International Journal of Pharmacognosy and Life Science

**E-ISSN:** 2707-2835
**P-ISSN:** 2707-2827
www.pharmacognosyjournal.com
IJPLS 2023; 4(2): 77-82
Received: 22-09-2023
Accepted: 26-10-2023

**Noor NAA Alhafidh**
Nineveh Health Directorate, Mosul, Iraq

**Ibrahim M Faisal**
College of Medicine, University of Mosul, Mosul, Iraq

**Mohammed G Saeed**
College of Veterinary Medicine, University of Mosul, Mosul, Iraq

**Corresponding Author:**
**Noor NAA Alhafidh**
Nineveh Health Directorate, Mosul, Iraq

# Beta carotene provides neuroprotection against amikacin induced toxicity

**Noor NAA Alhafidh, Ibrahim M Faisal and Mohammed G Saeed**

**DOI:** https://doi.org/10.33545/27072827.2023.v4.i2a.94

**Abstract**
**Background and objectives:** Beta carotene is a precursor of vitamin A and acts as a potent antioxidant in the body. Beta carotene, as an antioxidant, helps to protect cells from damage caused by these free radicals. This study aimed at investigating the cytoprotection provided by beta carotene against amikacin induced brain damage.
**Methods:** To do so, four groups of animals were used (seven rats in each group): the control group, the amikacin group, the beta carotene with the amikacin group, and the group given beta carotene first, then added amikacin later together with the beta carotene.
**Results:** The results revealed that amikacin has disrupted the brain architecture resulting in vascular congestion, brain oedema, and cellular vacuolization while beta carotene has protected the cells architecture maintain cellular architecture and providing tissue protection in particular in the group were beta carotene has administered before amikacin.
**Conclusion:** Beta-carotene has emerged as a promising therapeutic agent for reducing the neurotoxic effects induced by amikacin. Through histological findings, it has been demonstrated that beta-carotene exerts its protective effects by preserving neuronal integrity, reducing oxidative stress, and modulating neuroinflammatory responses. Further research is warranted to explore the exact mechanisms by which beta-carotene confers neuroprotection and to determine the optimal dosage and duration of treatment. Nonetheless, these findings highlight the potential of beta-carotene as a useful adjunct therapy in the management of amikacin-induced neurotoxicity.

**Keywords:** Amikacin, beta carotene, neurotoxicity, brain histology

## Introduction
Amikacin is a potent antibiotic that falls under the aminoglycoside class of drugs. It is primarily used in the treatment of severe bacterial infections caused by Gram-negative bacteria, including strains that are resistant to other antibiotics [1]. Amikacin works by inhibiting bacterial protein synthesis, preventing the production of essential proteins necessary for bacterial growth and survival [2]. This mechanism of action makes it an effective choice for treating infections caused by multidrug-resistant bacteria [3]. Amikacin is commonly used to treat respiratory tract infections, urinary tract infections, skin and soft tissue infections, bone and joint infections, and certain types of bloodstream infections [4]. It is often reserved for serious infections or cases where other antibiotics have failed due to its potential for side effects, including kidney and hearing damage [5]. Amikacin is usually administered intravenously or intramuscularly, and the dosage is determined based on the patient's age, weight, renal function, and the severity of the infection [6]. Close monitoring of kidney function and therapeutic drug monitoring are essential to ensure the drug's efficacy and minimize potential toxicity [7]. Despite its impressive efficacy against resistant bacteria, amikacin should be used judiciously and in accordance with antimicrobial stewardship principles to prevent the emergence of further drug resistance.
One of the crucial factors to consider when selecting an antibiotic is its ability to penetrate the blood-brain barrier (BBB) and reach the central nervous system (CNS) to effectively treat infections in the brain [8]. The blood-brain barrier is a highly selective semipermeable membrane that separates the circulating blood from the brain and spinal cord. It acts as a protective barrier, preventing the entry of harmful substances into the brain while allowing the passage of essential nutrients and molecules [9]. However, this barrier also poses a challenge when it comes to delivering drugs to the brain.

Fortunately, amikacin has demonstrated the ability to cross the blood-brain barrier, making it an effective treatment option for CNS infections caused by susceptible bacteria [10]. Studies have shown that amikacin can achieve therapeutic concentrations in the cerebrospinal fluid (CSF) after systemic administration, indicating its ability to penetrate the blood-brain barrier [11]. This property is particularly important in cases of meningitis, where the infection affects the meninges, the protective membranes surrounding the brain and spinal cord [12]. By crossing the blood-brain barrier, amikacin can directly target the bacteria causing the infection in the CNS, increasing the likelihood of a successful treatment outcome [10]. However, it is worth noting that the penetration of amikacin across the blood-brain barrier can vary depending on factors such as the dose, duration of treatment, and the presence of inflammation or disruption of the barrier [11]. Therefore, it is essential to consider these factors when prescribing amikacin for CNS infections. Overall, the ability of amikacin to cross the blood-brain barrier makes it a valuable antibiotic in the treatment of CNS infections, providing clinicians with an effective tool to combat bacterial infections in the brain [12].

Beta carotene is a naturally occurring pigment found in various fruits and vegetables, particularly in orange and yellow ones like carrots, sweet potatoes, and apricots [13]. Apart from its role as a precursor to vitamin A, beta carotene has gained significant attention for its potential neuroprotective properties [14]. Neuroprotection refers to the preservation of neuronal structure and function, ultimately leading to the prevention or delay of neurodegenerative diseases [15]. Numerous studies have suggested that beta carotene may play a crucial role in protecting the brain from oxidative stress and inflammation, both of which are implicated in the development and progression of conditions like Alzheimer's disease and Parkinson's disease [13]. As an antioxidant, beta carotene helps neutralize harmful free radicals that can damage brain cells and contribute to cognitive decline [14]. Additionally, it has been shown to modulate various signaling pathways involved in inflammation, thus reducing the risk of chronic neuroinflammation [15]. Furthermore, beta carotene may also support cognitive function by promoting the growth and development of new neurons, a process known as neurogenesis [13]. This compound's ability to enhance brain health and potentially prevent neurodegenerative diseases makes it a subject of great interest in the field of neuroscience [14]. However, further research is needed to fully understand the mechanisms underlying beta carotene's neuroprotective effects and to determine the optimal dosage and mode of administration for therapeutic purposes [15].

In the present study, we aimed to characterize the role of beta carotene in providing brain protection against amikacin induced neurotoxicity using rat model.

## Materials and Methods

Animals: In this study, a group of thirty-five male albino rats was chosen as the subjects, with an average weight ranging between 200 and 250 grams. These rats were obtained from the animal house in the College of Veterinary Medicine at the University of Mosul, ensuring that they were kept under controlled temperature conditions. The use of albino rats in research is common due to their physiological and genetic similarities to humans, making them suitable models for various scientific investigations. The rats were fed commercial pellets, which are widely used in laboratory settings to ensure consistent and standardized nutrition for the animals. By maintaining a controlled diet, researchers can eliminate potential confounding factors that may arise from variations in food intake. These experimental conditions will contribute to the accuracy and reliability of the findings obtained from this study.

Study settings: In this study, the effects of different treatments on rats were investigated. The control group consisted of rats that drank distilled water for a period of 23 days. Another group, the AMiKacin group, received 150 mg/kg/day of AMiKacin intraperitoneally for a duration of two weeks. The Beta carotene group, on the other hand, received 100 mg/kg/day of Beta carotene orally for a period of 9 days. Intriguingly, there was also a group that received both Beta carotene and AMiKacin simultaneously. This group, known as the Beta carotene + AMiKacin group, received 150 mg/kg/day of AMiKacin intraperitoneally and 100 mg/kg/day of Beta carotene orally for two weeks. This combination treatment aimed to explore any potential synergistic effects between the two substances. Furthermore, there was a unique group that received Beta carotene initially and then underwent a change in treatment. This group, referred to as the Beta carotene → (Beta carotene + AMiKacin) group, first received 100 mg/kg/day of Beta carotene orally for 9 days. After this initial period, the same group was then administered 150 mg/kg/day of AMiKacin intraperitoneally, while continuing to receive 100 mg/kg/day of Beta carotene orally for an additional two weeks.

Materials: In this study, the beta carotene utilized for the research was sourced from Turkey and manufactured by the reputable company PHARMAROYA®. Turkey, known for its rich agricultural resources, is renowned for producing high-quality ingredients for various industries, including pharmaceuticals. The beta carotene imported from Turkey underscores the commitment to obtaining top-notch components for the study, ensuring accurate and reliable results. Furthermore, the manufacturer, PHARMAROYA®, is recognized for its adherence to strict quality control measures and its dedication to producing pharmaceutical-grade substances. Additionally, the Aikacin 500 mg employed in this study was procured from local pharmacies in Iraq and manufactured by MedoChemie® in Cyprus. The availability of Aikacin from local pharmacies in Iraq emphasizes the accessibility and widespread use of this medication in the region. MedoChemie®, an esteemed pharmaceutical company based in Cyprus, specializes in the production of a wide range of high-quality medicines. The inclusion of Aikacin in the study highlights its relevance and importance in the field of medicine, specifically in the context of the research being conducted.

Histological analysis: In this study, the kidneys from each rat were carefully removed and subsequently divided into lobes after thorough cleaning. To ensure proper preservation and analysis, the lobes were fixed in 10% neutral buffered formalin, a commonly used fixative in histology. After fixation, the lobes were embedded in paraffin, a process that helps to provide structural support during sectioning for microscopy. The paraffin-embedded blocks were then cut into thin slices, measuring approximately 4-5 µm in thickness. These slices were stained with hematoxylin and eosin (H-E), a widely utilized staining technique in histopathological analysis. The H-E staining allows for visualization of cellular structures and tissue architecture, providing valuable information about any alterations or

abnormalities present. Following staining, the slides were meticulously examined using a light microscope, specifically the Olympus BX50 model, which offers high-resolution imaging capabilities. To ensure unbiased evaluations, all histological assessments were performed twice under blind conditions, meaning the evaluators were unaware of the specific treatment being investigated. This rigorous approach helps to minimize potential bias and ensures the validity and reliability of the study's findings. Overall, this methodology provides a comprehensive and systematic approach to studying the renal histology and allows for accurate analysis of potential treatment effects or pathological changes in the kidneys of the rats.

**Results**

The rat's brain of the control group exhibits a remarkable display of normal architectures within its cortex. The neurons (N) present in the cortex showcase a well-organized and intricate network, forming the foundation of the brain's functionality. Alongside the neurons, the glial cells (G) play a crucial role in supporting and protecting the neurons, ensuring their optimal functioning. The blood vessels (bv) can be observed traversing through the cortex, providing essential nutrients and oxygen to the brain cells, ensuring their survival and efficient operation. Moving on to the hippocampus, the molecular cell layer (MCL) within this region also displays a normal architecture, with its intricate arrangement of cells facilitating communication and information processing. The granular cell layer (GCL) further adds to the complexity, contributing to the hippocampus's role in memory formation and consolidation. Lastly, the Purkinje cells (PC) can be observed within the hippocampus, exhibiting a well-structured arrangement that is essential in coordinating motor movements and maintaining balance. Overall, the control group's rat brain showcases the healthy and functional architectures of its neurons, glial cells, blood vessels, as well as the molecular cell layer, granular cell layer, and Purkinje cells within the cortex and hippocampus (Figure 1).

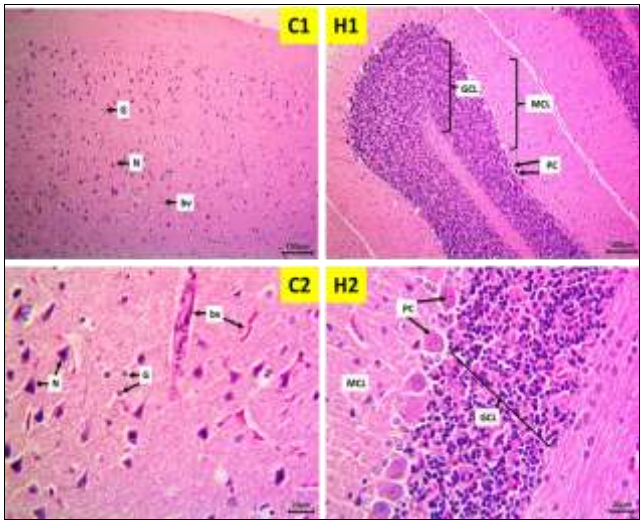


**Fig 1:** (C) A representative images of rat's brain of the control group showing the cortex with normal architectures of neurons (N), glial cells (G) and blood vessels (bv), (C1) Scale bar= 100 µm. (C2) Scale bar= 20µm. (H) A representative images rat's brain of the control group showing the hippocampus with normal architectures of molecular cell layer (MCL), granular cell layer (GCL), and Purkinje cells (PC). (H1) Scale bar= 100 µm. (H2) Scale bar= 20µm, H&E stain.

The examination of the rat brain from the Amikacin treated group reveals notable findings such as focal gliosis and congestion of blood vessels. Additionally, there is evidence of vacuolization surrounding neurons and vasogenic edema, indicating potential damage to the brain tissue. In comparison, the rat brain from the Amikacin with Beta-carotene treated group also shows congestion of blood vessels and vasogenic edema, suggesting that the administration of Beta-carotene did not alleviate these conditions. However, it is important to note that the rat brain from the Beta-carotene administration then Amikacin with Beta-carotene treated group exhibits a different outcome. In this case, the brain tissue displays a normal architecture of both nerve cells and glial cells. While there is a mild congestion of blood vessels, overall, the structure appears to be intact and healthy. These observations indicate that the administration of Beta-carotene prior to Amikacin treatment may have a protective effect, preserving the normal cellular architecture and reducing the occurrence of vascular congestion and edema in the rat brain (Figure 2).

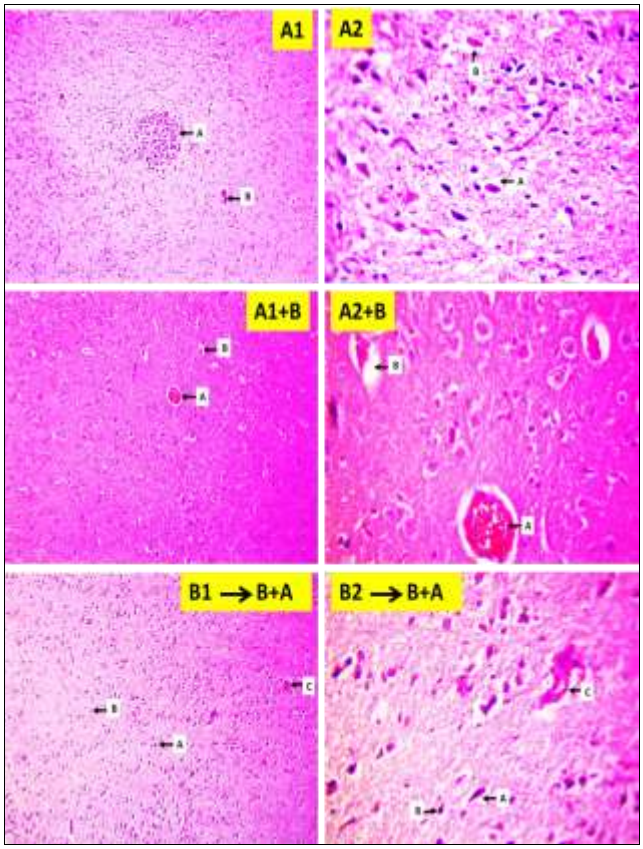


**Fig 2:** (A1 and A2) A representative images of rat brain of Amikacin treated group (A1) shows focal gliosis (A) and congestion of blood vessels (B). 100X. (A2) shows vacuolization surrounding neurons (A) and vasogenic edema (B). 400X. (A1+B) A representative images of rat brain of Amikacin with Beta-carotene treated group shows congestion of blood vessels (A) and vasogenic edema (B). H&E stain, 100X. (A2+B) A representative images of rat brain of Amikacin with Beta-carotene treated group shows congestion of blood vessels (A) and vasogenic edema (B). 400X. (B1 to B+A) A representative images of rat brain of Beta-carotene administration then Amikacin with Beta-carotene treated group shows normal architecture of nerve cells (A) and glial cells (B) with mild congestion of blood vessels (C). 100X. (B1 to B+A) A representative images of rat brain of Beta-carotene administration then Amikacin with Beta-carotene treated group shows normal architecture of nerve cells (A), glial cells (B) and blood vessels (C). 400X. H&E stain.

The rat brain of the amikacin group exhibits several notable findings. Firstly, there is congestion of blood vessels observed in the cortex of the cerebellum and meninges. Additionally, periaxonal and vasogenic edema are present, further indicating the pathological changes in this group. Furthermore, the rat brain of the amikacin with beta carotene group displays hemorrhage in the meninges, along with gliosis and congestion of blood vessels. These findings suggest that the administration of amikacin in combination with beta carotene may contribute to these specific alterations in the brain. Moreover, the rat brain of the beta carotene pretreated group, with continuous beta carotene use during amikacin exposure, reveals hemorrhage and congestion of blood vessels in the meninges. Similarly, congestion of blood vessels, periaxonal and vasogenic edema in the cortex of the cerebellum, accompanied by neuronophagia, are observed. These findings highlight the potential effects of beta carotene pretreatment in combination with amikacin, emphasizing the importance of further investigation into the underlying mechanisms and potential therapeutic interventions (Figure 3).

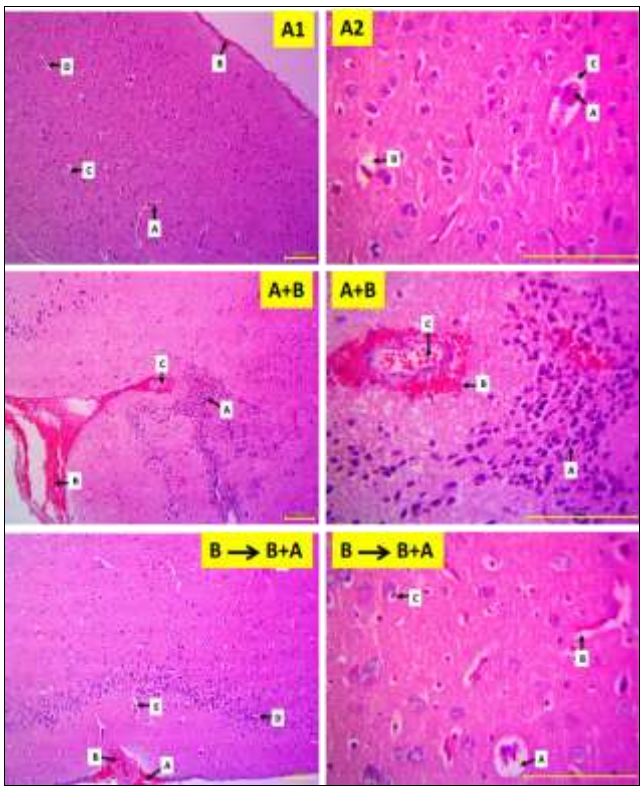


**Fig 3:** (A1 and A2) A representative images of rat brain of amikacin group (A1) shows congestion of blood vessels in the cortex of cerebellum (A) and meninges (B), periaxonal (C) and vasogenic edema (D). Scale bar = 100 µm. (A2) A representative images of rat brain of amikacin group shows congestion of blood vessels in the cortex of cerebellum (A), periaxonal (B) and vasogenic edema (C). Scale bar = 100 µm.(A+B) A representative images of rat brain of amikacin+beta carotene group shows hemorrhage in the meninges (A), gliosis (B) and congestion of blood vessels (C). Scale bar = 100 µm. (A+B) A representative images of rat brain of amikacin+beta carotene group shows gliosis (A), perivascular hemorrhage (B) and congestion of blood vessels in the cortex of cerebellum (C). Scale bar = 100 µm. (B to B+A) A representative images of rat brain of beta carotene pre-treated group shows hemorrhage (A) and congestion of blood vessels (B) in the meninges, congestion of blood vessels (C), periaxonal (D) and vasogenic edema (E) in the cortex of cerebellum. Scale bar = 100 µm. (B to B+A) A representative images of rat brain of beta carotene pre-treated group shows periaxonal (A) and vasogenic edema (B) with neuronophagia (C) (destruction of neurons by microglial cells) in the cortex of cerebellum. Scale bar = 100 µm. H&E stain.

## Discussion

The results of the study indicated that amikacin, a commonly used antibiotic, has had detrimental effects on the brain architecture. The administration of amikacin led to various negative outcomes, including vascular congestion, brain edema, and cellular vacuolization. These findings suggest that amikacin may disrupt the normal functioning of the brain, potentially leading to significant health complications. However, the study also revealed a potential solution to counteract the damaging effects of amikacin. It was observed that beta carotene, a precursor of vitamin A, played a protective role in maintaining the cellular architecture and providing tissue protection. In particular, when beta carotene was administered before amikacin, it demonstrated a significant ability to safeguard the brain cells against the adverse effects of the antibiotic. This suggests that beta carotene may have a beneficial impact on brain health and could potentially serve as a preventive measure when using medications that may have detrimental effects on brain architecture. Further research is needed to explore the mechanisms through which beta carotene exerts its protective effects and to determine the optimal dosage and timing for its administration in the context of amikacin treatment.

The exact mechanisms through which amikacin exerts its neurotoxic effects are not yet fully understood, but several hypotheses have been proposed. One possible mechanism is the disruption of mitochondrial function, leading to impaired energy production and increased oxidative stress within the neurons [16]. This oxidative stress can result in the generation of reactive oxygen species, causing cellular damage and apoptosis [17]. Additionally, amikacin has been shown to interfere with the normal function of neurotransmitters, such as gamma-aminobutyric acid (GABA), glutamate, and acetylcholine, which are crucial for proper neuronal communication [18]. This disruption in neurotransmitter balance can lead to excitotoxicity, where excessive activation of certain receptors, such as N-methyl-D-aspartate (NMDA) receptors, causes an influx of calcium ions into the neurons, triggering a cascade of events that eventually leads to neuronal death [19]. Furthermore, amikacin-induced neurotoxicity may also be attributed to its ability to disrupt the blood-brain barrier (BBB), a protective barrier that separates the CNS from the bloodstream [8]. By compromising the integrity of the BBB, amikacin may allow the entry of inflammatory cells and toxic substances into the CNS, further exacerbating neuroinflammation and neuronal damage [8]. Overall, while amikacin is an essential antibiotic for treating life-threatening infections, healthcare professionals need to be aware of its potential neurotoxic effects and carefully monitor patients receiving this medication, particularly those with pre-existing CNS conditions or compromised renal function.

Beta carotene, a precursor of vitamin A, has been recognized for its numerous health benefits, particularly in relation to neuroprotection against neuronal damage in the central nervous system (CNS) [13]. Extensive research has shown that beta carotene possesses potent antioxidant properties, which play a crucial role in combating oxidative

stress, a major contributor to neuronal damage [14]. By scavenging these free radicals, beta carotene helps to reduce oxidative stress, thereby protecting neurons from damage [15]. Additionally, beta carotene has been found to exhibit anti-inflammatory properties, which further contribute to its neuroprotective effects [14]. Inflammation is a key factor in various neurodegenerative diseases, such as Alzheimer's and Parkinson's, and by reducing inflammatory responses, beta carotene helps to mitigate neuronal damage. Furthermore, beta carotene has been shown to enhance the expression of neurotrophic factors, such as brain-derived neurotrophic factor, which promote the growth, survival, and maintenance of neurons. These factors play a crucial role in neuroplasticity, the brain's ability to adapt and form new connections, thereby contributing to the overall health and function of the CNS [19]. Overall, the neuroprotective properties of beta carotene make it an essential nutrient for maintaining and promoting brain health, and its inclusion in a well-balanced diet or as a supplement may have significant implications for the prevention and treatment of various neurological disorders [18].

Beta carotene, a precursor of vitamin A and a powerful antioxidant, has been studied for its potential protective effects against ototoxicity and nephrotoxicity induced by amikacin, a widely used antibiotic [20]. Amikacin, although effective in treating various bacterial infections, has been associated with these harmful side effects, which can lead to hearing loss and kidney dysfunction [19]. However, research suggests that beta carotene may offer a protective mechanism against these adverse effects. Studies have shown that beta carotene possesses antioxidant properties that can scavenge free radicals, which are highly reactive molecules that can cause cellular damage [14]. The oxidative stress caused by amikacin is believed to contribute to the development of ototoxicity and nephrotoxicity [19]. By neutralizing these free radicals, beta carotene may help reduce the oxidative stress and subsequent cellular damage in the auditory system and kidneys [20]. Furthermore, beta carotene has also been found to possess anti-inflammatory properties. Inflammation plays a crucial role in the development and progression of ototoxicity and nephrotoxicity [19]. By suppressing inflammatory responses, beta carotene may help mitigate the inflammatory damage caused by amikacin, thereby protecting against the adverse effects on the auditory system and kidneys [20]. Several animal studies have provided promising results regarding the potential protective effects of beta carotene against ototoxicity and nephrotoxicity induced by amikacin [19, 20]. These studies have demonstrated that beta carotene supplementation can reduce the severity of hearing loss and kidney damage caused by amikacin administration. However, more research is needed to fully understand the underlying mechanisms and determine the optimal dosage and duration of beta carotene supplementation. Additionally, human clinical trials are necessary to validate these findings and assess the safety and efficacy of beta carotene in preventing amikacin-induced ototoxicity and nephrotoxicity.

## Conclusion

In a study conducted on laboratory animals, it was observed that the administration of amikacin led to significant histological alterations in the nervous tissue, particularly in the form of neuronal degeneration and cell death. However, when beta-carotene was co-administered with amikacin, these histological changes were markedly reduced. The neuroprotective effects of beta-carotene were evident in the preservation of neuronal integrity, prevention of cellular damage, and reduction in the extent of neuroinflammation.

## References


1. Ramirez MS, Tolmasky ME. Amikacin: uses, resistance, and prospects for inhibition. Molecules. 2017 Dec 19;22(12):2267. https://doi.org/10.3390/molecules22122267.
2. Tenover FC. Mechanisms of antimicrobial resistance in bacteria. The American journal of medicine. 2006 Jun 1;119(6):S3-10. https://doi.org/10.1016/j.amjmed.2006.03.011.
3. Mahajan GB, Balachandran L. Antibacterial agents from actinomycetes-a review. Frontiers in Bioscience-Elite. 2012 Jan 1;4(1):240-53.
4. Ristuccia AM, Cunha BA. An overview of amikacin. Therapeutic drug monitoring. 1985 Jan 1;7(1):12-25. https://doi.org/10.1097/00007691-198503000-00003.
5. de Gatta MF, Mendez ME, Romano S, Calvo MV, Dominguez-Gil A, Lanao JM. Pharmacokinetics of amikacin in intensive care unit patients. Journal of clinical pharmacy and therapeutics. 1996 Dec;21(6):417-21. https://doi.org/10.1111/j.1365-2710.1996.tb00041.x.
6. Sarubbi Jr FA, Hull JH. Amikacin serum concentrations: prediction of levels and dosage guidelines. Annals of internal medicine. 1978 Nov 1;89(5_Part_1):612-8. https://doi.org/10.7326/0003-4819-89-5-612.
7. Ramirez MS, Tolmasky ME. Amikacin: uses, resistance, and prospects for inhibition. Molecules. 2017 Dec 19;22(12):2267. https://doi.org/10.3390/molecules22122267.
8. Huang Q, Zhou Q, Ju T, Xu H, Wang W. Meropenem and Amikacin for Management of Post-Neurosurgical Infections from Acinetobacter baumannii. Surgical Infections. 2019 Feb 1;20(4):292-7. https://doi.org/10.1089/sur.2018.242.
9. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clinical microbiology reviews. 2010 Oct;23(4):858-83. DOI: https://doi.org/10.1128/cmr.00007-10.
10. Li C, Zhou P, Liu Y, Zhang L. Treatment of Ventriculitis and Meningitis After Neurosurgery Caused by Carbapenem-Resistant Enterobacteriaceae (CRE): A Challenging Topic. Infection and Drug Resistance. 2023 Dec 31:3807-18.
11. Berning SE, Cherry TA, Iseman MD. Novel treatment of meningitis caused by multidrug-resistant Mycobacterium tuberculosis with intrathecal levofloxacin and amikacin: case report. Clinical infectious diseases. 2001 Feb 15;32(4):643-6. https://doi.org/10.1086/318698.
12. Kalan B, Soni A, Dwivedi VK, Chaudhary M, Shrivastava SM. Antioxidant and Blood Brain Barrier Status in Cerebrospinal Fluid of Bacterial Meningitis Rat Model after Vancoplus Treatment. J. Med. Sci. 2009 May 15;9(4):194-201.

13. Zhang Y, Zhu X, Huang T, Chen L, Liu Y, Li Q, Song J, Ma S, Zhang K, Yang B, Guan F. β-Carotene synergistically enhances the anti-tumor effect of 5-fluorouracil on esophageal squamous cell carcinoma *in vivo* and *in vitro*. Toxicology Letters. 2016 Nov 2;261:49-58. https://doi.org/10.1016/j.toxlet.2016.08.010.
14. Akkara PJ, Sabina EP. Pre-treatment with beta carotene gives protection against nephrotoxicity induced by bromobenzene via modulation of antioxidant system, pro-inflammatory cytokines and pro-apoptotic factors. Applied biochemistry and biotechnology. 2020 Feb;190(2):616-633. https://doi.org/10.1007/s12010-019-03111-0.
15. Zhu X, Zhang Y, Li Q, Yang L, Zhang N, Ma S, Zhang K, Song J, Guan F. β-Carotene Induces Apoptosis in Human Esophageal Squamous Cell Carcinoma Cell Lines via the Cav-1/AKT/NF-κB Signaling Pathway. Journal of Biochemical and Molecular Toxicology. 2016 Mar;30(3):148-57. https://doi.org/10.1016/j.toxlet.2016.08.010
16. Miller M, Singer M. Do antibiotics cause mitochondrial and immune cell dysfunction? A literature review. Journal of Antimicrobial Chemotherapy. 2022 May 1;77(5):1218-27. https://doi.org/10.1093/jac/dkac025.
17. Desa DE, Nichols MG, Smith HJ. Aminoglycosides rapidly inhibit NAD (P) H metabolism increasing reactive oxygen species and cochlear cell demise. Journal of biomedical optics. 2019 May 1;24(5):051403-.https://doi.org/10.1117/1.JBO.24.5.051403.
18. Hurkacz M, Dobrek L, Wiela-Hojeńska A. Antibiotics and the Nervous System—Which Face of Antibiotic Therapy Is Real, Dr. Jekyll (Neurotoxicity) or Mr. Hyde (Neuroprotection)?. Molecules. 2021 Dec 9;26(24):7456. https://doi.org/10.3390/molecules26247456.
19. Duan M, Agerman K, Ernfors P, Canlon B. Complementary roles of neurotrophin 3 and a N-methyl-D-aspartate antagonist in the protection of noise and aminoglycoside-induced ototoxicity. Proceedings of the National Academy of Sciences. 2000 Jun 20;97(13):7597-602. https://doi.org/10.1073/pnas.97.13.7597.
20. Khalaf MT, Althanoon ZA. The protective effect of beta carotene against amikacin induced nephrotoxicity. MMSL. 2023;92(3):247-58. DOI: 10.31482/mmsl.2022.037.