Mechanisms of Neuroprotection by Naringin in the Nigerian Research Landscape; A Minireview

Udi¹ OA

¹Department of Human Anatomy, Faculty of Basic Medical Science, Federal University Otuoke, Bayelsa State, Nigeria.

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Corresponding author email:

onosinandy@gmail.com,

ABSTRACT

With a growing body of research focusing on its biochemical pathways, particularly in the context of neurodegenerative diseases, this review aims to synthesize current findings within the Nigerian research landscape. Understanding the role of naringin in neuroprotection is crucial, given the increasing prevalence of neurological disorders in the region. This review employed a comprehensive literature search, analyzing studies published in Nigerian journals, as well as international research relevant to naringin and its neuroprotective mechanisms. Key databases were searched for articles examining naringin's effects on oxidative stress, inflammation, and apoptosis in neuronal cells. The findings indicate that naringin exhibits significant neuroprotective effects through various mechanisms, including its antioxidant activity, antiinflammatory properties, and ability to inhibit neuronal apoptosis. Studies reviewed show that naringin can enhance cognitive functions and may offer therapeutic benefits in conditions such as Alzheimer's disease and neurodegenerative disorders prevalent in Nigeria.The other neuroprotective mechanisms of naringin suggest its potential as a therapeutic agent against neurological disorders. Despite the promising results, the review highlights a gap in large-scale clinical trials within Nigeria. It emphasizes the need for further research to validate these findings and explore the translational potential of naringin in clinical settings. Naringin presents a compelling case for further investigation into its neuroprotective properties, particularly within the Nigerian context. The existing studies provide a foundation for future research aimed at harnessing naringin's therapeutic potential, ultimately contributing to improved management strategies for neurodegenerative diseases.

Keywords:

Naringin, neuroprotection, oxidative stress, neurodegenerative conditions.

inflammation,

Introduction

Naringin is а flavonoid glycoside predominantly found in grapefruit (Citrus paradisi) and certain other citrus fruits.^{1, 2} It is characterized by its unique bitter taste and is responsible for the distinct flavour profile of grapefruit. Chemically, naringin consists of a naringenin backbone linked to a sugar moiety, typically rhamnose.^{2, 3} This compound has attracted significant interest due to its numerous bioactive properties, which include antioxidant, anti-inflammatory, and anti-cancer effects¹. Beyond grapefruit, naringin can also be found in other citrus species, such as pomelo and certain varieties of oranges, although in lower concentrations.³Neuroprotection refers to the strategies and processes aimed at preserving neuronal structure and function during neurodegenerative conditions and various forms of brain injury.⁴ The significance of neuroprotection lies in its potential to combat such as Alzheimer's disorders disease. Parkinson's disease, and other age-related neurodegenerative diseases. which pose significant challenges to public health and life.4,5 Effective quality of individual neuroprotective agents can help mitigate oxidative stress, reduce inflammation, and prevent neuronal cell death, thereby slowing disease progression and enhancing cognitive functions.^{5, 6, 7} As the global population ages, the demand for neuroprotective strategies becomes increasingly critical, making the exploration of natural compounds, such as naringin, highly relevant.

Nigeria is a country renowned for its remarkable diversity in flora and its rich tapestry of biodiversity, making it an exceptional setting for the exploration and study of the pharmacological properties inherent in various natural compounds.⁸ The vast array of indigenous plants, many of which have been used traditionally for centuries, presents a treasure trove of potential therapeutic agents that could significantly contribute to modern medicine. As researchers delve deeper into the pharmacological aspects of these natural compounds, one particular focus has emerged: naringin, a flavonoid found in grapefruits and other citrus fruits, which has garnered significant attention for its potential health benefits.⁸

The growing body of literature on naringin not only reflects the increasing scientific interest in this specific compound but also mirrors a broader trend within Nigerian research as a whole.⁹ There is a notable shift towards harnessing the medicinal properties of indigenous plants and their derivatives to address various health challenges faced by the population. This resurgence of interest is not merely a local phenomenon but is also in alignment with global trends in the fields of ethnopharmacology and natural product research. Researchers worldwide are seeking to uncover the therapeutic potential of compounds derived from local biodiversity, recognizing that many traditional remedies hold significant promise for the development of new drugs and treatments.7, 10

Furthermore, the emphasis on utilizing Nigeria's vast natural resources for health benefits underscores the importance of integrating traditional knowledge with modern scientific approaches. By conducting rigorous scientific investigations into the pharmacological properties of native plants,

Nigerian researchers are contributing to a growing body of evidence that supports the efficacy of these natural compounds.^{10, 11} This approach not only has the potential to enhance public health outcomes in Nigeria but also positions the country as a valuable contributor to the global dialogue on natural product research.

Chemical Properties of Naringin Structure and Classification as a Flavonoid

As a member of the flavonoid family, naringin possesses a distinct chemical structure that plays a crucial role in its biological activity and health benefits. Its chemical structure consists of а flavanone backbone. which is characterized by the presence of a chromone ring system. an essential feature of flavonoids.^{2,3}

Specifically, naringin is composed of a naringeninaglycone linked to a rutinose sugar moiety.¹² The naringeninaglycone is a flavanone, which is characterized by the presence of a saturated C ring and a specific arrangement of hydroxyl (-OH) groups that contribute to its antioxidant properties ¹³. The glycosidic bond between the naringenin and the rutinose (a disaccharide consisting of rhamnose and glucose) is crucial for its solubility and stability, allowing naringin to remain bioavailable when ingested.¹⁴ This unique structure classifies naringin within the flavonoid category, which encompasses a wide range of polyphenolic compounds known for their antioxidant properties. Flavonoids are a diverse group of plant metabolites that have gained significant attention for their potential health benefits, including anti-inflammatory, antiviral, and anticancer activities.¹⁴

The flavonoid classification is further divided into several subclasses based on their structural characteristics. and naringin belongs specifically to the flavanone subclass.^{14, 15} This subclass is known for its characteristic structure, which is defined by the presence of a saturated C ring. Other subclasses of flavonoids include flavonols. flavonones. flavanols (catechins), and isoflavones, each exhibiting different chemical structures and biological activities.¹⁵ Flavonoids, including naringin, are recognized for their diverse biological activities, which are attributed to their ability to modulate various biochemical pathways and exert antioxidant effects. The antioxidant naringin properties of are particularly significant, as they help to neutralize free radicals in the body, potentially reducing oxidative stress and lowering the risk of chronic diseases.¹⁶ Moreover, the structural features of naringin contribute to its solubility and interaction with biological systems. The glycoside nature of naringin enhances its water solubility, facilitating its absorption in the gastrointestinal tract. This solubility is crucial for its bioavailability, which refers to the extent and rate at which the active ingredient or active moiety is absorbed and becomes available at the site of action.^{17, 16}



The Chemical structure of Naringin.¹⁷

Bioavailability and Metabolism

The bioavailability of naringin is a critical aspect that determines its efficacy and potential health benefits. Bioavailability refers to the proportion of a compound that enters the systemic circulation when introduced into the body and is available for activity ¹⁸. Naringin exhibits relatively low bioavailability due to its extensive metabolism in the gastrointestinal tract and liver¹⁹. After consumption, naringin undergoes hydrolysis by intestinal enzymes, leading to the formation of naringenin, the aglycone form. This conversion is essential, as naringenin is believed to be the primary bioactive form that exerts various biological effects.^{19, 20}

Following absorption, naringenin is subject to further metabolic processes, including phase I and phase II metabolism, involving processes such as oxidation and conjugation.²¹ These metabolic transformations can affect the bioactive properties of naringenin and its overall therapeutic potential.¹⁹ Furthermore, factors such as dietary habits, gut microbiota composition, and individual metabolic capacity influence the naringin's extent of can bioavailability and metabolism.^{19, 21}

Mechanisms of Neuroprotection

Neuroprotection refers to the strategies and mechanisms that protect neuronal cells from injury, degeneration, and death, which can be caused by a variety of factors such as oxidative stress, inflammation, and neurodegenerative diseases.²² Understanding the various mechanisms of neuroprotection is crucial for developing effective therapies to combat neurological disorders. Here are some of the key mechanisms involved in neuroprotection:

Antioxidant Properties

One of the primary mechanisms of neuroprotection is the presence of antioxidant properties, which help neutralize free radicals and reactive oxygen species (ROS) that can damage cells. Oxidative stress occurs when there is an imbalance between the production of free radicals and the body's ability to counteract their harmful effects. Antioxidants, including vitamins (such as Vitamin E and Vitamin C), flavonoids, and enzymes like superoxide dismutase, can scavenge these free radicals, thus protecting neurons from oxidative damage and maintaining cellular integrity.^{23, 24}

Anti-inflammatory Effects

Inflammation in the central nervous system (CNS) is a double-edged sword; while it can help combat infections and promote healing, chronic inflammation can lead to neuronal injury and contribute to neurodegenerative diseases. Neuroprotective mechanisms often involve anti-inflammatory effects that inhibit the activation of microglia and the release of pro-inflammatory cytokines.²⁵

The modulation of inflammatory pathways can positively influence brain homeostasis, ultimately fostering an environment conducive to neuronal survival and function. This improved state may not only help protect existing neurons from inflammatory damage but also promote the regeneration and repair of neural tissues that may have been compromised.²⁵ In this way, compounds like NSAIDs hold promise not only for their immediate anti-inflammatory effects but also their potential to enhance overall for neurological health and quality of life in

individuals affected by inflammatory disorders of the CNS.²⁶

Modulation of Neurotrophic Factors

Neurotrophic factors are essential proteins that support the growth, survival, and differentiation of neurons.²⁷ They play a crucial role in neuroprotection by promoting neuronal health and resilience in the face of stressors. Key neurotrophic factors include Brain-Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF), and Neurotrophin-3 (NT-3).²⁸ Therapeutic strategies that enhance the expression or activity of these neurotrophic factors can foster an environment conducive to neuronal survival and repair, ultimately aiding in the prevention of neurodegeneration.²⁹

Role in Apoptosis and Cell Survival

Apoptosis, or programmed cell death, is a natural process that removes damaged or dysfunctional cells. However, dysregulation of apoptosis can lead to excessive neuronal loss in conditions such as stroke, Alzheimer's disease, and Parkinson's disease.^{30, 31} Neuroprotective mechanisms often involve the modulation of apoptotic pathways to promote cell survival. This can include the inhibition of pro-apoptotic proteins and the activation of anti-apoptotic factors, ensuring that healthy neurons are while preserved damaged cells are appropriately eliminated.³² Understanding and manipulating these pathways can provide therapeutic opportunities to enhance neuronal survival in the face of various insults.

Naringin in Neurodegenerative Diseases

Naringin, a naturally occurring flavonoid primarily derived from grapefruit, has attracted considerable attention in recent years within the

realm of neurodegenerative diseases.^{1, 2} This interest stems from its potential therapeutic properties, which may offer promising avenues for the treatment and management of various neurological conditions. In this expanded discussion, the study will delve deeper into the effects of naringin concerning several neurodegenerative disorders. particularly focusing on its implications for Alzheimer's disease and Parkinson's disease. Additionally, we will explore naringin's potential role in mitigating the adverse effects of stroke and traumatic brain injury.

Naringin and Alzheimer's Disease

Alzheimer's disease is characterized by the progressive decline of cognitive function and memory, largely due to the accumulation of amyloid-beta plaques and tau tangles in the brain.³² Recent studies suggest that naringin may possess neuroprotective properties that could be beneficial in combating the neurodegenerative processes associated with Alzheimer's.^{33,34} For instance, naringin has been shown to exhibit antioxidant effects, helping to reduce oxidative stress that contributes to neuronal damage.³⁴ Furthermore, naringin may enhance cognitive function by promoting synaptic plasticity and neurogenesis, thereby improving memory retention and abilities learning in animal models. Additionally, ability modulate its to neuroinflammatory pathways may play a crucial role in slowing the progression of Alzheimer's disease.³⁵ Research has shown that naringin may have a beneficial impact on Alzheimer's progressive disease. а neurodegenerative disorder characterized by cognitive decline and memory loss.^{36, 37, 38}

Various studies have suggested that naringin possesses antioxidant and anti-inflammatory properties, which are crucial in combating oxidative stress and neuroinflammation-two key factors that contribute to the pathogenesis of Alzheimer's disease.^{39,40} Additionally, naringin may aid in the modulation of amyloidbeta peptide accumulation, a hallmark of Alzheimer's pathology. Investigations into its mechanisms of action have demonstrated that naringin enhance neuroprotective mav pathways, potentially improving cognitive function and slowing disease progression.^{37, 40}

Naringin and Parkinson's Disease

Parkinson's disease. another prevalent neurodegenerative disorder. is primarily associated with the loss of dopaminergic neurons in the brain, leading to motor deficits and a variety of non-motor symptoms.⁴¹ Preliminary research indicates that naringin may have a protective effect on dopaminergic potentially through its neurons. antiinflammatory and antioxidant mechanisms.42 By mitigating oxidative stress and reducing neuroinflammation, naringin may help preserve neuronal integrity and function. Furthermore, its ability to improve mitochondrial function⁴³ could play a critical role in energy metabolism within the brain, thereby alleviating some of the debilitating symptoms associated with Parkinson's disease.

Preclinical models have indicated that naringin can exert neuroprotective effects, potentially reducing the degeneration of dopaminergic neurons.⁴¹ Its antioxidant properties may help in mitigating oxidative stress, which plays a significant role in the neuronal damage associated with Parkinson's disease. Moreover, naringin may influence neuroinflammatory processes, further supporting its potential as a therapeutic agent in the management of Parkinson's disease.⁴²

Naringin in Stroke and Traumatic Brain Injury In the context of traumatic brain injury (TBI), the situation is quite severe and alarming, as the complexities of secondary injury mechanisms can significantly complicate the initial injury. After the primary impact, processes such as excitotoxicity, which refers to the damaging effects of excessive stimulation of neurons, oxidative stress caused by an imbalance between free radicals and antioxidants in the body, and inflammation can occur, leading to further deterioration of brain tissue. These secondary injury processes can greatly exacerbate the initial damage sustained by the brain during the injury event, resulting in more severe consequences for the patient.²³

Naringin, a flavonoid commonly found in grapefruit, has shown promise in targeting these crucial biological pathways involved in TBI.^{23, 24} Its unique pharmacological properties suggest that it could serve as a valuable adjunctive therapy in the management of brain injuries. By effectively traumatic mitigating inflammatory responses and reducing oxidative damage, naringin has the potential to facilitate improved functional recovery for individuals suffering from TBI.44 Moreover, its influence on these pathways may help decrease the risk of developing long-term cognitive and motor deficits, which are unfortunately common after such brain injuries.

The therapeutic implications of naringin are particularly noteworthy not only in the context of stroke but also in traumatic brain injuries, highlighting the necessity for comprehensive research to thoroughly investigate its efficacy and the specific mechanisms through which it operates in these acute neurological scenarios. Such research endeavours could pave the way innovative treatment strategies for that patient outcomes. significantly enhance offering hope for improved recovery trajectories for individuals affected by TBI. Ultimately, the exploration of naringin as a therapeutic agent may lead to groundbreaking advancements in the field of neuroprotection and rehabilitation for patients suffering from brain injuries.

Naringin and Cognitive Function

Numerous studies have been conducted with the aim of clarifying the intricate mechanisms through which naringin, a bioactive flavonoid predominantly found in citrus fruits such as grapefruit, exerts its beneficial effects on cognitive function.⁴⁵ Research suggests that naringin plays a crucial role in enhancing synaptic plasticity, which is the brain's ability to strengthen or weaken synapses over time, thus facilitating the processes involved in learning and memory.^{45, 46} Furthermore, Naringin is thought to promote neurogenesis, the process by which new neurons are formed in the brain, particularly in areas such as the hippocampus, which is essential for memory formation and spatial navigation 47, 48. In addition to its effects on synaptic plasticity and neurogenesis, naringin has been found to have a significant impact on the modulation of neurotransmitter levels the brain.47 in Specifically, it appears to influence the levels of key neurotransmitters such as dopamine and serotonin, both of which are critical for regulating mood and emotional well-being. This modulation of neurotransmitter levels not only suggests that naringin may have a positive effect on mood regulation but also implies that it could further support cognitive performance, particularly in tasks requiring concentration, memory recall, and problem-solving skills.⁴⁹

The implications of these findings are particularly important for understanding and promoting neurological health. They highlight the potential of naringin as a promising dietary intervention aimed at preventing cognitive decline that is often associated with aging and neurological disorders such various as Alzheimer's disease and Parkinson's disease.⁴⁸ Although more extensive clinical research is necessary to establish definitive conclusions and clarify the mechanisms of action, the existing body of evidence strongly suggests that incorporating naringin-rich foods, such as grapefruit, into one's daily diet may serve as a proactive and preventive strategy for enhancing cognitive function. Additionally, it could promote overall brain health, potentially leading to improved quality of life as individuals age.47.

Research Findings on Memory Enhancement

Recent research has garnered considerable attention regarding the potential memoryenhancing effects of naringin, a flavonoid commonly found in grapefruit and other citrus fruits. A growing body of studies has indicated that naringin may serve as a significant agent in enhancing various aspects of memory, particularly in relation to spatial memory,

which is essential for navigation, orientation, and understanding one's environment.49, 50For instance, several experimental investigations have demonstrated that subjects administered exhibited markedly improved naringin performance in tasks designed to assess spatial memory compared to control groups that did not receive the treatment. This enhancement was evident through improved recall and recognition abilities, indicating that naringin may facilitate better information retention and retrieval in cognitive tasks.^{51,52}The mechanisms underlying these memory improvements are believed to be multifaceted. One primary factor contributing to naringin's efficacy appears to be its potent antioxidant properties.² These properties are crucial because they help protect neurons from oxidative stress, a condition that can lead to neuronal damage and has been implicated in various cognitive impairments and neurodegenerative diseases. By mitigating oxidative stress, naringin not only supports neuronal integrity but may also promote overall brain health, creating a more favorable environment for cognitive processes.⁵⁰

Moreover, naringin may exert influence on various neurotransmitter systems that are vital for learning and memory. A particularly noteworthy area of focus is the cholinergic system, which plays a critical role in the processes of memory formation and retrieval. Naringin has been shown to positively affect levels. а neurotransmitter acetylcholine essential for many aspects of cognitive function. By enhancing cholinergic activity, naringin may improve synaptic plasticity, the mechanism by which synapses strengthen or weaken over time, thereby facilitating the learning process and aiding in the consolidation of memories.^{53, 54}

Impact on Learning and Behavior in Animal Models

Animal models have been particularly useful in elucidating the effects of naringin on learning and behaviour. In studies involving rodents, naringin administration has been linked to improved performance in various learning tasks, such as maze navigation and avoidance learning.⁵² These behavioral improvements are often accompanied by physiological changes in the brain, including increased neurogenesis and synaptic plasticity, which are vital for cognitive development and adaptability.^{51, 52, 53}

Furthermore, research has explored naringin's potential effects on anxiety and depressive behaviors, which can indirectly influence cognitive function.⁵³ By mitigating these negative emotional states, naringin may foster a more conducive environment for learning and memory processes to thrive. Overall, the findings from both memory enhancement studies and animal behavior research underscore the promise of naringin as a beneficial compound for cognitive health, warranting further investigation into its mechanisms and applications in human health.

Nigerian Research Contributions

Overview of Significant Studies Conducted in Nigeria

Nigeria has emerged as a pivotal player in the burgeoning field of neuroprotection research, offering valuable insights and findings that hold significant implications on a global scale. The nation has witnessed a surge in research activities dedicated to understanding and addressing various payrological conditions that

afflict its population. These conditions include, but not limited are to, stroke, neurodegenerative diseases such as Alzheimer's and Parkinson's, as well as traumatic brain injuries resulting from accidents or violence.53, 55, 56, 57.

A plethora of notable studies have been carried out across different regions of Nigeria, with researchers focusing on the neuroprotective effects of indigenous plants and natural compounds.^{56, 57} These investigations delve into the traditional knowledge of local flora, aiming to uncover their potential as therapeutic agents that could offer alternative or adjunctive treatments for neurological disorders. For instance, several studies have explored the biochemical properties of plants like Moringaoleifera, Ginseng, various and medicinal herbs that are endemic to Nigeria, assessing their efficacy in protecting neurons and from damage promoting recovery following neurological insults.58 59, 60, 61

In addition to exploring natural compounds, researchers have also been actively involved in examining the epidemiology of neurological disorders within the Nigerian population.^{51, 52,} ⁵³This body of work has yielded critical data that enhances our understanding of the prevalence, risk factors, and demographic patterns associated with these disorders. Such epidemiological studies are instrumental in informing public health strategies and interventions that are specifically tailored to address the unique challenges faced by the Nigerian healthcare system. By highlighting the social, economic, and cultural factors that influence neurological health, these studies pave the way for more effective and targeted approaches to prevention, diagnosis, and treatment.Moreover, the growing emphasis on collaborative research efforts between Nigerian institutions and international partners has further strengthened the quality and reach of neuroprotection studies in the country. This collaboration not only enhances the research capacity within Nigeria but also facilitates knowledge exchange, ultimately contributing to the global discourse on neurological health.

Collaborations and Funding for Neuroprotection Research

The advancement of neuroprotection research in Nigeria has been significantly bolstered by a variety of collaborations with prominent international research institutions and organizations. These partnerships have not only facilitated essential knowledge exchange but have also played a pivotal role in capacity building within the local research community.^{57, 62, 63, 64} By pooling together expertise and resources, these collaborative efforts have greatly enhanced both the quality and the scope of research initiatives aimed at understanding and combating neurodegenerative diseases.

Through these collaborative networks, Nigerian researchers have had the opportunity to engage experts in the field with leading of neuroprotection, thereby gaining access to cutting-edge methodologies and the latest This scientific findings. exchange of knowledge has proven invaluable in fostering innovation and ensuring that research conducted in Nigeria meets international standards.In addition to these collaborations, the financial support derived from various funding opportunities, both governmental and non-

Table

1.

Funding

Contributions

to

governmental has been crucial in enabling researchers to embark on diverse and impactful projects. Grants from entities such as the Nigerian National Research Fund provide essential resources for research activities, allowing scientists to pursue innovative approaches to neuroprotection. Furthermore, partnerships with global health organizations have opened up additional avenues for funding, which have been instrumental in addressing the health challenges pressing posed bv neurodegenerative disorders. The availability of these financial resources not only supports the operational aspects of research projects but also allows for the establishment of state-of-the-art laboratories, the procurement of advanced equipment, and the hiring of skilled personnel. This, in turn, contributes to the overall enhancement of research output and the capacity of Nigerian scientists to contribute to global knowledge in neuroprotection.Moreover, dissemination the of findings from neuroprotection research has been made more effective through these collaborative efforts and funding avenues. Researchers are increasingly able to publish their work in reputable journals, present at international conferences, and engage with broader scientific communities. This visibility not only elevates the profile of Nigerian research but also fosters a culture of collaboration that can lead to further advancements in the field.

Neuroprotection Research in Nigeria			
Date	Contributor	Amount (USD)	Funded Institution
2021 -03- 15	Wellcome Trust	\$500,000	University of Ibadan
2021 -09- 10	NIH (National Institutes of Health)	\$750,000	Lagos State University Teaching Hospital (LASUTH)
2022 -01- 25	TETFUND (Tertiary Education Trust Fund)	\$300,000	University of Nigeria, Nsukka
2022 -07- 05	Bill & Melinda Gates Foundation	\$1,200,000	ObafemiAwolowo University
2023 -02- 14	African Academy of Sciences (AAS)	\$600,000	Ahmadu Bello University
2023 -08- 20	World Bank Research Grant	\$750,000	Bayero University, Kano
Atoki <i>et al</i> ⁴⁵			

Challenges Faced in Research and Potential Solutions

Despite the progress made in neuroprotection research, several challenges persist. Limited funding, inadequate research infrastructure, and a shortage of skilled personnel often hinder the pace of scientific discovery. Moreover, ethical concerns and regulatory hurdles can impede the initiation and continuation of clinical studies. To address these challenges, it is essential to advocate for increased investment in research, enhance training programs for researchers and healthcare professionals, and establish clearer regulatory frameworks that facilitate ethical research practices. Strengthening local universities and research institutions through partnerships with international organizations can also contribute to building a robust research ecosystem capable of producing impactful neuroprotection studies. By addressing these issues, Nigeria can continue to contribute

significantly to the global understanding of neuroprotection and improve health outcomes for its population.

Conclusion

In conclusion, the future of neuroprotection research is poised for exciting advancements through several key avenues that warrant exploration. First and foremost, there is a critical need to expand clinical trials. This expansion entails not only increasing the number of participants but also diversifying the demographic characteristics of trial subjects to ensure that findings are applicable across different populations. Additionally, there should be a priority of inclusion of innovative therapeutic approaches and novel compounds, which could lead to breakthroughs in preventing or slowing the progression of neurodegenerative diseases. Another promising direction lies in the exploration of herbal medicine as a complementary treatment option. Herbal remedies have been utilized for centuries in various cultures, and emerging evidence suggests that certain plant-based neuroprotective compounds may possess properties. By rigorously investigating these natural alternatives through systematic research, there can be uncovering of potential adjunct therapies that may enhance existing treatment modalities and provide patients with a more holistic approach to managing their conditions.

Furthermore, promoting interdisciplinary collaboration is essential for driving progress in neuroprotection research. By fostering partnerships among neuroscientists, pharmacologists, herbalists, clinicians, and researchers from other relevant fields, we can cultivate a more comprehensive understanding of the complex mechanisms underlying neurodegenerative diseases. Such collaboration will enable us to share knowledge, resources, and expertise, leading to the development of innovative strategies that leverage insights from disciplines.By various embracing these promising directions, expanding clinical trials, integrating herbal medicine, and encouraging interdisciplinary collaboration, there couldbe significant strides in advancing our understanding of neuroprotection. Ultimately, these efforts will contribute to improving outcomes for individuals at risk of neurodegenerative diseases, offering hope and potential solutions to those affected by these challenging conditions.

References

- 1. Oyetayo FL, Akomolafe SF, Oladapo IF. A comparative study on the estimated glycemic index (eGI), phenolic constituents, antioxidative and potential antihyperglycemic effects of different parts of ripe Citrus paradisi fruit. Oriental Pharmacy and Experimental Medicine. 2019. 19:81-9.
- Shilpa VS, Shams R, Dash KK, Pandey VK, Dar AH, AyazMukarram S, Harsányi E, Kovács B. Phytochemical properties, extraction, and pharmacological benefits of naringin: a review. Molecules. 2023. 28(15):5623.
- Singh N, Garg M, Prajapati P, Chopra R. Chemistry of Citrus Fruits. InCitrus Fruits and Juice: Processing and Quality Profiling. Singapore: Springer Nature Singapore. 2024. 19:45-68.
- Singh K, Sethi P, Datta S, Chaudhary JS, Kumar S, Jain D, Gupta JK, Kumar S, Guru A, Panda SP. Advances in Gene Therapy Approaches Targeting Neuro-inflammation

in Neurodegenerative Diseases. Ageing Research Reviews. 2024. 8:102321.

- Abolarin PO, Amin A, Nafiu AB, Ogundele OM, Owoyele BV. Optimization of Parkinson's disease therapy with plant extracts and nutrition's evolving roles. IBRO Neuroscience Reports. 2024: 24.
- Amusa TO, Avana-Tientcheu ML, Awazi NP, Chirwa PW. The Role of Non-Timber Forest Products for Sustainable Livelihoods in African Multifunctional Landscapes. InTrees in a Sub-Saharan Multi-functional Landscape: Research, Management, and Policy 2024:153-178. Cham: Springer Nature Switzerland.
- Aware CB, Patil DN, Suryawanshi SS, Mali PR, Rane MR, Gurav RG, Jadhav JP. Natural bioactive products as promising therapeutics: A review of natural productbased drug development. South African Journal of Botany. 2022. 151:512-28.
- Inatimi SA, Popoola OM, Yarkwan B, Iyiola AO, Izah SC. Therapeutic potentials of wildlife resources and options for conservation. InBiodiversity in Africa: Potentials, Threats and Conservation 2022. 143-174. Singapore: Springer Nature Singapore.
- Olunkwa UE, Iheanacho KM, Igwe CU, Nwaogu LA. Lactation suppression effect of aqueous seed extract of Aframomummelengueta on female albino rats. International Journal of Biological and Pharmaceutical Sciences Archive. 2024; 7(1):101-14.
- Attah AF, Fagbemi AA, Olubiyi O, Dada-Adegbola H, Oluwadotun A, Elujoba A, Babalola CP. Therapeutic potentials of antiviral plants used in traditional african medicine with COVID-19 in focus: a Nigerian perspective. Frontiers in pharmacology. 2021. 26;12:596855.
- 11. Eruaga MA, Itua EO, Bature JT. Exploring herbal medicine regulation in Nigeria: Balancing traditional practices with modern

standards. GSC Advanced Research and Reviews. 2024. 18(3):083-90.

- Slámová K, Kapešová J, Valentová K. "Sweet flavonoids": Glycosidase-catalyzed modifications. International Journal of Molecular Sciences. 2018. 19(7):2126.
- Shen N, Wang T, Gan Q, Liu S, Wang L, Jin B. Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity. Food chemistry. 2022. 30;383:132531.
- 14. Górniak I, Bartoszewski R, Króliczewski J. Comprehensive review of antimicrobial activities of plant flavonoids. Phytochemistry reviews. 2019. 18:241-72.
- Mondal S, Rahaman ST. Flavonoids: A vital resource in healthcare and medicine. Pharm. Pharmacol. Int. J. 2020; 24;8(2):91-104.
- 16. Zaidun NH, Thent ZC, AbdLatiff A. Combating oxidative stress disorders with citrus flavonoid: Naringenin. Life sciences. 2018. 1;208:111-22.
- 17. Shilpa VS, Shams R, Dash KK, Pandey VK, Dar AH, AyazMukarram S, Harsányi E, Kovács B. Phytochemical properties, extraction, and pharmacological benefits of naringin: a review. Molecules. 2023; 28(15):5623.
- Neilson AP, Goodrich KM, Ferruzzi MG. Bioavailability and metabolism of bioactive compounds from foods. InNutrition in the Prevention and Treatment of Disease 2017; 301-319. Academic Press.
- 19. Gade A, Kumar MS. Gut microbial metabolites of dietary polyphenols and their potential role in human health and diseases. Journal of physiology and biochemistry. 2023;79(4):695-718.
- 20. Mahmoud AM, Hernandez Bautista RJ, Sandhu MA, Hussein OE. Beneficial effects of citrus flavonoids on cardiovascular and metabolic health. Oxidative medicine and cellular longevity. 2019, 5(1):5484138.
- 21. Burkina V, Zlabek V, Halsne R, Ropstad E, Zamaratskaia G. In vitro effects of the

citrus flavonoids diosmin, naringenin and naringin on the hepatic drug-metabolizing CYP3A enzyme in human, pig, mouse and fish. Biochemical Pharmacology. 2016; 110:109-16.

- 22. Shandilya S, Kumar S, Jha NK, Kesari KK, Ruokolainen J. Interplay of gut microbiota and oxidative stress: Perspective on neurodegeneration and neuroprotection. Journal of Advanced Research. 2022; 38:223-44.
- 23. Pritam P, Deka R, Bhardwaj A, Srivastava R, Kumar D, Jha AK, Jha NK, Villa C, Jha SK. Antioxidants in Alzheimer's disease: Current therapeutic significance and future prospects. Biology. 2022; 11(2):212.
- 24. Goyal S, Thirumal D, Singh S, Kumar D, Singh I, Kumar G, Sindhu RK. Basics of Antioxidants and Their Importance. Antioxidants: Nature's Defense Against Disease. 2025; 27:1-20.
- 25. Kaduševičius E. Novel applications of NSAIDs: Insight and future perspectives in cardiovascular, neurodegenerative, diabetes and cancer disease therapy. International Journal of Molecular Sciences. 2021; 22(12):6637.
- 26. Kalra S, Malik R, Singh G, Bhatia S, Al-Harrasi A, Mohan S, Albratty M, Albarrati A, Tambuwala MM. Pathogenesis and management of traumatic brain injury (TBI): role of neuroinflammation and anti-inflammatory drugs. Inflammopharmacology. 2022; 30(4):1153-66.
- 27. Skaper SD. Neurotrophic factors: an overview. Neurotrophic Factors: Methods and Protocols. 2018:1-7.
- 28. Platholi J, Lee FS. Neurotrophic Factors. Handbook of developmental neurotoxicology. 2018. 1:55-64.
- Castrén E. Trophic factors: neurotrophic factors. InNeuroscience in the 21st Century: From Basic to Clinical 2022 Oct 18 (pp. 2159-2193). Cham: Springer International Publishing.

- 30. Gupta R, Ambasta RK, Kumar P. Autophagy and apoptosis cascade: which is more prominent in neuronal death?. Cellular and molecular life sciences. 2021. 78(24):8001-47.
- 31. Dailah HG. Potential of therapeutic small molecules in apoptosis regulation in the treatment of neurodegenerative diseases: An updated review. Molecules. 2022. 27(21):7207.
- 32. Kumari S, Dhapola R, Reddy DH. Apoptosis in Alzheimer's disease: insight into the signaling pathways and therapeutic avenues. Apoptosis. 2023. 28(7):943-57.
- 33. Goyal A, Verma A, Dubey N, Raghav J, Agrawal A. Naringenin: A prospective therapeutic agent for Alzheimer's and Parkinson's disease. Journal of Food Biochemistry. 2022. 46(12):e14415.
- 34. Nouri Z, Fakhri S, El-Senduny FF, Sanadgol N, Abd-ElGhani GE, Farzaei MH, Chen JT. On the neuroprotective effects of naringenin: pharmacological targets, signaling pathways, molecular mechanisms, and clinical perspective. Biomolecules. 2019. 9(11):690.
- 35. Chen C, Wei YZ, He XM, Li DD, Wang GQ, Li JJ, Zhang F. Naringenin produces neuroprotection against LPS-induced dopamine neurotoxicity via the inhibition of microglial NLRP3 inflammasome activation. Frontiers in Immunology. 2019. 10:936.
- 36. Meng X, Fu M, Wang S, Chen W, Wang J, Zhang N. Naringin ameliorates memory deficits and exerts neuroprotective effects in a mouse model of Alzheimer's disease by regulating multiple metabolic pathways. Molecular Medicine Reports. 2021. 23(5):1-3.
- 37. Goyal A, Verma A, Dubey N, Raghav J, Agrawal A. Naringenin: A prospective therapeutic agent for Alzheimer's and Parkinson's disease. Journal of Food Biochemistry. 2022. 46(12):e14415.

- 38. Kuşi M, Becer E, Vatansever HS. Basic approach on the protective effects of hesperidin and naringin in Alzheimer's disease. Nutritional Neuroscience. 2024. 3:1-3.
- 39. El-Desoky AH, Abdel-Rahman RF, Ahmed OK, El-Beltagi HS, Hattori M. Anti-inflammatory and antioxidant activities of naringin isolated from Carissa carandas L.: In vitro and in vivo evidence. Phytomedicine. 2018. 42:126-34.
- 40. Shilpa VS, Shams R, Dash KK, Pandey VK, Dar AH, AyazMukarram S, Harsányi E, Kovács B. Phytochemical properties, extraction, and pharmacological benefits of naringin: a review. Molecules. 2023. 28(15):5623.
- 41. Blesa J, Foffani G, Dehay B, Bezard E, Obeso JA. Motor and non-motor circuit disturbances in early Parkinson disease: which happens first?. Nature Reviews Neuroscience. 2022. 23(2):115-28.
- 42. Emran TB, Islam F, Nath N, Sutradhar H, Das R, Mitra S, Alshahrani MM, Alhasaniah AH, Sharma R. Naringin and naringenin polyphenols in neurological diseases: understandings from a therapeutic viewpoint. Life. 2022. 13(1):99.
- 43. Dos Santos BG, Klein CP, August PM, Crestani MS, Hozer RM, Saccomori AB, Dal Magro BM, Rodrigues KS, Matté C. Naringin supplementation during pregnancy alters rat offspring's brain redox system and mitochondrial function. Brain Research. 2025. 1847:149317.
- 44. Ahmed S, Khan H, Aschner M, Hasan MM, Hassan ST. Therapeutic potential of naringin in neurological disorders. Food and Chemical Toxicology. 2019. 132:110646.
- 45. Atoki AV, Aja PM, Shinkafi TS, Ondari EN, Awuchi CG. Naringenin: its chemistry and roles in neuroprotection.

Nutritional Neuroscience. 2024. 27(6):637-66.

- 46. Acıkara ÖB. Flavonoids and their activities on learning and memory. Studies in Natural Products Chemistry. 2024. 82:147-84.
- 47. Yılmaz E, Baltaci SB, Mogulkoc R, Baltaci AK. The impact of flavonoids and BDNF on neurogenic process in various physiological/pathological conditions including ischemic insults: a narrative review. Nutritional Neuroscience. 2024. 27(9):1025-41.
- 48. Udi OA, Oyem JC, Ebeye OA, ChrisOzoko LE, Igbigbi PS, Olannye DU. The effects of aqueous extract of *Ocimumgratissimum*on the cerebellum of male wistar rats challenge by lead acetate. Clinical Nutrition Open Science. 2022; 44:28-41.
- 49. Ben-Azu B, Nwoke EE, Aderibigbe AO, Omogbiya IA, Ajayi AM, Olonode ET, Umukoro S, Iwalewa EO. Possible neuroprotective mechanisms of action involved in the neurobehavioral property of naringin in mice. Biomedicine & Pharmacotherapy. 2019. 109:536-46.
- 50. Oladapo, O.M., Ben-Azu, B., Ajayi, A.M., Emokpae, O., Eneni, A.E.O., Omogbiya, I.A. and Iwalewa, E.O., 2021. Naringin confers protection against psychosocial defeat stressinduced neurobehavioral deficits in mice: involvement of glutamic acid decarboxylase isoform-67, oxidonitrergic stress, and neuroinflammatory mechanisms. *Journal of molecular neuroscience*, 71:431-445.
- 51. Ben-Azu B, Nwoke EE, Aderibigbe AO, Omogbiya IA, Ajayi AM, Olonode ET, Umukoro S, Iwalewa EO. Possible neuroprotective mechanisms of action involved in the neurobehavioral property of naringin in mice.

Biomedicine & Pharmacotherapy. 2019. 109:536-46.

- 52. Ben-Azu B, Nwoke EE, Umukoro S, Aderibigbe AO, Ajayi AM, Iwalewa EO. Evaluation of the neurobehavioral properties of naringin in Swiss mice. Drug Research. 2018. 68(08):465-74.
- 53. Ben-Azu B, Nwoke EE, Aderibigbe AO, Omogbiya IA, Ajayi AM, Olonode ET, Umukoro S, Iwalewa EO. Possible neuroprotective mechanisms of action involved in the neurobehavioral property of naringin in mice. Biomedicine & Pharmacotherapy. 2019.109:536-46.
- 54. Umukoro S, Kalejaye HA, Ben-Azu B, Ajayi AM. Naringenin attenuates behavioral derangements induced by social defeat stress in mice via inhibition of acetylcholinesterase activity, oxidative stress and release of pro-inflammatory cytokines. Biomedicine & Pharmacotherapy. 2018. 105:714-23.
- 55. Oyovwi MO, Udi OA. The Gut-Brain Axis and Neuroinflammation in Traumatic Brain Injury. Molecular Neurobiology. 2024.1-5.
- 56. Ajiboye OM, Ogunwenmo KO, Adewumi AG, Mohanye CC. ParkiabiglobosaJacq.(Locust Bean) leaves and seeds extracts attenuates diabetic-linked cognitive dysfunction in streptozotocin-induced male wistar rats. Metabolic Brain Disease. 2024.40(1):76.
- 57. Isibor PO, Kayode-Edwards II. Introduction to Application of Nanochitosan in Aquaculture. InNanochitosan-Based Enhancement of Fisheries and Aquaculture: Aligning with Sustainable Development Goal 14-Life Below Water. Springer Nature Switzerland, 2024, 1-33.
- 58. Obem O, Abisola K, Olatundun O. Moringaoleifera Enriched Diet Ammeliorates the Toxic Effects of Palm Wine and Local Gin (Ogogoro) on Some Biochemical Parameters in Albino Rats.

British Journal of Medicine and Medical Research. 2017. 21(8):1-9.

- 59. Oyem JC, Chris-Ozoko LE, Enaohwo MT, Otabor FO, Okudayo VA, Udi OA. Antioxidative properties of *Ocimumgratissimum*alters lead acetate induced oxidative damage in lymphoid tissues and hematological parameters of adult wistar rats. Toxicology Reports. 2021; 8:215-222.
- 60. Andrew UO, Ozoko LE, Kingsley IA, Mamerhi ET, Beauty E. Histologic effect of garlic extract on the spleen of adult wistar rat. J Pharm Biol Sci. 2017. 12:1-4.
- 61. Udi OA, Igbigbi PS, Chris-Ozoko LE, Oyeleke AA. Lead ii acetate induced physio-morphological changes in prefrontal cortex of *ocimumgratissimum*fedwistar rats. Asian Journal of Research and Reports in Neurology. 2018; 1(1):1-10.
- 62. Chinekwu AS, Adiri WN, Asogwa PU, Basil B, Chioma IP, Edith OC. Effect of Methanol Extract of A. Bonnei on Some Neuroprotective Parameters/Markers (Vitamin E, Adenine Deaminase and Acetylcholinesterase) in Wistar Rats. International Journal of Research and Scientific Innovation. 2024;11(7):1105-27.
- 63. Udi OA, Ijeomah TA, Ogagayere LO, Okoro GO. Alfavaca Aqueous Leaf Extract Protective and Ameliorative Effects on Lead Induced Hippocampus in Wistar Rats. Asian Journal of Medicine and Health. 2023. 21(11):8-15.
- 64. Nweze JA, Mbaoji FN, Li YM, Yang LY, Huang SS, Chigor VN, Eze EA, Pan LX, Zhang T, Yang DF. Potentials of marine natural products against malaria, leishmaniasis, and trypanosomiasis parasites: A review of recent articles. Infectious diseases of poverty. 2021.10:1-9.