introduction

The liver is the primary target for the harmful effects of toxic agents due to its central role in metabolizing and detoxifying xenobiotics. It is also a key organ in protein metabolism, being responsible for the synthesis, modification, and breakdown of various plasma proteins[1]. In recent years, interest has increasingly shifted toward complementary and alternative therapeutic approaches for managing liver related disorders.

Coumarins represent a large class of naturally occurring compounds, with approximately 1,300 known derivatives identified in dietary sources such as citrus fruits and green tea. In addition to their natural occurrence, several coumarins can also be chemically synthesized. Their rising popularity is largely attributed to a broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, hepatoprotective, and antifibrotic effects[2-4].

Carbon tetrachloride (CCl_4) is a commonly utilized industrial solvent and a recognized hepatotoxin. It is frequently employed in experimental models to induce oxidative stress, lipid peroxidation, and liver damage, mimicking human liver diseases. Hepatotoxicity caused by CCl_4 results in changes to the hepatic protein profile[5,6], triggers inflammatory responses, and promotes fibrosis, making it a valuable model for investigating liver injury and potential therapeutic approaches.

In addition to CCl_4, several other agents are commonly used to induce experimental hepatotoxicity, such as thioacetamide (TAA), acetaminophen, and aflatoxins. These agents cause liver damage in a way similar to CCl_4[7-9].

Albumin, a key protein produced by the liver, is essential for regulating the osmotic pressure of blood[10]. Hepatocyte damage caused by CCl_4 reduces albumin synthesis, leading to hypoalbuminemia. Coumarins may help restore albumin levels by reducing oxidative stress and promoting liver cell regeneration[11]. Similarly, globulins play a key role in immune response and may fluctuate due to inflammatory processes triggered by CCl_4 exposure. As liver damage progresses, globulin levels increase[12]. The anti-inflammatory properties of coumarins may help regulate globulin synthesis and immune balance.

Changes in albumin and globulin levels directly affect total protein levels. CCl_4 toxicity impairs hepatic protein synthesis, leading to a decline in total protein levels. Coumarins may help preserve total protein levels by supporting liver function and reducing oxidative damage[13].

Enzymes responsible for drug metabolism play a crucial role in detoxifying various xenobiotic compounds; however, they can also activate certain substances, increasing their toxicity[14]. In such instances, the liver is the primary organ affected by these newly generated toxic metabolites. Hence, understanding the protective mechanisms of the liver is essential.

Although coumarin has been reported to exhibit hepatotoxic effects in rodents, primarily due to the production of coumarin 3,4-epoxide, which leads to elevated plasma alanine transaminase (ALT) and aspartate transaminase (AST) levels, other studies have highlighted its potential protective properties against toxicity[15-18].

Considering the conflicting findings in the literature, this study seeks to determine whether coumarin derivatives exert a protective influence against CCl_4-induced liver damage. Furthermore, we aim to explore how structural variations among different coumarin derivatives impact the protein profile in rats with experimentally induced hepatotoxicity.

Materials and Methods

In this study, male Sprague–Dawley rats weighing between 150 and 200 grams were utilized. Throughout the experimental period, the animals were housed in a controlled environment maintained at 21 ± 2°C with a 12-hour light/dark cycle. They were provided with unrestricted access to standard pellet feed and drinking water. The study protocol was reviewed and approved by the Animal Ethics Committee of Dicle University.

Chemicals: CCl_4, coumarin, and 4-methylumbelliferone were supplied by Sigma Chemicals Company. Scoparone and esculetin were purchased from Aldrich Chemicals Company (Figure 1). Corn oil was acquired from a local supplier.

Experimental Design and Treatment Protocol: The rats were randomly divided into six groups, each comprising six weight matched animals (150–200 g). Hepatic injury related hyperlipidemia was induced by administering carbon tetrachloride (CCl_4) at a dose of 1.25 ml/kg, dissolved in corn oil (20% v/v), through oral gavage.

The control group received four oral doses of saline (3 ml/kg) at 12-hour intervals over a period of 48 hours, followed by a single oral dose of corn oil one hour after the final saline administration. The CCl_4 group followed the same saline dosing schedule, but instead of corn oil, received CCl_4 one hour after the last saline dose. Treatment groups receiving coumarin or its derivatives were handled similarly to the CCl_4 group; however, esculetin (30 mg/kg), scoparone (35 mg/kg), 4-methylumbelliferone (35 mg/kg), or coumarin (35 mg/kg) were administered in place of the final saline dose.

Twenty-four hours following the final administration, the rats were anesthetized with ketamine, and blood samples were obtained through cardiac puncture. Serum levels of total protein, albumin, and

globulin were measured using standard automated techniques at the Biochemistry Laboratory of Dicle University Faculty of Medicine.

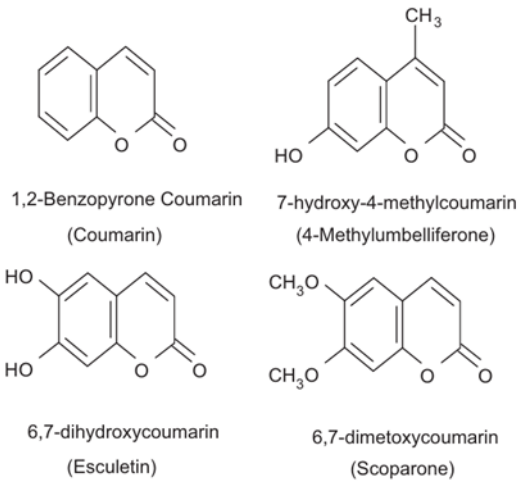

Figure 1. *Structural representations of coumarin and its derivatives.*

Statistics: All statistical evaluations were carried out using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk tests. For variables that did not exhibit normal distribution, the Kruskal-Wallis test was used to compare three or more groups. In cases where statistically significant differences were found, pairwise comparisons were conducted using the Dunn test with Bonferroni correction. Continuous data are presented as median values along with their minimum and maximum ranges. A p-value below 0.05 was considered indicative of statistical significance.

Results

Albumin Levels:

Compared to the control group, the CCl_4-treated group showed a marked reduction in serum albumin levels ($p < 0.001$). Treatment with each of the coumarin derivatives led to a significant elevation in albumin concentrations, indicating a potential restorative effect. However, coumarin and 4-metyl umbelliferone exhibited a weaker effect compared to esculetin and scoparone, as their levels

did not completely return to control values (Figure 2).

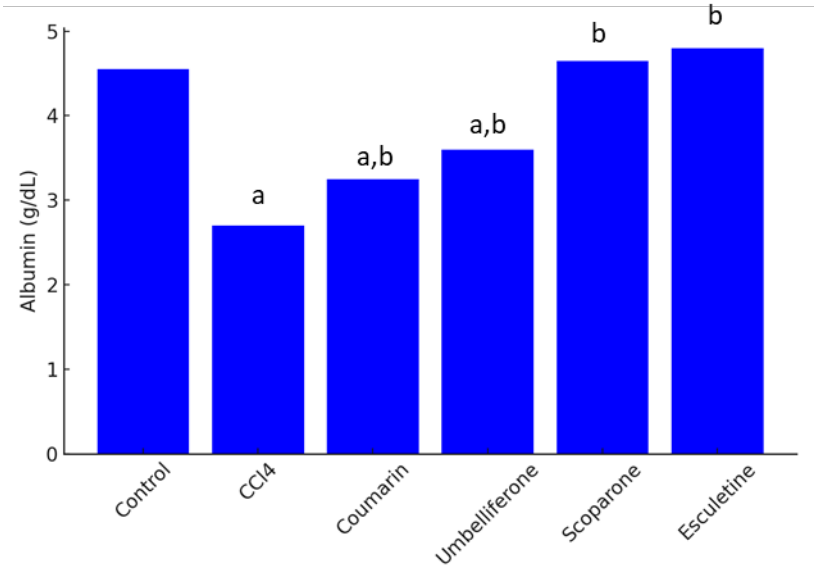

Figure 2. *Serum albumin levels. a: Significantly different from the control group (p < 0.001). b: Significantly different from the CCl_4-treated group (p < 0.001).*

Globulin Levels

CCl_4 exposure led to a significant increase in globulin levels ($p < 0.001$). The administration of all coumarin derivatives resulted in a statistically significant reduction in globulin levels, among the applied coumarins, esculetin administration exhibited the strongest effect, indicating a potential hepatoprotective effect ($p < 0.001$) (Figure 3).

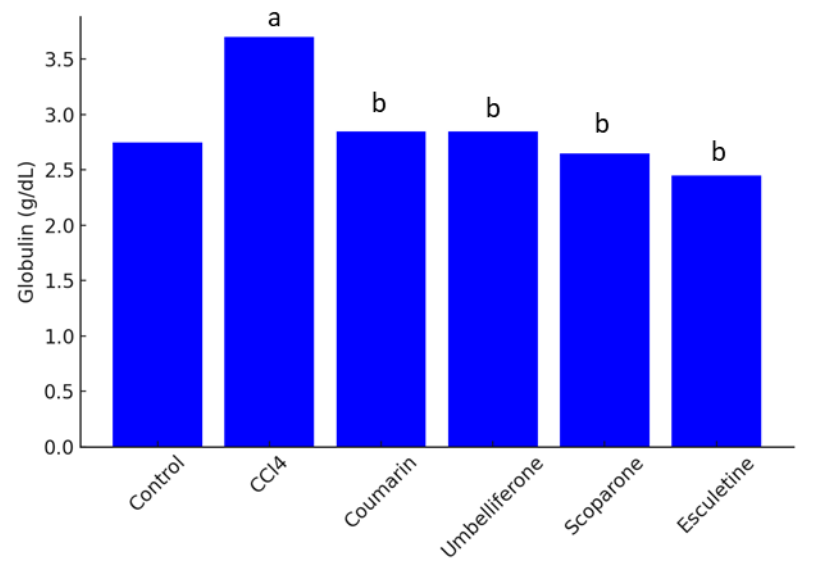

Figure 3. *Serum globulin levels a: Statistically significant difference compared to the control group (p<0.001. b: Statistically significant difference compared to the CCl_4 group (p<0.001).*

Albumin/Globulin Ratio (A/G)

The albumin/globulin (A/G) ratio was significantly lower in the CCl_4 treated group compared to the control group ($p < 0.001$). The administration of all coumarin derivatives led to a significant increase in the A/G ratio relative to the CCl_4 group, Even though all coumarins have significant effect on A/G ratio. It has been observed that esculetin and scopoletin preserve protein balance more effectively and show a greater hepatoprotective effect compared to coumarin and 4-metylumbelliferone ($p < 0.001$) (Figure 4).

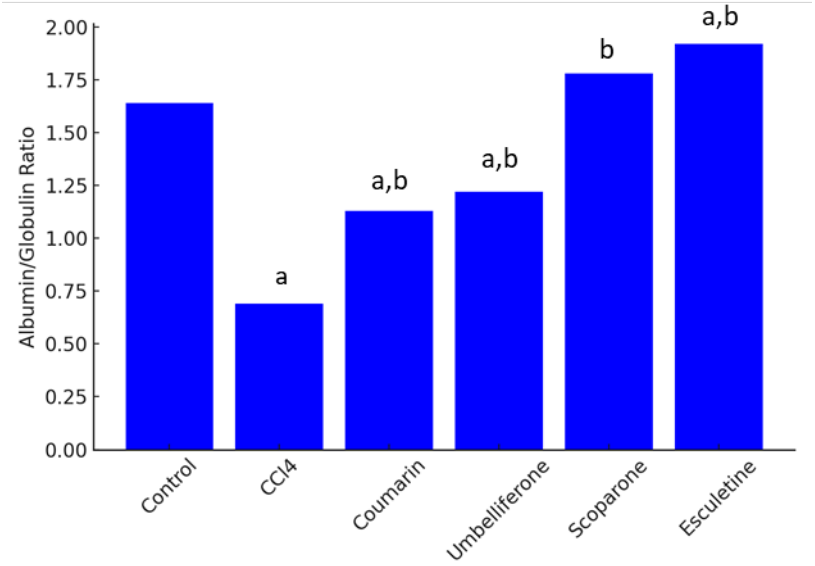

Figure 4. *Albumin/Globulin ratio. a: Statistically significant difference compared to the control group ($p<0.001$). b: Statistically significant difference compared to the CCl_4 group ($p<0.001$).*

Total Protein Levels

In the CCl_4 induced hepatotoxicity group, a significant reduction in total protein levels was observed compared to the control group ($p < 0.001$). The administration of coumarin and umbelliferone did not lead to a significant change in total protein levels, indicating a lack of protective effect in this parameter. However, both esculetin and scoparone significantly increased total protein levels, restoring them to control levels ($p < 0.001$), suggesting a potential hepatoprotective effect (Figure 5.).

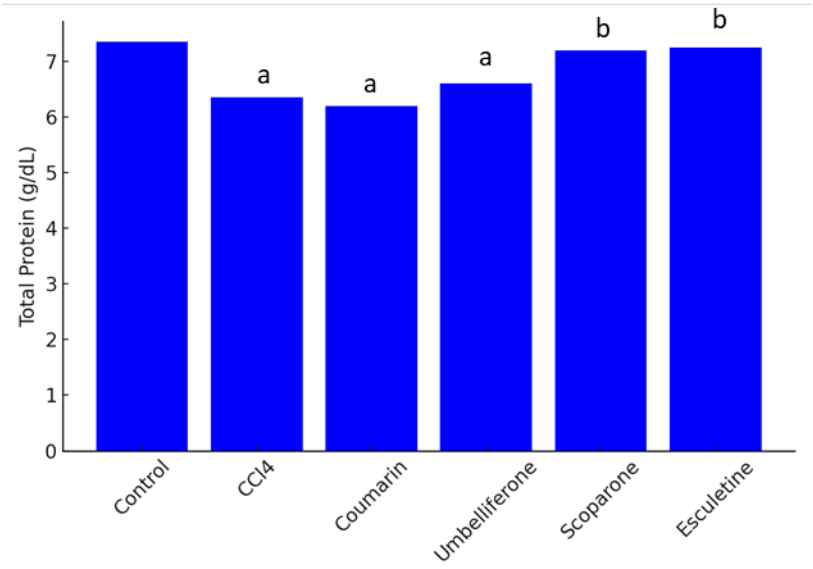

Figure 5. *Serum total protein levels. a: Statistically significant difference compared to the control group (p<0.001). b: Statistically significant difference compared to the CCl_4 group (p<0.001).*

Discussion:

The liver is the largest internal organ and a vital metabolic hub in the human body. It plays a crucial role in detoxification, metabolism, protein synthesis, and immune system regulation. Assessing liver function in experimental hepatotoxicity models involves measuring biochemical parameters such as albumin, globulin, total protein and A/G ratio[10]. Albumin is a major plasma protein synthesized by the liver, reflecting its synthetic capacity. A decline in albumin levels suggests hepatic dysfunction. Globulin is a group of proteins involved in immune responses. Elevated globulin levels may indicate chronic inflammation or liver disease. Total Protein is the sum of albumin and globulin, serving as an indicator of nutritional status and liver function. Albumin/Globulin (A/G) ratio is a sensitive marker of liver health. A decreased A/G ratio is associated with hepatic impairment and systemic inflammation.

Given the central role of oxidative stress in liver injury, antioxidants are widely studied for their hepatoprotective effects. Many natural compounds, including coumarins, exhibit antioxidant, anti-inflammatory, and free radical scavenging properties, potentially mitigating liver damage by reducing lipid peroxidation and enhancing endogenous antioxidant defenses (e.g., glutathione and superoxide dismutase).

Coumarins have distinctive chemical structure serves as a foundation for numerous synthetic derivatives with enhanced pharmacological properties[19]. Coumarins act as potent free radical scavengers, reducing oxidative stress and preventing lipid peroxidation, which is implicated in various chronic diseases[20].

Carbon tetrachloride (CCl_4)-induced liver injury is one of the most extensively utilized experimental models for investigating hepatotoxicity and assessing the protective or therapeutic potential of various agents[21,22]. CCl_4 causes hepatic damage primarily through the induction of oxidative stress, which disrupts cellular integrity. In the current study, CCl_4 administration resulted in significant hepatic injury in rats, as evidenced by reduced serum levels of total protein, albumin, and the albumin/globulin (A/G) ratio, alongside elevated globulin levels. Consistent with these findings, Ali *et al*. also reported that CCl_4 exposure led to decreased serum concentrations of total protein and albumin, while globulin, ALT, ALP and AST levels were markedly increased[23].

Coumarin and some coumarin analogs such as esculetin and scoparone have been shown to protect hepatocytes against CCl_4 induced toxicity, primarily through antioxidant and anti-inflammatory mechanisms[24].

Our previous studies indicate that chemical structure of coumarins plays an important role in the prevention of oxidative stress, regulation of serum lipid profiles and prevention of liver toxicity against CCl_4 induced acute hepatotoxicity in rats[25,26].

This research investigated the effects of coumarin and its derivatives—esculetin, scoparone, and 4-methylumbelliferone—on CCl_4-induced alterations in protein profiles in male Sprague-Dawley rats. The dosages of coumarins were determined based on previous research findings[27,28].

The hepatotoxicity of CCl_4 primarily occurs through reductive dehalogenation catalyzed by cytochrome P4502E1 (CYP2E1), leading to the formation of the highly reactive trichloromethyl free radical. These radical initiates biochemical reactions that result in liver cell damage[29,30]. It can covalently bind to proteins and lipids, interact with oxygen to generate trichloromethyl peroxy radicals, or undergo hydrogen abstraction, leading to the formation of chloroform[31].

Inhibiting CYP2E1 can reduce the levels of reactive metabolites and, consequently, minimize tissue injury. Therefore, considering the central role of reactive oxygen species and free radicals, dietary antioxidants such as coumarins have been explored as potential therapeutic agents to mitigate liver damage[32-34].

The current investigation revealed that animals treated with esculetin and scoparone exhibited a notable decline in the CCl_4-induced increase in serum globulin levels, the decreased albumin levels and A/G ratio were restored. The effects of scoparone and esculetin were comparable, showing similar protective properties in the study. Compared to esculetin and scoparon, coumarin and another coumarin derivative, 4-methylumbelliferone, have been observed to exhibit weaker hepatoprotective effects against CCl_4-induced liver damage. The present study demonstrated that another coumarin

derivative, scoparone, appeared to effectively preserve liver architecture and counteract the CCl_4-induced reduction in serum albumin, total protein levels, and the A/G ratio.

According to Lin et al. and Okamoto et al., esculetin (6,7-dihydroxycoumarin), which contains two hydroxyl groups, exhibits potent antioxidant properties and effectively neutralizes free radicals[28,35]. This effect is attributed to the molecular structure of coumarins. Studies have demonstrated that an increased number of hydroxyl groups improves free radical neutralization. In contrast, coumarin, which lacks hydroxyl or methoxy groups, was ineffective in preventing hepatic damage induced by CCl_4 [16].

Conversely, pretreatment with 4-methylumbelliferone (7-hydroxy-4-methyl) and coumarin (1,2-benzopyrone) exhibited a weaker protective effect against CCl_4-induced liver toxicity. This result aligns with previous studies suggesting that the hydroxylation pattern is a key determinant of coumarins' antioxidant and hepatoprotective properties[27,28].

In our study, esculetin (6,7-dihydroxycoumarin) provided the most effective protection against CCl_4 induced hepatotoxicity, while its 6,7-methoxy derivative, scoparone, showed a weaker compared to esculetin, but still protective effect. These findings are consistent with previous studies indicating that hydroxyl groups enhance the protective effects of coumarins[24,26].

In our earlier research, the suppression of CCl_4-induced increases in AST, ALT, and ALP levels was observed as follows: esculetin (approximately 90–94%), scoparone (63–78%), 4-methylumbelliferone (10–49%), and coumarin (18–20%). These results are in agreement with histological findings, which demonstrated reduced liver damage. The outcomes of this study align closely with our previous investigations and are further supported by various reports in the literature[26,36,37].

Conclusion

Based on the findings of this study and existing literature, it can be inferred that the hepatoprotective effects of coumarins against CCl_4-induced liver damage may be attributed to their antioxidant properties, particularly their capacity to neutralize free radicals and enhance serum protein profiles. Among the tested compounds, esculetin and scoparone demonstrated the most pronounced effects in regulating albumin, globulin, total protein levels, and the albumin/globulin ratio within this hepatotoxicity model. These results indicate that hydroxy-substituted and dimethoxy coumarins hold promise as potential hepatoprotective agents, likely through mechanisms involving antioxidant, anti-inflammatory, and radical scavenging activities. However, further research is essential to elucidate their exact modes of action and assess their applicability in clinical settings. Should future studies

confirm their therapeutic efficacy and safety, coumarins could be considered for development as dietary supplements aimed at liver disease prevention.

References

1. **Farrell GC, Larter CZ.** Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology. 2006 Feb;43(2 Suppl 1):S99-s112. PubMed PMID: 16447287. eng.
2. **Voora D, McLeod HL, Eby C, Gage BF.** The pharmacogenetics of coumarin therapy. Pharmacogenomics. 2005 Jul;6(5):503-13. PubMed PMID: 16014000. eng.
3. **Ozaki Y, Ohashi T, Niwa Y. A** comparative study on the effects of inhibitors of the lipoxygenase pathway on neutrophil function. Inhibitory effects on neutrophil function may not be attributed to inhibition of the lipoxygenase pathway. Biochem Pharmacol. 1986 Oct 15;35(20):3481-8. PubMed PMID: 3021173. eng.
4. **Hoult JR, Payá M.** Pharmacological and biochemical actions of simple coumarins: natural products with therapeutic potential. Gen Pharmacol. 1996 Jun;27(4):713-22. PubMed PMID: 8853310. eng.
5. **Ozturk F, Ucar M, Ozturk IC, Vardi N, Batcioglu K.** Carbon tetrachloride-induced nephrotoxicity and protective effect of betaine in Sprague-Dawley rats. Urology. 2003 Aug;62(2):353-6. PubMed PMID: 12893363. eng.
6. **Ohta Y, Nishida K, Sasaki E, Kongo M, Ishiguro I.** Attenuation of disrupted hepatic active oxygen metabolism with the recovery of acute liver injury in rats intoxicated with carbon tetrachloride. Res Commun Mol Pathol Pharmacol. 1997 Feb;95(2):191-207. PubMed PMID: 9090755. eng.
7. **Kadir FA, Kassim NM, Abdulla MA, Yehye WA.** Hepatoprotective Role of Ethanolic Extract of Vitex negundo in Thioacetamide-Induced Liver Fibrosis in Male Rats. Evid Based Complement Alternat Med. 2013;2013:739850. PubMed PMID: 23762157. PMCID: PMC3671533. Epub 20130519. eng.
8. **Lee WM.** Acetaminophen (APAP) hepatotoxicity-Isn't it time for APAP to go away? J Hepatol. 2017 Dec;67(6):1324-31. PubMed PMID: 28734939. PMCID: PMC5696016. Epub 20170720. eng.
9. **Hamid AS, Tesfamariam IG, Zhang Y, Zhang ZG.** Aflatoxin B1-induced hepatocellular carcinoma in developing countries: Geographical distribution, mechanism of action and prevention. Oncol Lett. 2013 Apr;5(4):1087-92. PubMed PMID: 23599745. PMCID: PMC3629261. Epub 20130131. eng.
10. **Trefts E, Gannon M, Wasserman DH.** The liver. Curr Biol. 2017 Nov 6;27(21):R1147-r51. PubMed PMID: 29112863. PMCID: PMC5897118. eng.
11. **Ma Z, Peng L, Chu W, Wang P, Fu Y.** Osthole Alleviates D-Galactose-Induced Liver Injury In Vivo via the TLR4/MAPK/NF-κB Pathways. Molecules. 2023 Jan 3;28(1). PubMed PMID: 36615637. PMCID: PMC9824625. Epub 20230103. eng.
12. **Batista M, Brito P, Miranda P, Barbosa S, Cotter J.** Liver Failure in Autoimmune Hepatitis Overlap Syndrome With Primary Biliary Cholangitis: A Case Report. Cureus. 2024 Nov;16(11):e73574. PubMed PMID: 39677227. PMCID: PMC11638799. Epub 20241113. eng.

13. **Saadati F, Modarresi Chahardehi A, Jamshidi N, Jamshidi N, Ghasemi D.** Coumarin: A natural solution for alleviating inflammatory disorders. Curr Res Pharmacol Drug Discov. 2024;7:100202. PubMed PMID: 39398983. PMCID: PMC11470182. Epub 20240925. eng.
14. **Jaeschke H, Gores GJ, Cederbaum AI, Hinson JA, Pessayre D, Lemasters JJ.** Mechanisms of hepatotoxicity. Toxicol Sci. 2002 Feb;65(2):166-76. PubMed PMID: 11812920. eng.
15. **Lake BG, Evans JG, Lewis DF, Price RJ.** Studies on the acute effects of coumarin and some coumarin derivatives in the rat. Food Chem Toxicol. 1994 Apr;32(4):357-63. PubMed PMID: 8206431. eng.
16. **Lake BG, Evans JG, Chapuis F, Walters DG, Price RJ.** Studies on the disposition, metabolism and hepatotoxicity of coumarin in the rat and Syrian hamster. Food Chem Toxicol. 2002 Jun;40(6):809-23. PubMed PMID: 11983276. eng.
17. **Khan RA, Khan MR, Sahreen S.** Evaluation of Launaea procumbens use in renal disorders: A rat model. Journal of Ethnopharmacology. 2010 2010/03/24/;128(2):452-61.
18. **Kizir D, Yeşilkent EN, Öztürk N, Karağaç MS, Isıyel M, Tosun H, et al.** The protective effects of esculetin against Doxorubicin-Induced hepatotoxicity in rats: Insights into the modulation of Caspase, FOXOs, and heat shock protein pathways. J Biochem Mol Toxicol. 2024 Oct;38(10):e23861. PubMed PMID: 39305037. eng.
19. **Kumari S, Sharma A, Yadav S.** Pharmacological potential of coumarin-based derivatives:(a comprehensive brief review). Orient J Chem. 2023;39:568-76.
20. **Kim SH, Kang KA, Zhang R, Piao MJ, Ko DO, Wang ZH,** et al. Protective effect of esculetin against oxidative stress-induced cell damage via scavenging reactive oxygen species. Acta Pharmacol Sin. 2008 Nov;29(11):1319-26. PubMed PMID: 18954526. eng.
21. **Brent JA, Rumack BH.** Role of free radicals in toxic hepatic injury. I. Free radical biochemistry. J Toxicol Clin Toxicol. 1993;31(1):139-71. PubMed PMID: 8433411. eng.
22. **Brautbar N, Williams J.** 2nd. Industrial solvents and liver toxicity: risk assessment, risk factors and mechanisms. Int J Hyg Environ Health. 2002 Oct;205(6):479-91. PubMed PMID: 12455270. eng.
23. **Ali S, Khan MR, Shah SA, Batool R, Maryam S, Majid M, Zahra Z.** Protective aptitude of Periploca hydaspidis Falc against CCl(4) induced hepatotoxicity in experimental rats. Biomed Pharmacother. 2018 Sep;105:1117-32. PubMed PMID: 30021348. Epub 20180621. eng.
24. **Atmaca M, Bilgin HM, Obay BD, Diken H, Kelle M, Kale E.** The hepatoprotective effect of coumarin and coumarin derivates on carbon tetrachloride-induced hepatic injury by antioxidative activities in rats. J Physiol Biochem. 2011 Dec;67(4):569-76. PubMed PMID: 21656273. Epub 20110609. eng.
25. **Taşdemir E, Atmaca M, Yıldırım Y, Bilgin HM, Demirtaş B, Obay BD,** et al. Influence of coumarin and some coumarin derivatives on serum lipid profiles in carbontetrachloride-exposed rats. Hum Exp Toxicol. 2017 Mar;36(3):295-301. PubMed PMID: 27185181. Epub 20160711. eng.
26. **Murat Bilgin H, Atmaca M, Deniz Obay B, Ozekinci S, Taşdemir E, Ketani A**. Protective effects of coumarin and coumarin derivatives against carbon tetrachloride-induced acute hepatotoxicity in rats. Exp Toxicol Pathol. 2011 May;63(4):325-30. PubMed PMID: 20207117. Epub 20100305. eng.

27. **Martin-Aragón S, Benedi JM, Villar AM.** Effects of the antioxidant (6,7-dihydroxycoumarin) esculetin on the glutathione system and lipid peroxidation in mice. Gerontology. 1998;44(1):21-5. PubMed PMID: 9436011. eng.
28. **Okamoto T, Yoshida S, Kobayashi T, Okabe S.** Inhibition of concanavalin A-induced mice hepatitis by coumarin derivatives. Jpn J Pharmacol. 2001 Jan;85(1):95-7. PubMed PMID: 11243581. eng.
29. **Zangar RC, Benson JM, Burnett VL, Springer DL**. Cytochrome P450 2E1 is the primary enzyme responsible for low-dose carbon tetrachloride metabolism in human liver microsomes. Chem Biol Interact. 2000 Mar 15;125(3):233-43. PubMed PMID: 10731522. eng.
30. **Weber LW, Boll M, Stampfl A**. Hepatotoxicity and mechanism of action of haloalkanes: carbon tetrachloride as a toxicological model. Crit Rev Toxicol. 2003;33(2):105-36. PubMed PMID: 12708612. eng.
31. **Liu GT, Li Y, Wei HL, Zhang H, Xu JY, Yu LH.** Mechanism of protective action of bicyclol against CCl-induced liver injury in mice. Liver Int. 2005 Aug;25(4):872-9. PubMed PMID: 15998439. eng.
32. **Balsano C, Alisi A.** Antioxidant effects of natural bioactive compounds. Current Pharmaceutical Design. 2009;15(26):3063–73. PMCID: item type: Journal article. English.
33. **Kaplan M, Mutlu EA, Benson M, Fields JZ, Banan A, Keshavarzian A**. Use of herbal preparations in the treatment of oxidant-mediated inflammatory disorders. Complement Ther Med. 2007 Sep;15(3):207-16. PubMed PMID: 17709066. Epub 20060821. eng.
34. **Loguercio C, Federico A.** Oxidative stress in viral and alcoholic hepatitis. Free Radic Biol Med. 2003 Jan 1;34(1):1-10. PubMed PMID: 12498974. eng.
35. **Lin HC, Tsai SH, Chen CS, Chang YC, Lee CM, Lai ZY, Lin CM**. Structure-activity relationship of coumarin derivatives on xanthine oxidase-inhibiting and free radical-scavenging activities. Biochem Pharmacol. 2008 Mar 15;75(6):1416-25. PubMed PMID: 18201686. Epub 20071215. eng.
36. **Kaneko T, Baba N, Matsuo M**. Protection of coumarins against linoleic acid hydroperoxide-induced cytotoxicity. Chem Biol Interact. 2003 Jan 6;142(3):239-54. PubMed PMID: 12453663. eng.
37. **Gilani AH, Janbaz KH, Shah BH**. Esculetin prevents liver damage induced by paracetamol and CCL4. Pharmacol Res. 1998 Jan;37(1):31-5. PubMed PMID: 9503477. eng.

International Archives of Medical Research 17:1 (2025) 13-19

ORIGINAL RESEARCH

The Effect Of Immunotherapy on Seizure Frequency in Drug Resistant Focal Seizures

Received Date: 07.03.2025, Accepted Date: 25.03.2025 **DOI: 10.56484/iamr.1653396**

Derya BAYRAK[1a*], Mehmet Fevzi ÖZTEKİN[1b]

[1] Ministry of Health Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Department of Neurology, Ankara

[a]*ORCID: 0009-0007-2501-3982*, [b]*ORCID: 0000-0003-3582-2832*

Abstract

Objective: *Epilepsy is an important neurological disorder with serious consequences for both patients and society. Even though most cases of epilepsy can be controlled with antiseizure drugs, some types are resistant to medication.The present study,aims to investigate the effect of methylprednisolone treatment on seizure frequency in patients with drug resistant focal impaired awareness seizures.*

Materials and Methods:*This study involved 20 patients with focal impaired awareness seizures who had used multiple antiseizure drugs but had not experienced a seizure-free period longer than six months. The clinical and demographic characteristics of the patients were assessed. Each patient received 1000 mg intravenous (IV) pulse methylprednisolone therapy for 5 consecutive days. Patients were followed up for three months before and after the treatment. Seizure frequencies and electroencephalogram (EEG) findings,during the three months pre-treatment and post-treatment periods were compared. Patients experiencing a decrease in seizure frequency of more than 50% three months after treatment, in comparison to the pre-treatment period,were considered responders to the therapy.*

Results: *As a result of the study,4 patients responded positively to the treatment.One of these 4 patients became completely seizure-free.However,no statistically significant difference was found between pre-treatment and post-treatment seizure frequencies.Among nine patients with epileptiform findings on their pre-treatment EEG, these findings disappeared in four patients post-treatment.Nevertheless, the differences in EEG findings before and after treatment were also not statistically significant.*

Conclusion: *In our study, a single course of IV methylprednisolone therapy in patients with focal impaired awareness seizures did not yield a significant therapeutic response.It has been surmised that,a more efficient response to treatment would be achieved in case of continuing corticosteroid therapy with repeated doses in patients with treatment refractory focal impaired awareness seizures.*

Key words: *Refractory epilepsy,focal epilepsy,immünotheraphy,antiseizure drugs,epilepsy*

Introduction

Epilepsy affects millions of individuals worldwide[1].While the majority of patients with epilepsy can be controlled with antiseizure drugs, approximately one third of them are resistant to drug treatment. Accordingly, the mortality and morbidity rate of the disease increases. Drug resistant epilepsy is the inability to achieve seizure freedom despite the use of two or more appropriate anti-seizure drugs as monotherapy or combined treatment[2].Although drug-resistant epilepsies are seen in all types of epilepsies, they are more common in focal epilepsies[3,4]. In focal epilepsies, the underlying cause is the most important factor affecting prognosis and seizure recurrence[5].Recent studies indicated that neuroinflammation might play a role in the etiology of these

Corresponding author: E-mail: deryabyrk@hotmail.com

refractory epilepsies.When there is any neuronal damage in the central nervous system,a neuroinflammation due to proinflammatory molecules occurs, and this neuroinflammation causes the seizure threshold to decrease[6].Consequently, numerous immunotherapy studies were carried out targeting neuroinflammation in refractory epilepsies; however, a definitive treatment protocol has yet to be established[7,8].This study evaluates the response to high dose corticosteroid therapy in patients with refractory focal impaired awareness seizures.The effects of treatment on seizures and electroencephalogram were examined in these patients.

Materials and Methods

The study was approved by Ministry of Health Ankara Diskapi Yildirim Beyazit Training and Research Ethics Committees (approval number: 28/22, date:04.04.2016).Twenty patients with focal impaired awareness seizures were involved in the present study. Patients who experienced focal impaired awareness seizures,had used more than one antiseizure drug and had not been seizure free for >6 months were classified as refractory epilepsy patients. The demographic characteristics are summarized in Table 1.The disease duration in the patient group ranged between 10 and 59 years, and the mean disease duration was found to be 24 years.The duration of use antiseizure drug ranged between 7 and 48 years,while the mean duration was found 20.5 years.All 20 patients exhibited focal impaired awareness seizures, and three of them had focal to bilateral tonic-clonic seizures.Eleven patients were using more than two antiseizure drugs.Inflammatory findings (Mesial temporal sclerosis) were detected on cranial MRI in 5 patients, while the cranial MRI findings were normal in 15 patients.Epileptiform activity was observed on pre-treatment EEG recordings in 9 patients (Table 2).All patients received intravenous methylprednisolone pulse steroid therapy at a dose of 1000 mg/day for five days.The patients were followed for three months before and after the treatment.Seizure frequencies and EEG findings during the three-month periods before and after treatment were evaluated.Patients who had a >50% decrease in seizure frequency in comparison to the pre-treatment period were classified as having a significant response to treatment.Brain wave activities of the patients were recorded using a Nihon Kohden EEG device, and the EEG tracings were analyzed in a double-blinded manner to assess the presence of epileptiform activity.The results were statistically analyzed using SPSS version 16.0. For the evaluation of treatment response, the Wilcoxon test,a non-parametric analysis method, was used. Fisher’s Exact Test was employed for subgroup analyses.

Table1. Demographic characteristics of patients

	Number (Median)
Age	38 (21-71)
	Number (%)
Sex	
Female	10(50)
Male	10 (50)
Education	
Illiterate	3(15)
Elementary	8(40)
Middle	4(20)
High School	3(15)
University	2 (10)
Employment	
Employed	5(25)
Unemployed	15(75)

Table 2. Medical assessment of patients

	Number (%)
Type of seizure	
Focal impaired awareness seizures	20 (100)
Focal to bilateral tonic-clonic seizures	3 (15)
Those with abnormal MRI findings	5 (25)
Number of antiseizure drugs > 2	11 (55)
Those with epileptiform findings in pretreatment EEG	9 (45)
Those with epileptiform findings in posttreatment EEG	6 (30)
	Number (Median)
Disease duration (Years)	24 (10-59)
Treatment duration (Years)	20.5 (7-48)

Results

Four patients (20%) responded to treatment (≥50% decrease in seizure frequency), whereas 16 patients (80%) did not respond. Among the patients who responded to treatment, 1 patient was completely seizure-free after treatment. However, there was no significant difference between the number of seizures before and after treatment ($p = 0.18$). All patients who responded to treatment were female. Among the non-responders, 6 (37%) were female, and 10 (63%) were male. No significant difference was found between responders and non-responders regarding sex ($p = 0.9$). One patient (25%) among the responders and 2 patients (12.5%) among the non-responders experienced focal to bilateral tonic-clonic seizures. No significant difference in seizure types was observed between the groups ($p = 0.51$). All patients who responded to treatment had normal cranial MRI findings, whereas 5 (31.3%) of the non-responders exhibited abnormal cranial MRI findings. There was

no statistically significant difference in cranial MRI findings between the groups (p = 0.53). All treatment responders were using more than two antiseizure drugs, while 7 non-responders were also using more than two antiseizure drugs. No significant difference was observed in the number of antiseizure drugs used between responders and non-responders (p = 0.9). (Table 3)

Table 3. Clinical Characteristics of Patients Who Benefited from Treatment (≥50% Reduction in Seizure Frequency) vs. Those Who Did Not

	Responders (n:4)	Non-responders (n:16)	p-value
Sex Female Male	 4 (100) 0 (0)	 6 (37) 10 (63)	 0.90
Seizure type Focal to bilateral tonic-clonic seizures	 1 (25)	 2 (12.5)	 0.51
Number drugs before treatment >2 <2	 4 (100) 0 (0)	 0 (0) 9 (56.3)	 0.90
Those with inflammatory change in MRI	0 (0)	5 (31.3)	0.53

Epileptiform findings on EEG disappeared in 4 patients (20%) after the treatment, while no changes were detected in 16 patients (80%). There was no significant difference between pre-treatment and post-treatment EEG findings (p = 0.18). Among the patients whose epileptiform findings resolved on EEG, 2 (50%) were female and 2 (50%) were male. In the group with unchanged EEG findings, 8 (50%) were female and 8 (50%) were male. No significant gender difference was observed between the two groups (p = 1.0). One patient (25%) whose epileptiform findings resolved on EEG and 2 patients (12.5%) with unchanged EEG findings had secondary generalized seizures. No significant difference was observed in seizure types between these groups (p = 0.51). Inflammatory cranial MRI findings were present in 2 patients (50%) whose epileptiform findings resolved on EEG and in 3 patients (18.8%) with unchanged EEG findings. This difference was not statistically significant (p = 0.25). Three patients (75%) whose epileptiform findings resolved on EEG and 8 patients (50%) with unchanged EEG findings were using more than two antiseizure drugs. No significant difference was observed in the number of antiseizure drugs used between these groups (p = 0.59). (Table 4)

Table 4. Characteristics of those having EEG findings resolved after treatment and those having EEG findings not resolved

	Those with EEG findings resolved after treatment (n:4)		Those with EEG findings not resolved after treatment (n:16)	p-value	
Sex Female	2(50)		8 (50)	1.0	

Seizure type Focal to bilateral tonic-clonic seizures	1 (25)		2 (12.5)	0.51	
Number of drugs before treatment >2 <2	3 (75) 1 (25)		8 (50) 8 (50)	0.59	
Those with abnormal MRI	2 (50)		3 (18.8)	0.25	

Discussion:

Neuroinflammation plays a role in the pathogenesis of many neurological disorders[9]. Inflammatory conditions in the central nervous system increase the risk of epileptic seizure[10]. Moreover, some studies suggested that epileptic seizures may trigger neuroinflammation and may lead to a progression of epileptogenesis[11]. These results indicate that, in addition to antiseizure drugs , immunomodulatory treatments could be utilized in the management of epilepsy. Intravenous (IV) methylprednisolone is a well established, safe immunomodulatory treatment used for various inflammatory neurological diseases[12-15]. High-dose IV corticosteroid therapy is a recognized treatment approach for several neurological syndromes, such as multiple sclerosis. Recent studies reported that this therapy may prevent epilepsy related side effects and achieve long term treatment efficacy in the field of epilepsy[16-19]. The action mechanism of corticosteroids in epilepsy is complex and has not been fully explained yet. Potential neuromodulatory effects of corticosteroids include correcting deficiencies or dysfunctions in enzymes, addressing intracellular and extracellular electrolyte imbalances, increasing intracellular glucose levels, modulating intracellular adenosine levels, and contributing to neuronal lipid production[20]. Corticosteroids primarily modulate neurotransmitters, particularly gamma aminobutyric acid (GABA), to achieve acute seizure inhibition. However, previous studies indicated that antiepileptic effects cease if the medication is discontinued, leading to an increase in seizure frequency and drug resistance. This result suggests that corticosteroids not only provide acute seizure control but also contribute to the reestablishment of homeostatic mechanisms in the brain[21-22]. Approximately one third of epilepsy cases involve seizures that are resistant to antiseizure drugs with focal impaired awareness seizures comprising the majority of these cases[23]. In the light of all this information, when we evaluated the effectiveness of pulse methylprednisolone treatment as a single cure in patients with focal impaired awareness seizures in our study,a significant decrease in seizure frequency (over 50%) was observed in four patients after treatment,with one patient achieving complete seizure freedom.These results suggest that methylprednisolone therapy could serve as a beneficial treatment option for drug resistant epilepsies.In four of nine patients who had epileptiform discharges on EEG before treatment,epileptiform activity findings disappeared after treatment.However, these patients did not have a significant decrease in seizure frequency, supporting previous studies indicating that IV methylprednisolone may have a transient suppressive effect on seizure activity, which diminishes over time[24]. In our study,the fact that no statistically significant difference was observed in the number of seizures

after a single course of IV methylprednisolone treatment,does not completely eliminate the idea that the underlying cause may be a neuroinflammatory pathology in patients with refractory focal impaired awareness seizures .It suggests that a more effective response may be obtained in the treatment of these seizures,if corticosteroid treatment is continued in repeated doses.However,since the study population was small, the treatment results need to be repeated in studies with a larger patient population in order to generalize these findings.

References

1. **Poonam Nina B.,David F,W Allen H.** The descriptive epidemiology of epilepsy-a review Epilepsy Res.2009; 85(1): 31–45. https://doi.org/10.1016/j.eplepsyres.2009.03.003
2. **Kwan P, Arzimanoglou A, Berg AT, et al.** Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia. 2010;51(6):1069-1077. doi: 10.1111/j.1528-1167.2009.02397.
3. **Mohanraj R, Brodie MJ.** Outcomes of newly diagnosed idiopathicgeneralized epilepsy syndromes in a non-pediatric setting. Acta NeurolScand. 2007;115(3):204–208. doi: 10.1111/j.1600-0404.2006.00791
4. **Szaflarski JP, Lindsell CJ, Zakaria T, Banks C, Privitera MD.** Seizure control in patients with idiopathic generalized epilepsies:EEG determinants of medication response. Epilepsy Behavior.2010;17(4):525–530. doi:10.1016/j.yebeh.2010.02.005
5. **Mohanraj R., Brodie M.J.:** Early predictors of outcome in newly diagnosed epilepsy. Seizure 2013; 22: pp. 333-344. doi: 10.1016/j.seizure.2013.02.002.
6. **Heida JG, Pittman QJ.** Causal links between brain cytokines and experimental febrile convulsions in the rat. Epilepsia. (2005) 46:1906– 13. doi: 10.1111/j.1528-1167.2005.00294
7. **Van Vliet EA, Aronica E, Vezzani A, Ravizza T.** Review: neuroinflammatory pathways as treatment targets and biomarker candidates in epilepsy: emerging evidence from preclinical and clinical studies. Neuropathol Appl Neurobiol. 2018; 44:91–111 doi: 10.1111/nan.12444.
8. **Orsini A, Foiadelli T, Costagliola G, Michev A, Consolini R, Vinci F, et al.** The role of inflammatory mediators in epilepsy: focus on developmental and epileptic encephalopathies and therapeutic implications. Epilepsy Res. 2021; 172:106588. doi: 10.1016/j.eplepsyres.2021.106588.
9. **Nylander A., Hafler D.A.** Multiple sclerosis. J. Clin. Invest. 2012;122 doi: 10.1172/JCI58649
10. **Ong M.-S., Kohane I.S., Cai T., Gorman M.P., Mandl K.D.** Population-Level Evidence for an Autoimmune Etiology of Epilepsy. JAMA Neurol. 2014; 71:569–574.
11. **Meng F., Yao L.** The role of inflammation in epileptogenesis. Acta Epileptol. 2020; 2:15.
12. **Aykut-Bingol C, Arman A, Tokol O, et al.** Pulse methylprednisolone therapy in Landau-Kleffner syndrome. 1996; J Epilepsy 9:189-191.
13. **Tsuru T, Mori M, Mizuguchi M, et al.** Effects of high-dose intravenous corticosteroid therapy in Landau-Kleffner syndrome. 2000; Pediatr Neurol 22:145-147. doi: 10.1016/s0887-8994(99)00127-7.
14. **Okuyaz C, Aydin K, Gücüyener K, et al.** Treatment of electrical status epilepticus during slow-wave sleep with high-dose corticosteroid. 2005; Pediatr Neurol 32:64-67. doi: 10.1016/j

15. **Sevilla-Castillo RA, Palacios GC, Ramirez-Campos J, et al.** Methylprednisolone for the treatment of children with refractory epilepsy. 2009; Neuropediatrics 40:265-268. doi:10.1055/s-0030-1249653
16. **Lichtenfeld R, Heyman E, Gandelman-Marton R, et al.** Intravenous methylprednisolone pulse therapy in a young girl with intractable absence seizures. 2010. Isr Med Assoc J 12:181-182
17. 17-Mytinger JR, Quigg M, Taft WC, et al (2010). Outcomes in treatment of infantile spasms with pulse methylprednisolone. J Child Neurol 25:948-95. doi:10.1177/08830 73809356107.
18. **Heyman E, Lahat E, Gandelman-Marton R .** Interictal encephalography can influence patient selection for methylprednisolone therapy in pediatric refractory epilepsy. 2012; J Child Neurol 27:162-167. doi:10.1177/0883073811414905
19. **Almaabdi KH, Alshehri RO, Althubiti AA, et al.** Intravenous methylprednisolone for intractable childhood epilepsy. Pediatr Neurol. 2014; 50:334-336. doi: 10.1016/j.
20. **Marchi N, Granata T, Freri E, et al.** Efficacy of anti-inflammatoryütherapy in a model of acute seizures and in a populationof pediatric drug resistant epileptics. PLoS One. 2011; 28;6(3):e18200. 6:e18200.doi: 10.1371/journal.pone.0018200.
21. **Vezzani A, Granata T.** Brain inflammation in epilepsy:experimental and clinical evidence. Epilepsia. 2005; 46:1724-1743. doi: 10.1111/j.1528-1167.2005.00298
22. **Özkara Ç, Vigevano F**. Immuno- and antiinflammatory therapies in epileptic disorders. Epilepsia. 2011; 3:45-51. doi:10.1111/j.1528-1167.2011.03036
23. **Bien CG, Urbach H, Schramm J, et al.** Limbic encephalitis as a precipitating event in adult-onset temporal lobe epilepsy. Neurology 2007; 69:1236–1244. doi: 10.1212/01.wnl.0000276946.08412.ef.
24. **Maria Carmela Pera,Giovanna Randazzo,Silvia Masnada,et al.** Intravenous methylprednisolone pulse therapy for children with epileptic encephalopathy. Functional Neurology 2015; 30(3): 173-179. doi:10.11138/fneur/2015.30.3.173

International Archives of Medical Research 17:1 (2025) 20-30

ORIGINAL RESEARCH

Health workers' perspectives on mediators of elongated parturition among females of reproductive age: A descriptive study

Received Date: 10.03.2025, Accepted Date: 21.04.2025 **DOI: 10.56484/iamr.1654548**

Godson Chukwuemeka AJUZİE[1a], Adaobi Linda OKERULU[2b], Osah Martins ONWUKA[3c*]

[1] Gastroenterology, Department of Human Physiology Faculty of Basic Medical Sciences, Gregory University Uturu, Abia State, Nigeria

[2] Body fluid and Renal physiology, Department of Human Physiology, Faculty of Basic Medical Sciences, Gregory University Uturu, Abia State, Nigeria

[3] Applied, Clinical and Experimental Physiology, Department of Human Physiology, Faculty of Basic Medical Sciences, Gregory University, Uturu, Abia State, Nigeria

[a]*ORCID: 0009-0003-5791-3775,* [b]*ORCID: 0009-0008-3187-8429,* [c]*ORCID: 0000-0002-2451-4466*

Abstract

Objective: *Prolonged labor, also known as elongated parturition, poses significant health risks to mothers and newborns, contributing to maternal and fetal morbidity and mortality. This study explores health workers' perspectives on the mediators of elongated parturition among females of reproductive age to identify and address contributing factors.*

Methods: *This descriptive study was conducted among 100 health workers from two health centers in Rivers State, Nigeria. Data were collected using open-ended questionnaires and audio recordings and analyzed using percentage distribution.*

Results: *Among the 100 participants, 30% were male, 70% female; 5% were trained health workers, and 13% were students. Most (82%) had tertiary education, 87% were Christians, and 13% practiced other religions. Factors influencing prolonged labor included inadequate antenatal care (40%), incompetent pelvis (20%), and maternal inability to push (40%). All participants (100%) had witnessed cases, with occurrences reported annually (53%) or depending on the woman (41%). Psychological and physiological effects included maternal distress (33%), maternal death (32%), child death (12%), and other health issues (23%). Suggested interventions included improved antenatal care (55%), health education (30%), and community mobilization (15%), with 68% of participants supporting these measures, 5% opposing, and 27% supporting them conditionally. Constraints included women's choice (25%), religion (25%), unskilled health workers (40%), and reliance on traditional birth attendants (10%).*

Conclusion: *Health workers' perspectives indicate that elongated parturition significantly impacts maternal and fetal outcomes. Addressing mediators such as inadequate antenatal care and unskilled health workers, while increasing community awareness and health education, is crucial for reducing associated risks and improving maternal and neonatal health.*

Keywords*: Elongated parturition, mediators, maternal health, reproductive age, health workers.*

Corresponding author: E-mail: osahmartinz@gmail.com

Introduction

Parturition, also known as childbirth or labor, marks the culmination of pregnancy around 36 weeks after conception, involving the delivery of the fetus from the womb[1,2]. The process occurs in three stages: Stage 1, characterized by fetal descent into the pelvis and cervical softening in preparation for labor; Stage 2, involving intense contractions, full cervical dilation, delivery of the baby, and placental expulsion; and Stage 3, where maternal recovery begins, fostering physical restoration and maternal-infant bonding[2-4]. Hormones such as estrogen, oxytocin, relaxin, and prostaglandins play crucial roles in this physiological process, influencing both physical and emotional experiences for the mother[5].

Childbirth complications can arise when uterine contractions fail to occur, preventing cervical dilation and leading to abnormal labor. One such complication is prolonged labor, also referred to as elongated parturition[6]. Prolonged labor, also known as "failure to progress," refers to labor lasting more than 20 hours in nulliparous women (first-time mothers) or more than 14 hours in multiparous women (those who have previously given birth). It is typically marked by slow cervical dilation and/or delayed fetal descent. Prolonged labor can lead to complications such as dystocia, a condition characterized by difficult labor due to factors like fetal size, position, or maternal pelvic structure[7]. Uterine hypocontractility, characterized by insufficient uterine contractions in strength or frequency to progress labor, is another common issue[8]. Pelvic disproportion, where the baby's head cannot pass through the maternal pelvis due to its size, can also occur[9]. Also, fetal distress, a critical condition requiring immediate monitoring and intervention may put the fetus at risk[10]. Maternal exhaustion, caused by fatigue from prolonged labor, may further prevent effective pushing during delivery[11]. Both the mother and fetus require close monitoring to ensure a successful delivery. Interventions for prolonged labor include cesarean section, the use of instruments such as forceps or vacuum extractors, and the administration of oxytocin to enhance uterine contractions[12].

Several mediators contribute to elongated parturition, including: hormonal factors responsible for faint and inconsistent contractions (e.g., oxytocin), cervical preparation for vaginal delivery, and uterine contractions (e.g., prostaglandins); premature and prolonged labor associated with elevated or decreased levels of corticotropin-releasing hormone[13]; factors that prolong labor due to fetal size and positioning, as well as maternal pelvic abnormalities[14]; uterine factors leading to diminished contractions and structural anomalies contributing to prolonged labor[8]; cervical factors such as cervical dystocia (inability to dilate and efface) and cervical scarring from previous surgeries, which hinder dilation[15]; maternal factors, including primiparity, advanced maternal age, and underlying conditions like obesity, diabetes, and hypertension, which can lead to extended labor[16]; psychological

factors, including stress, anxiety, lack of emotional support, and an unfavorable environment, which may impede labor progress[17]; and inadequate methods of induction or the use of anesthetics and other pain-relief measures, which can contribute to delayed labor progression[18].

Prolonged parturition is associated with increased morbidity and mortality rates among women of childbearing age[19]. The management and monitoring of the factors contributing to prolonged labor are crucial to ensuring safe and effective labor and delivery[20].

Aim of research was to investigate health workers' perspectives on mediators of elongated parturition among females of reproductive age in order to identify and address these issues.

Materials and Methods

This study employed a descriptive research design to explore the factors contributing to prolonged labor and to propose potential interventions. The study was conducted in two selected health centers in Elibrada community, Emohua Local Government Area, Rivers State, Nigeria**,** from June to September 2023. The selection of these health centers was based on their accessibility, availability of health workers, and their role in providing maternal healthcare services in the community.

A total of 182 healthcare workers were identified within the study area. From this population, 100 participants were selected using a simple random sampling technique to ensure unbiased and equal representation. Specifically, 50 participants were recruited from each of the two selected health centers. The sample size was influenced by the number of healthcare workers available and willing to participate at the time of the study. All eligible individuals who met the inclusion criteria and consented to participate were considered, which helped to maximize representation within the constraints of the study setting.

Inclusion Criteria: The study included male and female healthcare workers, trained health workers, student health workers, and those with tertiary education, regardless of religious affiliation (Christian, Islamic, or other). Participants were between 21 and 46 years old, with an average age of 33.5 ± 0.79 years.

Exclusion Criteria: Children, non-health workers, and individuals with educational levels below tertiary education were excluded from the study.

Ethical Considerations: The study was conducted in accordance with the Declaration of Helsinki (2013) and was approved by the Human Physiology Department, Gregory University Uturu (8/03/023)**.** A preliminary visit was made to the selected health centers to inform the Matron and management about the study and to seek their cooperation. Verbal consent was obtained from all

participants after explaining the research purpose, methods, and measures taken to ensure confidentiality.

Data Collection: Data were collected using semi-structured interviews with open-ended questions, allowing for in-depth responses. A recording device was used to document the responses, with precautions taken to duplicate recordings onto another storage device to prevent data loss. The collected data were subjected to quantitative content analysis. Responses were categorized and coded into thematic units, which were then quantified to identify trends and frequency distributions. This approach enabled the presentation of findings using numerical data and percentages. Consequently, the study employed a mixed-methods approach, combining qualitative data collection with quantitative analysis to provide a more comprehensive understanding of the research questions.

Study Variables:

- Independent variables: These include healthcare workers' demographics, as well as their knowledge and experiences regarding cases of prolonged labor.
- Dependent variables: These are the factors contributing to prolonged labor, including its psychological and physiological effects, as well as the healthcare workers' suggested interventions for managing prolonged labor.

Data Analysis: Data were analyzed using SPSS version 25, with results presented as frequency and percentage distributions for clarity.

Results

Demographic History

The demographic history of the respondents is as follows: Out of the 100 participants, 30 (30.0%) were males and 70 (70.0%) were females. Among the respondents, 5 (5.0%) were trained health workers, 13 (13.0%) were student health workers, and 82 (82.0%) had attained tertiary-level education. Regarding religious affiliation, 0 (0.0%) practiced Islam, 87 (87.0%) practiced Christianity, and 13 (13.0%) practiced neither Islam nor Christianity (Table 1).

Table 1. *Demographic History*

Variable	Category	Frequency	Percentage (%)
Sex	Male	30	30.0
	Female	70	70.0
	Total	100	100.0
Educational level	Trained health workers	5	5.0
	Student health workers	13	13.0

	Tertiary level of education	82	82.0
	Total	100	100.0
Religion	Islamic	0	0.0
	Christianity	87	87.0
	None	13	13.0
	Total	100	100.0

Factors that influence elongated parturition

Among the 100 respondents, 40 (40.0%) identified lack of proper antenatal care as a factor, 20 (20.0%) cited an incompetent pelvis, and 40 (40.0%) reported the inability of the mother to push as contributing factors to prolonged parturition (Table 2).

Table 2. *Factors that influences elongated parturition*

Variables	**Frequency**	**Percentage (%)**
Lack of proper antenatal	40	40.0
Incompetent Pelvis	20	20.0
Inability of the mother to push	40	40.0
Total	100	100.0

Cases of elongated parturition

Among the 100 respondents, 100 (100.0%) have witnessed cases of prolonged parturition, while 0 (0.0%) have not encountered such cases (Table 3).

Table 3. *Cases of elongated parturition*

Variables	**Frequency**	**Percentage (%)**
Yes	100	100.0
No	0	0.0
Total	100	100.0

Occurrence of elongated parturition

Among the 100 respondents, 53 (53.0%) stated that prolonged parturition occurs only a few times a year, 41 (41.0%) indicated that its occurrence depends on the woman, and 6 (6.0%) were unsure (Table 4).

Table 4. *Occurrence of elongated parturition*

Variables	**Frequency**	**Percentage (%)**
Few times in a year	53	53.0
Depending on the woman	41	41.0
Don't really know	6	6.0
Total	100	100

Psychological and Physiological Effects of Prolonged Parturition as Reported by Health Workers

Among the 100 respondents, 87 (87.0%) responded positively about the effects of prolonged labor on affected women while 13(13.0%) responded negatively (Table 5)

Table 5. *Reported by Health Workers on Psychological or Physiological effects on the affected women*

Variables	Frequency	Percentage (%)
Yes	87	87.0
No	13	13.0
Total	100	100.0

Psychological and Physiological Effects of elongated Parturition

Among the 100 respondents, 33 (33.0%) identified maternal distress, 32 (32.0%) reported maternal death, 12 (12.0%) mentioned fetal death, and 23 (23.0%) highlighted other health complications as effects of prolonged labor (Table 6).

Table 6. *Some of the psychological or physiological effects of elongated parturition*

Variables	Frequency	Percentage (%)
Distress to the mother	33	33.0
Sometimes death may occur	32	32.0
Fetal death	12	12.0
Other health complications	23	23.0
Total	100	100.0

Possible Ways to Reduce Maternal Mortality resulting from elongated parturition

Among the respondents, 73 (73.0%) believed that maternal mortality resulting from prolonged parturition could be reduced, 0 (0.0%) said it could not be reduced, while 27 (27.0%) stated that it could be reduced sometimes. From the results, 55 (55.0%) of respondents identified improved antenatal care services, 30 (30.0%) mentioned health education and counseling, and 15 (15.0%) cited community mobilization as ways to create awareness and reduce prolonged parturition. Regarding the implementation of these measures, 68 (68.0%) of respondents affirmed that the measures are practiced, 5 (5.0%) stated that they are not practiced, while 27 (27.0%) indicated that the measures are implemented when resources are available. The constraints identified in reducing maternal mortality include the choices made by pregnant women regarding antenatal care services (25.0%), religious beliefs (25.0%), the presence of unskilled health workers during labor (40.0%), and the influence and actions of Traditional Birth Attendants (TBA's) (10.0%) (Table 7)

Table 7. *Possible Ways to Reduce Maternal Mortality resulting from elongated parturition*

Variables	**Frequency**	**Percentage (%)**
Possibility of reducing maternal mortality resulting from elongated parturition		
Yes	73	73.0
No	0	0.0
Sometimes	27	27.0
Total	100	100
Measures taken to reduce occurrence of elongated parturition		
Improved antenatal services	55	55.0
Health education/counseling	30	30.0
Community mobilization	15	15.0
Total	100	100.0
Practice of Measures to Reduce Maternal Mortality		
Yes	68	68.0
No	5	5.0
When available	27	27.0
Total	100	100.0
Constraints experienced in reducing maternal mortality		
Women's choice	25	25.0
Religion	25	25.0
Unskilled health workers on duty	40	40.0
Presence of TBA's	10	10.0
Total	100	100.0

Discussion:

Table 2 highlights several factors contributing to prolonged parturition, including lack of proper antenatal care, incompetent pelvis, and the mother's inability to push, all of which place both the mother and child at significant risk. These findings align with the study by, which identified similar factors as key contributors to prolonged labor. Such factors delay the parturition process, thereby endangering maternal and neonatal health. Table 3 reveals that all health workers surveyed had encountered cases of prolonged parturition. This observation is consistent with, who noted that even mothers often witness prolonged labor cases and sometimes resort to traditional practices to facilitate labor, reduce its duration, and alleviate maternal discomfort[21,22].

As shown in Table 4, the occurrence of prolonged parturition varies, with some respondents indicating that it happens frequently, while others suggest that it depends on the individual woman. This finding corresponds with, who reported that maternal death due to prolonged labor is a

significant issue, with prolonged labor accounting for 20% of maternal deaths in Bangladesh. The study, as seen in Table 5, reveals that prolonged parturition has profound psychological and physiological effects on women. This result is supported by, who highlighted that childbirth and related experiences, such as prolonged labor, can have short- and long-term physical and psychological impacts on women. Table 6 identifies some of the psychological and physiological effects of prolonged parturition, including maternal distress, maternal and fetal death, and other health complications. These findings align with, who described birth trauma, including prolonged labor, as an event during labor and delivery that may involve serious injury or death of the mother or infant, causing the birthing woman to experience fear, helplessness, and horror[23-25].

Table 7 shows that most health workers believe maternal mortality resulting from prolonged parturition can be reduced. This is consistent with, who emphasized the need to strengthen knowledge among women and healthcare professionals to improve maternal health and reduce mortality rates. The study highlights measures such as improved antenatal care services, health education and counseling, and community mobilization as key strategies to address prolonged parturition[26,27]. Supports this by stating that antenatal care allows for screening and support, fostering healthy lifestyles and self-care, and ultimately reducing maternal and perinatal mortality. Most health workers reported practicing measures to reduce prolonged parturition, while others implemented them only when resources were available. This finding is consistent with, who noted that early initiation of antenatal care in the first or second trimester is associated with reduced maternal mortality compared to care initiated in the third trimester[28]. Constraints identified include women's choices regarding antenatal services, religious beliefs, unskilled health workers during labor, and the involvement of traditional birth attendants (TBAs) (Table 7). These findings are supported by, who highlighted that socioeconomic and cultural practices significantly contribute to maternal mortality[29,30]. To address these issues, policymakers and healthcare providers must encourage women with low maternal healthcare utilization rates to access formal services. Educational programs should target not only women but also husbands, parents, and in-laws to promote the benefits of formal maternal healthcare.

The limitation of the study. The research was limited by a small, localized sample, self-reported data from health workers only, and a lack of diverse perspectives or longitudinal insights. Additionally, the analysis was constrained by qualitative methods and cultural homogeneity.

Prospects for further research. Future studies should include larger, more diverse populations, incorporate patient perspectives, and utilize quantitative and mixed-methods approaches to better understand the mediators and effects of elongated parturition.

Further research should focus on evaluating targeted interventions such as health worker training, antenatal care improvement, community health education, and the use of technology to mitigate elongated parturition and improve maternal and neonatal outcomes.

Conclusion

The study results suggest that prolonged labor remains a critical contributor to maternal and fetal mortality, underscoring the urgent need for targeted interventions in maternal healthcare. This study highlighted the perspectives of health workers, identifying the mediators such as inadequate antenatal care, unskilled health workers, and reliance on traditional birth practices, which exacerbate the risks associated with elongated parturition. The study also showed that addressing these factors requires a multi-faceted approach involving enhanced antenatal care services to identify and manage risk factors for prolonged labor early, ensuring timely and appropriate interventions.

Equipping healthcare providers with the necessary skills and knowledge to handle complications effectively is crucial. Community education and mobilization efforts are equally important, as they help raise awareness about the dangers of prolonged labor and promote evidence-based birthing practices through outreach programs. Advocacy for supportive health policies that prioritize maternal and neonatal health, including investments in healthcare infrastructure and professional development, is essential for long-term improvements.

Further research into culturally and contextually relevant strategies, along with leveraging technology to improve access to maternal healthcare services, will enhance the efficacy of these interventions. By implementing these measures, the risks associated with prolonged labor can be significantly reduced, contributing to safer pregnancies and deliveries and ultimately improving maternal and neonatal health outcomes on a broader scale.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

Funding

The study was performed without financial support.

Data availability

Data will be made available on reasonable request.

References

1. **Ajuzie G C, Onwuka O M, Okerulu A L.** Pregnancy termination, consequences, and influencing factors: A study on perceptions of women of childbearing age. Yemen J Med. 2024; 3(1):43-7.

2. **Thornton J M, Ramphul M.** Mechanisms and management of normal labour. Obstet Gynecol Reprod Med. 2023; 33(6):160-7.
3. **Cohen W R, Friedman E A.** The second stage of labor. Am J Obstet Gynecol. 2024; 230(3):S865-75.
4. **Delgado-Pérez E, Rodríguez-Costa I, Vergara-Pérez F, Blanco-Morales M, Torres-Lacomba M.** Recovering sexuality after childbirth. What strategies do women adopt? A qualitative study. Int J Environ Res Public Health. 2022; 19(2):950.
5. **Lozic M, Ludwig M.** Oxytocin. Encycl Mol Pharmacol. 2022; 1203-9. Cham: Springer International Publishing.
6. **Badejoko O, Onwudiegwu U.** Management of Normal and Abnormal Labour. Cont Obstet Gynecol Dev Countries. 2021; 117-27.
7. **Cohen W R, Friedman E A.** Clinical evaluation of labor: an evidence-and experience-based approach. J Perinat Med. 2021; 49(3):241-53.
8. **Young R C, Marinescu P S, Seligman N S.** Monitoring uterine contractions during labor: current challenges and future directions. Am J Obstet Gynecol. 2023; 228(5):S1192-208.
9. **Pavličev M, Romero R, Mitteroecker P.** Evolution of the human pelvis and obstructed labor: new explanations of an old obstetrical dilemma. Am J Obstet Gynecol. 2020; 222(1):3-16.
10. **Wilson R D.** The real maternal risks in a pregnancy: a structured review to enhance maternal understanding and education. J Obstet Gynaecol Can. 2020; 42(11):1364-78.
11. **Pouca M C, Ferreira J P, Parente M P, Jorge R M, Ashton-Miller J A.** On the management of maternal pushing during the second stage of labor: a biomechanical study considering passive tissue fatigue damage accumulation. Am J Obstet Gynecol. 2022; 227(2):267-e1.
12. **Doğan E K, Çevik S.** Determining the Impact of Cervical Dilation at Admission on Intrapartum Interventions and Labor Satisfaction in Pregnant Women. J Educ Res Nurs. 2024; 21(2).
13. **Uvnäs-Moberg K.** The physiology and pharmacology of oxytocin in labor and in the peripartum period. Am J Obstet Gynecol. 2024; 230(3):S740-58.
14. **Cohen W R, Friedman E A.** The second stage of labor. Am J Obstet Gynecol. 2024; 230(3):S865-75.
15. **Jaiyesimi R A, Ojo O E, Awe A F.** Caesarean delivery and peripartum hysterectomy. Cont Obstet Gynecol Dev Countries. 2021; 203-21.
16. **Langley-Evans S C, Pearce J, Ellis S.** Overweight, obesity and excessive weight gain in pregnancy as risk factors for adverse pregnancy outcomes: A narrative review. J Hum Nutr Diet. 2022; 35(2):250-64.
17. **Jallu S Y, Manja E K, Ba-an M T.** Work Place Factors Contributing To Stress Among University Teachers And Coping Strategies: A Study Of Tamale Technical University. Ind J Econ Bus Manag. 2023; 3(1):8-21.
18. **Callahan E C, Lee W, Aleshi P, George R B.** Modern labor epidural analgesia: implications for labor outcomes and maternal-fetal health. Am J Obstet Gynecol. 2023; 228(5):S1260-9.
19. **Ermatov N J, Bobomuratov T A, Sagdullaeva M A.** Prolonged newborns and prolong pregnancy: A modern view on the problem. Int J Health Med Sci. 2022; 5(1):26-30.
20. **Chang K J, Seow K M, Chen K H.** Preeclampsia: Recent advances in predicting, preventing, and managing the maternal and fetal life-threatening condition. Int J Environ Res Public Health. 2023; 20(4):2994.

21. **Vasquez V, Desai S.** Labor and delivery and their complications. Rosen's emergency medicine: concepts and clinical practice. 2018; 2296-312.
22. **Solomon N, Tesfaye M.** Traditional practices during pregnancy and childbirth among mothers in Shey Bench District, South West Ethiopia. SAGE Open Med. 2022; 20503121221098139.
23. **Head S K, Yount K M, Sibley L M.** Delays in recognition of and care-seeking response to prolonged labor in Bangladesh. Soc Sci Med. 2011; 72(7):1157-68.
24. **Hosseini Tabaghdehi M, Kolahdozan S, Keramat A, Shahhossein Z, Moosazadeh M, Motaghi Z.** Prevalence and factors affecting the negative childbirth experiences: a systematic review. J Matern Fetal Neonatal Med. 2020; 33(22):3849-56.
25. **Pop-Jordanova N.** Childbirth-related psychological trauma. Prilozi. 2022; 43(1):17-27.
26. **Ramazani I B, Ntela S D, Ahouah M, Ishoso D K, Monique R T.** Maternal mortality study in the Eastern Democratic Republic of the Congo. BMC Pregnancy Childbirth. 2022; 22(1):452.
27. **Wafula S T, Nalugya A, Kananura R M, Mugambe R K, Kyangwa M, Isunju J B et al.** Effect of community-level intervention on antenatal care attendance: a quasi-experimental study among postpartum women in Eastern Uganda. Glob Health Action. 2022; 15(1):2141312.
28. **Sundari T K.** The untold story: how the health care systems in developing countries contribute to maternal mortality. Women Health Polit Policy. 2020; 173-90.
29. **Withers M, Kharazmi N, Lim E.** Traditional beliefs and practices in pregnancy, childbirth and postpartum: A review of the evidence from Asian countries. Midwifery. 2018; 56:158-70.
30. **Dewi I S, Anggraini H, Silaban T D.** Relationship between Mal Presentation, Contractions and Baby Weight with Prolonged Parturition in the Teluk Lubuk Health Center Working Area in 2020. Sci Midwifery. 2022; 10(2):574-9.

International Archives of Medical Research 17:1 (2025) 31-42

REVIEW

Bibliometric Analysis of Colistin-Related Theses in Türkiye

Received Date: 02.02.2025, Accepted Date: 25.02.2025 **DOI: 10.56484/iamr.1631580**

Mehmet Nuri GÖRDÜK[1a*], İlker KELLE[1b]

[1] Dicle University, Faculty of Medicine, Department of Medical Pharmacology, Diyarbakır, Turkey

[a]*ORCID: 0000-0001-6475-7983,* [b]*ORCID: 0000-0003-3232-7019*

Abstract

Objective: *In recent years, due to the limited number of novel antibiotics and the developing resistance to existing ones have become significant challenges. Colistin, an antibiotic known for its efficacy against some gram-negative bacteria especially Acinetobacter spp. and Klebsiella spp., was previously restricted due to its adverse effects, has reintroduced into clinical practice as a last-resort treatment option. In this study, it was aimed to conduct a bibliometric analysis of the thesis studies on colistin in Türkiye.*

Methods: *In this descriptive study, a search was made on the database of the National Thesis Center of the Council of Higher Education of Türkiye, which includes theses written in Türkiye, on December 10, 2024, using the keyword "colistin". 121 theses identified as a result of the screening were included in the study without applying any exclusion criteria. The data obtained are presented as numbers and percentages.*

Results: *It was determined that the majority of the studies were medical specialty theses. There has been an increase in the number of theses on colistin over the years, and the most studies were conducted in 2021. Most studies were conducted in the fields of Microbiology and Clinical Microbiology and Infectious Diseases. The studies focused not only on the efficacy of colistin but also on resistance mechanisms and side effect profiles. Among the 15 studies that specifically evaluated nephrotoxicity in human subjects, an average nephrotoxicity rate of 50% was reported.*

Conclusion: *This study reveals the growing academic interest and research trends regarding colistin in Türkiye. The findings show that as colistin re-enters clinical practice, its place in the scientific literature is strengthened. Further research on colistin's efficacy and adverse effect profile is essential to provide comprehensive insights for its clinical use.*

Keywords*: Bibliometrics, Colistin, Nephrotoxicity*

Corresponding author: E-mail: mngorduk@artuklu.edu.tr

Introduction

After the development of antibiotics, which marked a significant breakthrough in medical history, their effectiveness gradually diminished due to the emergence of antimicrobial resistance. In the absence of efficient novel antibiotics, older drugs that had not been used for decades were reintroduced into clinical practice. Colistin, developed nearly 70 years ago but largely abandoned due to its nephrotoxicity and other side effects, began to be widely used again after the 2000s as a last-line treatment option for infections caused by multidrug-resistant bacteria[1-3].

However, resistance to colistin has also been increasing recently [4]. Moreover, despite its growing clinical use, colistin continues to pose a significant risk due to its side effects, particularly nephrotoxicity, making it a "double-edged sword" [5].

As a result, colistin has received significant attention in academic research. This is evident from the increasing number of theses at various levels such as master's, PhD and medical specialization. Researchers have focused on topics such as the emergence and mechanisms of resistance, side effects, efficacy, combination therapy, and pharmacokinetics/ pharmacodynamics.

Objective: The aim of this study is to analyze the research trends related to colistin, identify the specific topics explored by researchers, and conduct a bibliometric analysis of the theses published in this field in Türkiye.

Materials and Methods

Data Collection: For this study, a search was conducted on December 10, 2024, using the National Thesis Center database of the Council of Higher Education of Türkiye, accessible at “tez.yok.gov.tr”. The keyword “colistin” was used to identify theses containing the term in their titles. A total of 121 postgraduate theses were identified and included in the study, with no exclusion criteria applied.

The collected data included the publication year, author, title, type of thesis (master's, PhD, or specialty in medicine), branch of science, university, and language of publication.

Data Analysis: A descriptive analysis was conducted on all collected data. The distribution of theses was analyzed based on university, thesis type, and branch of science. Titles and abstracts were reviewed, and the theses were grouped into main topics (e.g., resistance, efficacy, combination therapy, side effects). Keywords associated with each thesis were also recorded. Additionally, 15 theses focusing on nephrotoxicity in human studies were examined in detail. The methods of these theses, the characteristics and numbers of individuals participating in the research, and the findings regarding nephrotoxicity were analyzed. The results obtained were evaluated within the scope of our study and the findings were presented.

Word clouds were generated to visualize frequently used terms in thesis titles. Additionally, changes in thesis topics and keywords over time were examined, with the top five most frequently used keywords for each year identified and analyzed.

All analyses were performed using the R programming language, and the results were presented as numbers and percentages.

Ethical Approval: Ethical approval was not required, as the study utilized publicly available data.

Results

In the research conducted on the thesis database, a total of 121 theses related to colistin were identified. The earliest thesis was published in 2007, and the number of theses has generally increased over time. The year 2021 had the highest number of theses, with a total of 18 (Figure 1).

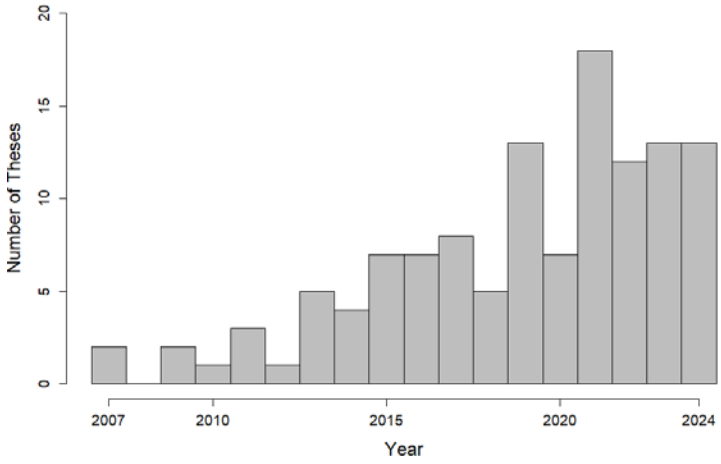

Figure 1. Distribution of Thesis Numbers Over Time.

The theses included Master's, PhD and Specialty in Medicine theses. Majority of theses was Specialty in Medicine theses completed after residency programs and they were almost all specialty in medicine also include one in pharmacy. These theses were conducted at 46 different universities, with the top 10 universities contributing more than 55% of all theses (Table I).

Table 1. Distribution of theses types and top 10 universities contribute most of theses.

	n(%)
Thesis type	
Specialty in Medicine	70(57.8)
Master's	36(29.8)
PhD	15(12.4)
Total	121(100.0)
University	
Sağlık Bilimleri University	19(15.7)
İstanbul University	8(6.6)

Erciyes University	6(5.0)
İstanbul University-Cerrahpaşa	6(5.0)
Marmara University	6(5.0)
Dicle University	5(4.1)
Hacettepe University	5(4.1)
Ondokuz Mayıs University	5(4.1)
Koç University	4(3.3)
Akdeniz University	3(2.5)
Total	67(55.4)

A total of 18 different branches contributed theses on colistin. The top three fields were Microbiology, which accounted for nearly half of the theses with 60 theses (49.6%), Clinical Microbiology and Infectious Diseases with 26 theses (21.5%), and Child Health and Diseases with 6 theses (5%). In the early years, Microbiology and Clinical Microbiology and Infectious Diseases were the primary dominant fields in colistin-related theses. While these fields remain dominant in later years, other branches of science, such as Stem Cell Sciences, Veterinary Microbiology, and Pharmacy and Pharmacology, have also begun to contribute. This trend reflects a growing multidisciplinary interest in colistin research (Figure 2).

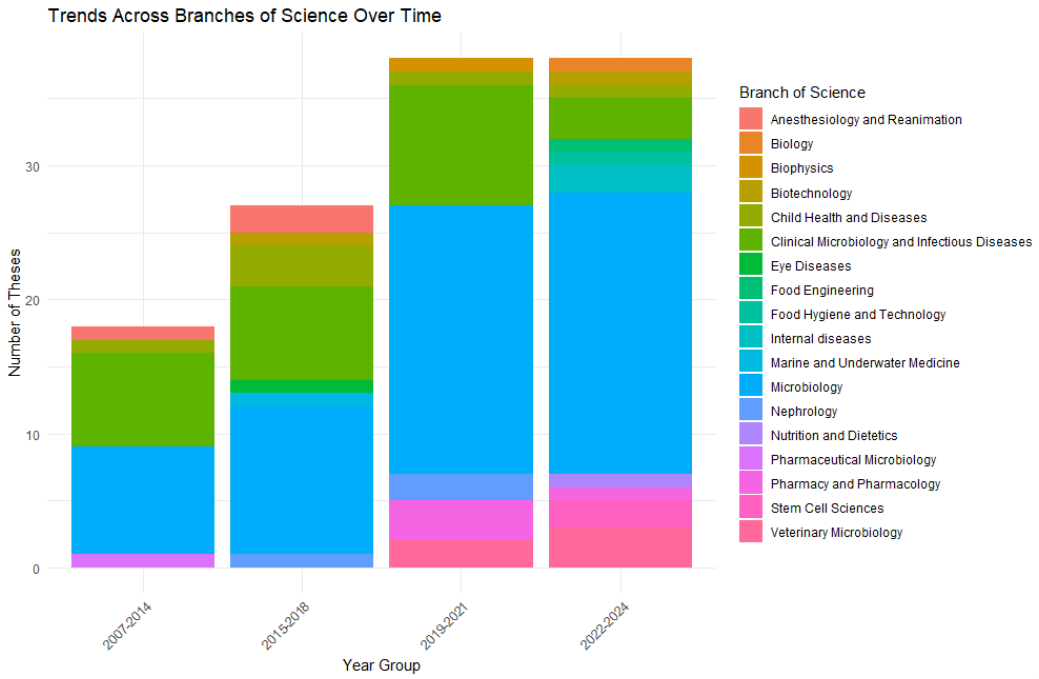

Figure 2. Trends in Colistin-Related Theses by Branch of Science Over Time.

The wordcloud in the name of colistin-related theses highlights the central focus areas in colistin research. The prominent appearance of "colistin" at the center underscores its pivotal role in the studies. Terms such as "resistance", "resistant, "acinetobacter", "baumannii" and "klebsiella" suggest

a significant emphasis on antimicrobial resistance and its impact on specific pathogens. Other notable terms such as "isolates", "strains", "evaluation" and "methods" indicate a focus on laboratory studies, clinical microbiology, and methodological approaches to studying colistin's efficacy and resistance mechanisms. Additionally, words like "combination," "efficacy," and "treatment" highlight the exploration of colistin in combination therapies and its clinical applications. The presence of terms such as "nephrotoxicity" and "intensive care" points to concerns about colistin's adverse effects and its critical role in treating infections in high-risk settings, such as intensive care units. This word cloud reflects a diverse and multidisciplinary approach to colistin research, spanning microbiology, clinical application, and pharmacological studies (Figure 3).

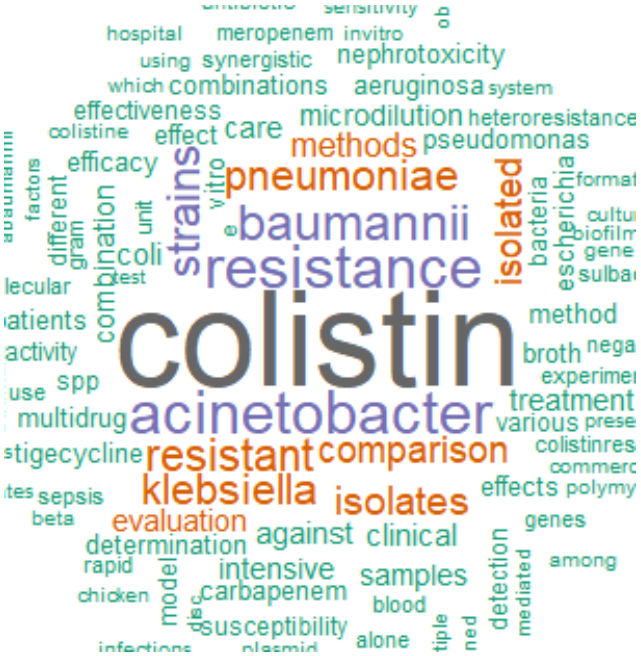

Figure 3. Wordcloud of Title of Theses about Colistin.

Keywords used in the theses are analyzed, and the most frequently used ones are identified. The results align with the word cloud of thesis titles, emphasizing the focus on colistin's effects on specific bacteria, such as *Acinetobacter baumannii* and *Klebsiella pneumoniae*. The findings also highlight key topics, including resistance mechanisms like the Mcr-1 gene, nephrotoxicity and combination therapies, particularly with tigecycline and carbapenem.

The analysis of the top five keywords across four time periods (2007–2024) reveals that the primary focus of colistin-related research has remained largely consistent, with "antibiotic resistance" and key bacterial pathogens such as *Acinetobacter baumannii* and *Klebsiella pneumoniae* being dominant throughout. In the earliest period (2007–2014), "tigecycline" emerged as a notable keyword, reflecting early investigations into alternative treatments alongside colistin. However, in later years,

research interest expanded beyond resistant bacteria and colistin's efficacy to include concerns about its toxicity, as indicated by the growing presence of "nephrotoxicity" in the 2015–2018 and 2019–2021 periods. Additionally, in more recent years (2019–2024), the Mcr-1 gene has gained prominence, reflecting increasing interest in genetic mechanisms contributing to colistin resistance (Table II).

Table 2. Most 5 Frequently Used Keywords in Colistin-Related Theses Over Time.

Keywords	**Frequency**
2007-2014	
Acinetobacter baumannii	13
antibiotic resistance	8
tigecycline	7
pneumonia	4
carbapenem	3
2015-2018	
Antibiotic resistance	10
nephrotoxicity	8
Acinetobacter baumannii	8
Klebsiella pneumoniae	3
Multiple drug resistance	3
2019-2021	
antibiotic resistance	13
Klebsiella pneumoniae	11
Acinetobacter baumannii	10
Mcr-1	8
Nephrotoxicity	4
2022-2024	
Antibiotic resistance	14
Acinetobacter baumannii	11
Klebsiella pneumoniae	8
Mcr-1	8
Escherichia coli	7

When theses were grouped according to research topics, it was seen that the most studied topic in all years was resistance. Combination therapies and monotherapy are among the most frequently researched topics. In addition, it has been found that studies on resistance in colistin-related thesis topics have become increasingly popular in recent years (Figure 4).

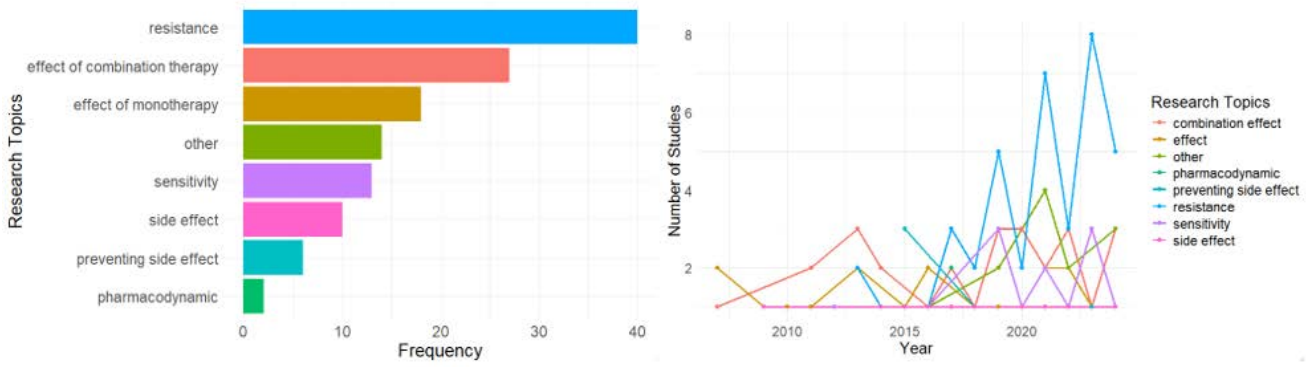

Figure 4. Distribution and Trends over time of Research Topics in Colistin-Related Theses.

As a result of analyzing 15 thesis studies conducted on human subjects that provided consistent data on nephrotoxicity, it was determined that nephrotoxicity rates ranged from 8.3% to 69.6%, with a median value of approximately 50% (Figure 5) (Table III) [6-20].

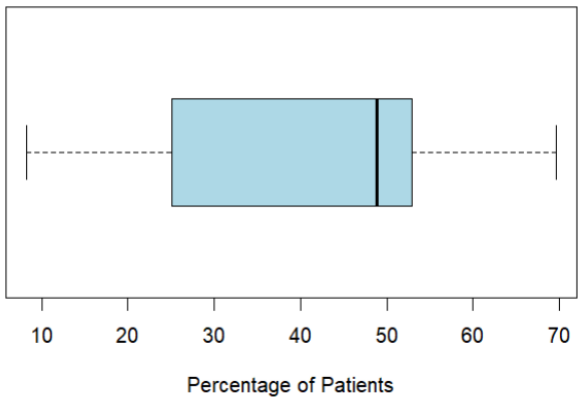

Figure 5. Distribution of Nephrotoxicity Rates Among Patients Using Colistin.

Most studies reported that colistin was used in combination therapy with other antibiotics and, in many cases, with additional medications. Additionally, many patients had underlying comorbidities, and some were critically ill intensive care unit (ICU) patients. Furthermore, the studies encompassed different age groups; some focused exclusively on premature newborns, others on children and adolescents, and some on adults or elderly individuals. Moreover, there were variations in the mode of colistin administration and dosing regimens across studies.

Table 3. A Summary of Colistin-Related Nephrotoxicity in Human Studies.

Title of the Thesis	Patients included/excluded	Nephro toxicity ratio (%)
The comparison of colistin and colistin/sulbactam combination therapies for treatment of multidrug resistant acinetobacter baumannii ventilator associated pneumonia [6]	Age: ≥16; 89 patients with ventilator-associated pneumonia(VAP) due to multiple drug-resistant Acinetobacter baumannii, treated with colistin or colistin/sulbactam	24.7
Nephrotoxicity rates among critically ill patients receiving colistin [7]	Age: >18; 56 patients, not pregnant, no chronic kidney disease history, colistin use >72 hours	69.6
Prospective monitoring of adverse events of colistin treatment in critically ill patients after implementation of a new dosing strategy [8]	Age: >18; 59 ICU (intensive care unit) patients with A. baumannii, colistin use >48 hours; Excluded: nephrotoxicity before >48h colistin treatment, dialysis patients.	52.5
Assessment of colistin treatment in multi-drug resistant gram negatif bacterial infections [9]	Age: >18; 130 patients, normal creatinine, receiving colistin empirically or for targeted therapy.	25.4
The evaluation of colistin efficacy and safety in preterm infants [10]	Birth <37 weeks; 121 patients receiving colistin; excluded: renal or liver dysfunction before treatment.	10.7
Evaluation of efficiacy and safety of low and high dose colistin use in intensive care unit patients who had ventilator-associated pneumonia due to enteric or non-enteric bacteria [11]	Age: ≥17; 185 ICU patients intubated or tracheostomized ≥48h with clinical VAP diagnosis, receiving colistin for MDR(multi drug resistant) K. pneumoniae, A. baumannii, or Pseudomonas spp.	51.4
Colymisin treatment effectiveness by loading dose in infections caused by multiresistant gram-negative bacteria [12]	Age: >18; study sample: 323 randomly selected from 896 hospitalized patients receiving appropriate-dose colistin.	53.3
Retrospective evaluation of the colistin- related nephrotoxicity rates and effectiveness of C vitamin use to prevent nephrotoxicity [13]	Age: >18; 100 patients receiving colistin (empirically or targeted) and with daily creatinine monitoring; Excluded: chronic kidney failure, dose adjustment prior to treatment, and contrast use for imaging during therapy.	52.0
Monitoring and evaluation of colistin blood level at intensive care units [14]	Age >18; 30 ICU patients with multi-drug resistant gram-negative infections treated with IV colistin for ≥3 days included. Excluded: receiving renal replacement therapy before treatment or with advanced kidney failure.	40.0
Comparison of ABH development related to the use of colistin in the stage 3 intensive care unit according to RIFLE and KDIGO[15]	145 ICU patients with >48 hours of colistin treatment; excluded: those diagnosed with chronic kidney failure on ICU admission or the day colistin started.	53.8
Investigation of neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid binding protein (l-FABP) levels in the urinary for early detection of nefrotoxicity asociated colistin therapy [16]	Age: >18, 45 ICU patients with ≥5 days of colistin treatment, no pre-treatment acute or chronic renal failure, no other nephrotoxic drugs, and urine samples collected on the 3rd, 5th, and 7th days of treatment; Excluded: history of malignancy, autoimmune disease, or trauma/invasive procedure in the past week.	48.9
Evaluation of biochemical parameters and intensive care scores in child intensive care patients using colistin [17]	Age: 0-18, 48 patients who received ≥10 doses or >120 hours of intravenous (IV) colistin treatment, either empirically or documented by culture; Excluded: neonates	8.3
Comparison of kim-1, NGAL and il-18 biomarkers as early markers in prognosis of colistin nephrotoxicity [18]	Age >18, 58 patients on colistin; excluded: pre-treatment renal failure, contrast use in the last 3 days, pregnancy, sepsis, moderate/high-dose norepinephrine during the study, PCR positive COVID-19 patients within 10 days, and those receiving concurrent nephrotoxic agents.	36.2
Investigation of the effect of colistin monotherapy and colistin-meropenem combine therapy on mortality in patients with colistin-resistant a.baumannii bacteriama in Ankara City Hospital intensive care unit [19]	Age: ≥18; Carbapenem-resistant A. baumannii infection, 160 ICU patients: 62 on colistin, 98 on colistin+meropenem; excluded: growth of other Acinetobacter species or polymicrobial growth in blood cultures, colistin resistance in antibiogram, and colistin treatment <48 hours.	20.0
Comparison of renal function tests of intensive care unit patients using polymyxin or colistin [20]	Age: >18, <80; 93 ICU patients who received ≥7 days of colistin; excluded: received both polymyxin B and colistin, history of renal replacement therapy (RRT) or RRT during ICU stay.	64.5

Discussion

Since the first colistin-related thesis was published in the National Thesis Center database database in 2007, the number of theses focusing on colistin has gradually increased. This trend aligns with colistin-related research indexed in Pubmed. A PubMed search for the term "colistin" reveals that studies on colistin were relatively popular before the mid-1970s, experienced a decline, and then significantly increased after the early 2000s, corresponding to its renewed clinical use [21]. In 2020, a bibliometric analysis based on the Scopus database examined colistin resistance in Klebsiella pneumoniae and found that 50.2% of the research published between 2017 and 2019 focused on this topic [22]. Another bibliometric study, conducted in 2019 using Scopus data, revealed that while only 35 publications on colistin were available between 1973 and 2009, this number rose to 1,070 between 2010 and 2019 [23], further highlighting the growing academic interest in colistin.

Among the universities contributing the most to colistin-related research, “Sağlık Bilimleri Üniversitesi” (University of Health Sciences) ranks first. This is likely due to its extensive network of 60 training and research hospitals across Türkiye[24]. Given the breadth of clinical settings affiliated with this institution, it is unsurprising that it leads in the number of contributions. Other leading universities are among Türkiye’s oldest institutions, with large faculty and student populations, reflecting their established research capacity.

From 2007 to 2014, nearly all colistin-related theses were conducted in Microbiology and Clinical Microbiology and Infectious Diseases departments. However, in recent years, a noticeable increase in contributions from other scientific disciplines indicates growing multidisciplinary interest in colistin research, expanding beyond its traditional fields.

The findings of the keyword analysis indicate that antibiotic resistance, nephrotoxicity, targeted bacterial pathogens, and combination therapies are among the most frequently studied topics in colistin-related research. In recent years, the Mcr-1 gene, one of the key resistance mechanisms, has also gained significant research interest[25]. A PubMed search for “Mcr-1 and colistin” shows that the first article appeared in 2015, with a gradual increase in publications thereafter, peaking in 2021[26]. This shift suggests a broader research focus, transitioning from an emphasis on alternative treatments and resistant pathogens to a deeper exploration of colistin’s limitations, genetic resistance mechanisms, and clinical side effects, while still maintaining strong attention on key bacterial threats.

The variability in nephrotoxicity levels reported in studies conducted on human subjects may be attributed to differences in study methodologies. Inclusion criteria vary across studies, and differences exist in age groups, underlying diseases, comorbidities, and reasons for hospitalization among patient populations [6-20]. Additionally, most patients were receiving multiple pharmacological agents

alongside colistin [6-14,17,19]. Moreover, there were variations in the mode of colistin administration and dosing regimens across studies, which could have influenced nephrotoxicity outcomes. Therefore, nephrotoxicity cannot be solely attributed to colistin, as multiple factors likely contribute to its occurrence.

The variability in levels of nephrotoxicity reported in human studies may be attributable to differences in study methodologies. Inclusion criteria vary between studies and there are differences among patient populations in terms of age groups, underlying diseases, comorbidities and reasons for hospitalization. Additionally, it has been found that most patients use multiple pharmacological agents alongside colistin. In addition, the method of application and dosing regimens of colistin also vary between studies, which can be considered as a factor that may affect nephrotoxicity results. Therefore, nephrotoxicity cannot be attributed solely to colistin, as multiple factors may contribute to this condition.

Strengths and Limitations:

The primary strength of this study is its comprehensive inclusion of all colistin-related theses conducted in Türkiye, as publishing in the National Thesis Center database of the Council of Higher Education is mandatory. This ensures a complete and systematic analysis of research trends in the field. Additionally, the study provides valuable insights into multidisciplinary contributions and evolving topics, such as antimicrobial resistance and combination therapies, through bibliometric and keyword analyses.

The main limitation of this study is that it only includes theses published in Türkiye, excluding studies conducted in other countries and other types of research. Additionally, apart from the 15 studies on human subjects that examined nephrotoxicity, only the abstracts and descriptive data of the remaining theses were analyzed, without a detailed examination of their full content or findings.

Conclusion:

This study provides a comprehensive analysis of colistin-related research in Türkiye, providing valuable information on research trends and multidisciplinary contributions. By examining the theses in the National Thesis Center database, it has been revealed that colistin is an important focal point in academic research. Although the study has limitations such as being limited to Türkiye and relying on abstracts rather than full-text analyses, it provides a basis for future studies, particularly in addressing emerging challenges such as resilience and interdisciplinary research.

Conflict of interest: None

Funding: Self-funded

References

1. **Li J, Nation RL, Turnidge JD, et al.** Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infect Dis. 2006;6(9):589-601. doi:10.1016/S1473-3099(06)70580-1.
2. **Nation RL, Li J.** Colistin in the 21st century. Curr Opin Infect Dis. 2009;22(6):535-543. doi:10.1097/QCO.0b013e328332e672.
3. **El-Sayed Ahmed MAEG, Zhong LL, Shen C, et al.** Colistin and its role in the era of antibiotic resistance: an extended review (2000–2019). Emerg Microbes Infect. 2020;9:868–885. doi:10.1080/22221751.2020.1754133.
4. **Bostanghadiri N, Narimisa N, Mirshekar M, et al.** Prevalence of colistin resistance in clinical isolates of Acinetobacter baumannii: a systematic review and meta-analysis. Antimicrob Resist Infect Control. 2024;13(1):24. doi:10.1186/s13756-024-01376-7.
5. **Mirjalili M, Mirzaei E, Vazin A.** Pharmacological agents for the prevention of colistin-induced nephrotoxicity. Eur J Med Res. 2022;27(1):64. doi:10.1186/s40001-022-00689-w.
6. **Kalın G.** The comparison of colistin and colistin/sulbactam combination therapies for treatment of multidrug resistant Acinetobacter baumannii ventilator-associated pneumonia. Specialty Thesis in Medicine, Clinical Microbiology and Infectious Diseases. Erciyes Üniversitesi; 2013. Kayseri.
7. **Özkarakaş H.** Nephrotoxicity rates among critically ill patients receiving colistin. Specialty Thesis in Medicine, Anesthesiology and Reanimation. İzmir Tepecik Eğitim Hastanesi; 2014. İzmir.
8. **Özel AS.** Prospective monitoring of adverse events of colistin treatment in critically ill patients after implementation of a new dosing strategy. Specialty Thesis in Medicine, Clinical Microbiology and Infectious Diseases. Marmara University; 2015. İstanbul.
9. **Çoşkun B.** Assessment of colistin treatment in multi-drug resistant gram-negative bacterial infections. Specialty Thesis in Medicine, Clinical Microbiology and Infectious Diseases. Ankara University; 2015. Ankara.
10. **Cantay B.** The evaluation of colistin efficacy and safety in preterm infants. Specialty Thesis in Medicine, Child Health and Diseases. Kahramanmaraş Sütçü İmam University; 2016. Kahramanmaraş.
11. **Aliyev V.** Evaluation of efficacy and safety of low and high dose colistin use in intensive care unit patients who had ventilator-associated pneumonia due to enteric or non-enteric bacteria. Specialty Thesis in Medicine, Clinical Microbiology and Infectious Diseases. İstanbul University; 2016. İstanbul.
12. **Dindar Demiray EK.** Colymsin treatment effectiveness by loading dose in infections caused by multiresistant gram-negative bacteria. Specialty Thesis in Medicine, Clinical Microbiology and Infectious Diseases. Manisa Celal Bayar University; 2018. Manisa.
13. **Moroğlu Ç.** Retrospective evaluation of the colistin-related nephrotoxicity rates and effectiveness of vitamin C use to prevent nephrotoxicity. Specialty Thesis in Medicine, Clinical Microbiology and Infectious Diseases. Sağlık Bilimleri University; 2018. İstanbul.
14. **Ecemiş S.** Monitoring and evaluation of colistin blood level at intensive care units. Pharmacy and Pharmacology Master's Thesis. Hacettepe University; 2019. Ankara.
15. **Keserci Ö.** Comparison of ABH development related to the use of colistin in stage 3 intensive care unit according to RIFLE and KDIGO. Specialty Thesis in Medicine, Internal Medicine. Dicle University; 2020. Diyarbakır.

16. **Özkaraman Y.** Investigation of neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid binding protein (l-FABP) levels in the urinary for early detection of nephrotoxicity associated with colistin therapy. Specialty Thesis in Medicine, Clinical Microbiology and Infectious Diseases. Sağlık Bilimleri University; 2021. Antalya.
17. **Aksoy P.** Evaluation of biochemical parameters and intensive care scores in child intensive care patients using colistin. Specialty Thesis in Medicine, Child Health and Diseases. Sağlık Bilimleri University; 2022. İstanbul.
18. **Cengiz B.** Comparison of KIM-1, NGAL, and IL-18 biomarkers as early markers in prognosis of colistin nephrotoxicity. Specialty Thesis in Medicine, Internal Diseases. Sağlık Bilimleri University; 2022. Ankara.
19. **Akça HN.** Investigation of the effect of colistin monotherapy and colistin-meropenem combined therapy on mortality in patients with colistin-resistant A. baumannii bacteremia in Ankara City Hospital Intensive Care Unit. Specialty Thesis in Medicine, Clinical Microbiology and Infectious Diseases. Ankara Yıldırım Beyazıt University; 2023. Ankara.
20. **Tutar Selçuk MF.** Comparison of renal function tests of intensive care unit patients using polymyxin or colistin. Specialty Thesis in Medicine, Internal Diseases. Tekirdağ Namık Kemal University; 2024. Tekirdağ.
21. PubMed. Search for "colistin". National Library of Medicine. Available at: https://pubmed.ncbi.nlm.nih.gov/?term=colistin. Accessed December 21, 2024.
22. **Nwabor OF, Terbtothakun P, Voravuthikunchai SP, Chusri S.** A bibliometric meta-analysis of colistin resistance in Klebsiella pneumoniae. Diseases. 2021;9(2):44. doi:10.3390/diseases9020044.
23. **Yacouba A, Olowo-Okere A.** Global trends and current status in colistin resistance research: a bibliometric analysis (1973-2019). F1000Research. 2020 Jul 31;9:856. doi:10.12688/f1000research.25124.1.
24. Sağlık Bilimleri Üniversitesi. Tarihçemiz. Available at: https://sbu.edu.tr/universitemiz/kurumsal-bilgilerimiz/tarihcemiz/. Accessed December 24, 2024.
25. **Liu YY, Wang Y, Walsh TR, et al.** Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis. 2016 Feb;16(2):161-8. doi:10.1016/S1473-3099(15)00424-7.
26. PubMed. Search for "colistin". National Library of Medicine. Available at: https://pubmed.ncbi.nlm.nih.gov/?term=mcr1+and+colistin. Accessed February 2, 2025.