DERLEME / REVİEW

Exploring The Therapeutic Potential of Celastrol in Neurodegenerative Disorders: A Revıew Study

Nörodejeneratif Bozukluklarda Celastrol'ün Terapötik Potansiyelinin Araştırılması: Bir Derleme Çalışması

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ABSTRACT

Neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, have a significant global impact due to progressive neuronal loss. The search for effective therapeutic strategies to address the burden of these conditions is crucial. Celastrol, a natural compound with anti-inflammatory and antioxidant properties, shows promise as a neuroprotective agent in various neurodegenerative disorders. This review aims to explore the therapeutic potential of Celastrol in neurodegenerative disorders by conducting a systematic review of existing literature. Specifically, we investigate its effects on neuroinflammation, oxidative stress, neuroprotection, and neuronal survival while elucidating the signalling mechanisms. The reviewed studies consistently demonstrated Celastrol's potential in attenuating neuroinflammation, reducing oxidative stress, providing neuroprotection, and promoting neuronal survival in neurodegenerative disorders. Activation of specific signalling pathways, including Nrf2/HO-1, JAK2/STAT3, and PI3K/AKT, was identified as mediating Celastrol's therapeutic effects. This review study highlights the therapeutic potential of Celastrol in neurodegenerative disorders. The findings suggest that Celastrol may serve as a neuroprotective agent by modulating neuroinflammation, oxidative stress, and neuronal survival pathways. Nevertheless, additional research, including clinical trials, is necessary to validate these findings and determine the optimal utilization of Celastrol in the management and treatment of neurodegenerative diseases.

Key Words: Celastrol, neurodegenerative disorders, neuroinflammation, oxidative stress, neuroprotection

ÖZET

Alzheimer hastalığı ve Parkinson hastalığı gibi nörodejeneratif bozukluklar, ilerleyici nöron kaybı nedeniyle önemli bir küresel etkiye sahiptir. Bu koşulların yükünü ele almak için etkili terapötik stratejilerin araştırılması çok önemlidir. Anti-enflamatuar ve antioksidan özelliklere sahip doğal bir bileşik olan Celastrol, çeşitli nörodejeneratif bozukluklarda nöroprotektif bir ajan olarak umut vaat etmektedir. Bu derleme, mevcut literatürün sistematik bir incelemesini yaparak Celastrol'ün nörodejeneratif bozukluklardaki terapötik potansiyelini keşfetmeyi amaçlamaktadır. Bu derlemede, özellikle Celastrol'ün sinyal mekanizmalarına etkisini aydınlatırken, nöroinflamasyon, oksidatif stres, nöroproteksiyon ve nöronal sağkalım üzerindeki etkilerini araştırdık. İncelenen çalışmalar, Celastrol'ün nöroinflamasyonu hafifletme, oksidatif stresi azaltma, nöroproteksiyon sağlama ve nörodejeneratif bozukluklarda nöronal sağkalımı teşvik etme potansiyelini tutarlı bir şekilde göstermiştir. Nrf2/HO-1, JAK2/STAT3 ve PI3K/AKT dahil olmak üzere spesifik sinyal yollarının aktivasyonunun Celastrol'ün terapötik etkilerine aracılık ettiği tespit edilmiştir. Bu derleme çalışması, Celastrol'ün nörodejeneratif hastalıklardaki terapötik potansiyelini vurgulamaktadır. Bulgular, Celastrol'ün nöroinflamasyon, oksidatif stres ve nöronal sağkalım yolaklarını modüle ederek nöroprotektif bir ajan olarak hizmet edebileceğini göstermektedir. Bununla birlikte, bu bulguları doğrulamak ve Celastrol'ün nörodejeneratif hastalıkların yönetimi ve tedavisinde en uygun kullanımını belirlemek için klinik çalışmalar da dahil olmak üzere ek araştırmalar gereklidir.

Anahtar Kelimeler: Celastrol, nörodejeneratif bozukluklar, nöroinflamasyon, oksidatif stres, nöroproteksiyon

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GİRİŞ

Because of their progressive nature and lack of effective treatment options, neurodegenerative illnesses such as Alzheimer's disease, Parkinson's disease, and Huntington's disease offer substantial challenges to worldwide healthcare systems (Holtzmann et al., 2011; Kalia & Lang, 2015; Ross & Poirier, 2004). These devastating illnesses are characterized by neuronal degeneration and loss, resulting in cognitive and physical deficits (Hardy, 2017; Lees et al., 2019). Given the growing frequency and significance of neurodegenerative illnesses, there is an urgent need to identify and develop innovative treatment techniques that can prevent or delay disease progression.

Celastrol, a natural chemical originating from traditional Chinese medicine, is one intriguing possibility that has received significant attention in recent years. Celastrol has been shown to have a number of pharmacological activities, including anti-inflammatory, antioxidant, and neuroprotective qualities (Gan & Johnson, 2010; Lin et al., 2019; Zhang et al., 2018). These properties make Celastrol a potentially promising treatment drug for neurodegenerative illnesses.

A thorough study of the available research on Celastrol's therapeutic potential in this context, however, is necessary. Several review studies have been conducted concerning the effects of Celastrol on Neurological Diseases (Table 1). These studies collectively contribute to the understanding of Celastrol's therapeutic potential in neurodegenerative disorders. The findings highlight its neuroprotective effects, including cognitive improvement, attenuation of neuroinflammation, and protection of dopaminergic neurons.

Smith et al. (2021) conducted a systematic review focusing on the potential treatment of Alzheimer's disease with Celastrol. Their comprehensive analysis of preclinical studies demonstrated that Celastrol exhibits neuroprotective effects by improving cognitive function and reducing neuroinflammation. The findings suggest that Celastrol holds promise as a potential therapeutic intervention for Alzheimer's disease by targeting key pathological processes (Smith, 2021).

Zhang et al. (2021) conducted a systematic review and meta-analysis to investigate the effects of Celastrol on cognitive impairment in animal models of Alzheimer's disease. Their rigorous analysis revealed that Celastrol treatment significantly improved cognitive function, supporting its potential as a therapeutic agent for Alzheimer's disease. The findings provide evidence for the cognitive-enhancing effects of Celastrol and its potential in mitigating the cognitive decline associated with Alzheimer's disease (Zhang et al., 2021).

Chen et al. (2021) conducted a systematic review and meta-analysis to investigate the neuroprotective effects of Celastrol in Parkinson's disease. Their analysis revealed that Celastrol treatment significantly improved motor function and reduced dopaminergic neuron loss. The findings suggest that Celastrol holds promise as a potential therapeutic agent for Parkinson's disease by protecting dopaminergic neurons and improving motor symptoms (Chen et al., 2021).

This review study makes a significant contribution by identifying noteworthy and promising findings in Celastrol research within the academic realm. Through examining the relevant studies, it highlights consistent outcomes, such as the attenuation of neuroinflammation, reduction of oxidative stress, neuroprotection, and promotion of neuronal survival. These significant findings lay the groundwork for further exploration and can serve as a guiding framework for future investigations and clinical trials focused on Celastrol as a potential therapeutic agent.

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Moreover, this review study offers valuable insights to researchers and clinicians interested in understanding the therapeutic applications of Celastrol. By compiling and summarizing the existing literature, it provides a concise and easily accessible overview of the current knowledge in the field. This contribution simplifies the process of reviewing previous research, saving time and effort for researchers embarking on new studies or clinicians seeking evidence-based interventions. Understanding the role of Celastrol in these debilitating illnesses is critical because it could pave the way for the development of innovative treatment options and help to improve overall patient outcomes.

Celastrol in Alzheimer's Disease

Celastrol has shown promise in alleviating cognitive impairment in animal models of Alzheimer's disease. According to one study, "Celastrol treatment significantly improved cognitive function in the tested animal model, as evidenced by better performance in memory-related tasks" (Zhang et al., 2021). Celastrol has anti-inflammatory effects and has been shown to reduce neuroinflammation in Alzheimer's disease patients. Celastrol treatment effectively reduced neuroinflammation in the transgenic mouse model, leading to improved memory and cognitive function (Wang et al., 2020). Celastrol modulates several signaling pathways implicated in Alzheimer's disease pathogenesis. Celastrol regulates the JAK2/STAT3 and PPAR/NF-kB pathways, which contribute to its anti-inflammatory and cognitive-enhancing properties (Huang et al., 2018; Zhang et al., 2019).

When these relevant sources and data are compared and analyzed, it is clear that Celastrol offers potential in ameliorating cognitive decline and decreasing neuroinflammation in Alzheimer's disease models. These benefits are achieved through its anti-inflammatory characteristics and regulation of signaling pathways involved in disease development.

It should be noted that more study, including clinical trials, is required to confirm these findings and establish Celastrol's potential as a therapeutic intervention for Alzheimer's disease. Furthermore, the exact doses, administration methods, and potential adverse effects related to Celastrol therapy must be considered.

Celastrol And Parkinsons Disease

Neuroprotection: Celastrol has been shown to be neuroprotective in Parkinson's disease mice. It is found that "Celastrol treatment showed significant neuroprotective effects, as evidenced by improved motor function and reduced dopaminergic neuron loss in the Parkinson's disease model" (Chen et al., 2021).

Reduced Neuroinflammation and Oxidative Stress: Celastrol can reduce neuroinflammation and oxidative stress in Parkinson's disease. Celastrol treatment effectively reduced neuroinflammatory responses and oxidative stress levels, thereby contributing to neuroprotection in the Parkinson's disease model (Wang et al., 2020).

Activation of the Nrf2/HO-1 Pathway: Celastrol stimulates the Nrf2/HO-1 pathway, which is important for neuroprotection. The relevance of the Nrf2/HO-1 pathway in mediating Celastrol's actions, such as lowering oxidative stress, inflammation, and enhancing neuronal survival, is highlighted (Li et al., 2020; Zhang et al., 2019).

Signal Pathway Modulation: Celastrol affects signaling pathways such as JAK2/STAT3 and PI3K/AKT, which contributes to its neuroprotective benefits in Parkinson's disease. Celastrol increases neuronal viability and prevents apoptosis via these routes (Lin et al., 2019).

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Disease	Experiment	Experiment effect of mechanism	Reference
Neuroinflammation and oxidative stress	*in vivo*	Attenuates neuroinflammation and neurological deficits via the p38/Nrf2/HO-1 signaling axis in a rat model of traumatic brain injury	Liu et al., 2020 Li et al., 2020
	in vivo	attenuates neuroinflammation and brain injury via the NF-κB signaling pathway in a rat model of intracerebral hemorrhage	Li et al., 2020
Parkinson's Disease	*in vivo, in vitro*	Improves motor function, reduces dopaminergic neuron loss	Chen et al., 2021
	in vivo	Reduces neuroinflammatory responses and oxidative stress levels	Wang et al., 2021
	in vivo	Activates Nrf2/HO-1 pathway in to reduce oxidative stress and inflammation, resulting in improved neuronal viability	Li et al., 2020, Zhang et al., 2019
	in vivo, in vitro	Exerts neuroprotection by activating mitophagy to degrade impaired mitochondria and further inhibit dopaminergic neuronal apoptosis	Lin et al. 2019
Alzheimer's Disease	*in vivo*	Promotes degradation of phosphorylated Tau aggregates and improves memory deficiency in AD animal models *via* activating TFEB-mediated autophagy.	Yang et al, 2022.
	in vivo	prevents the amyloid-β oligomer-induced neuroinflammation and memory impairment in a transgenic mouse model of Alzheimer's disease	Wang et al., 2020
	in vivo	ameliorates inflammation in a mouse model of Alzheimer's disease by regulating the JAK2/STAT3 signaling pathway	Zhang et al., 2019
	in vivo	ameliorates cognitive decline in a mouse model of Alzheimer's disease via the PPARγ/NF-κB pathway	Huang et al., 2018
Neuroprotection/Neuronal Survival	*in vivo*	prevents memory impairment and neuroinflamatory responses via Nrf2 activation	Liu et al., 2020
	in vivo	protects dopaminergic neurons via the Nrf2/HO-1 pathway	Li et al., 2020
	in vivo , *in vitro*	attenuates neuroinflammation and brain injury via the NF-κB signaling pathway	Lu et al.,2020
	in vivo, *in vitro*	inhibits dopaminergic neuronal death through activating mitophagy	Lin et al. 2019

Table 1. Effects of celastrol on neurological diseases

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When these relevant sources and studies are compared and analyzed. It becomes clear that Celastrol has the ability to produce neuroprotective benefits, reduce neuroinflammation, and alleviate oxidative stress in Parkinson's disease models. These effects are achieved by activation of the Nrf2/HO-1 pathway and regulation of neuronal viability and apoptosis signaling pathways. It is critical to recognize that further study, including clinical trials, is required to verify these findings and investigate the best dose, administration, and long-term benefits of Celastrol in Parkinson's disease. Furthermore, given the complexity of the pathogenesis of Parkinson's disease, a multidimensional strategy combining Celastrol with other treatment techniques may offer promise for improved results.

Celastrol in Neuroinflammation and Oxidative Stress

Neuroprotective Effects: Celastrol has neuroprotective properties in a number of neurodegenerative diseases. Celastrol has shown promising therapeutic potential in the treatment of neurodegenerative diseases by attenuating neuroinflammation and oxidative stress (Lu et al., 2020).

Neuroinflammation Reduction: Celastrol significantly lowers neuroinflammation in a variety of neurological diseases. Celastrol treatment significantly attenuated neuroinflammation and improved neurological deficits in a rat model of traumatic brain injury (Li et al., 2020).

Signaling Pathway Modulation: Celastrol exerts its effects by modulating numerous signaling pathways, including the p38/Nrf2/HO-1 and NF-kB pathways. Role of these pathways in mediating Celastrol's anti-inflammatory and neuroprotective actions (Li et al., 2020; Liu et al., 2020).

By comparing and analyzing these pertinent sources and data, it is clear that Celastrol has the ability to reduce neuroinflammation and oxidative stress in a variety of neurodegenerative disorders. Celastrol's neuroprotective effects are most likely achieved by regulation of signaling pathways linked with inflammation and oxidative stress.

It is critical to recognize that further study is required to completely understand Celastrol's mechanisms of action and therapeutic potential in neuroinflammation and oxidative stress. Additionally, clinical studies are necessary to validate these findings and explore the optimal dosage, administration, and long-term effects of Celastrol in neurodegenerative diseases.

Celastrol And Neuroprotection/Neuronal Survival

Neuroinflammation protection: Celastrol has been shown to inhibit neuroinflammatory reactions, which contribute to neurodegenerative processes.Celastrol protects against amyloid-induced memory impairment and neuroinflammatory responses via Nrf2 activation (Liu et al., 2020).

Neuroprotection: Celastrol has neuroprotective effects by increasing neuronal survival and reducing apoptosis. Celastrol improves neuronal viability and inhibits apoptosis through the JAK2/STAT3 and PI3K/AKT pathways in a cellular model of Parkinson's disease (Lin et al., 2019).

Activation of Protective Pathways: Celastrol protects neurons by activating particular pathways such as the Nrf2/HO-1 pathway. Celastrol protects dopaminergic neurons via the Nrf2/HO-1 pathway in a mouse model of Parkinson's disease (Li et al., 2020).

Attenuation of Brain damage: Celastrol lowers brain damage by attenuating neuroinflammation. "Celastrol attenuates neuroinflammation and brain injury via the

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NF-kB signaling pathway in a rat model of intracerebral hemorrhage (Liu et al., 2020).

By comparing and analyzing these pertinent sources and data, it is clear that Celastrol has the potential to provide neuroprotection and promote neuronal survival. Its benefits are linked to its capacity to reduce neuroinflammation, increase neuronal survival, activate protective pathways such as Nrf2/HO-1, and protect against brain damage.

It is crucial to emphasize, however, that further study, including clinical trials, is required to confirm these findings and investigate the best dose, administration, and long-term benefits of Celastrol in various neurodegenerative disorders. Additionally, the specific mechanisms underlying Celastrol's neuroprotective effects require further investigation.

DISCUSSION

The findings of the reviewed research reveal that Celastrol has substantial potential for reducing neuroinflammation and oxidative stress, as well as providing neuroprotection and boosting neuronal survival in a variety of neurodegenerative illnesses. Several mechanisms, including the activation of particular signaling pathways such as Nrf2/HO-1, JAK2/STAT3, and PI3K/AKT, as well as the regulation of transcription factors such as NF-kB, have been discovered to contribute to these effects

Celastrol, for example, inhibits amyloid-induced memory impairment and neuroinflammatory responses via Nrf2 activation (Liu et al., 2020). This is consistent with our findings on Celastrol's capacity to reduce neuroinflammation and promote neuroprotection. Similarly, Celastrol increases neuronal viability and prevents apoptosis via the JAK2/STAT3 and PI3K/AKT pathways, which is compatible with our findings on neuroprotection and neuronal survival (Lin et al. 2019).

Celastrol's capacity to alter key molecular pathways involved in these processes explains its effectiveness in decreasing neuroinflammation and oxidative stress. The activation of the Nrf2/HO-1 pathway, as observed (Li et al., 2020). Results in the overexpression of antioxidant and cytoprotective genes, counteracting oxidative damage. Furthermore, as proven (Liu et al., 2020). Celastrol's capacity to block NF-kB signaling leads to the regulation of pro-inflammatory mediators and the mitigation of brain damage.

It is crucial to emphasize that, while the findings of the evaluated studies are encouraging, more study is needed. To begin, more detailed mechanistic investigations are required to determine the particular molecular mechanisms via which Celastrol exerts its neuroprotective benefits. Furthermore, human clinical trials are required to evaluate the safety, appropriate dose, and long-term effectiveness of Celastrol in the treatment of neurodegenerative illnesses. Future studies relating to formulation, pharmacokinetics, dosage, and toxicity studies will be valuable for the optimization of Celastrol. The development of new celastrol derivatives and analogs may be important for therapeutic treatment.

The findings of this review study support the potential therapeutic value of Celastrol in neurodegenerative disorders. The ability of Celastrol to mitigate neuroinflammation, reduce oxidative stress, provide neuroprotection, and promote neuronal survival offers promising avenues for the development of novel therapeutic strategies. Further research and clinical investigations will be instrumental in realizing the full therapeutic potential of Celastrol in the management of these devastating conditions.

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CONCLUSION

This review has offered useful insights into the potential mechanisms of action and therapeutic uses of Celastrol in the setting of neurodegenerative illnesses by integrating and assessing the current information. Furthermore, while this evaluation focused on Celastrol's possible therapeutic efficacy, it is critical to examine potential adverse effects, medication interactions, and long-term safety.

Further study should address the shortcomings noted above, with an emphasis on well-designed clinical trials, standardizing outcome measurements, assessing safety profiles, and exploring the underlying mechanisms of Celastrol's effects. Obezite, sağlık hizmetlerinin müdahalelerine rağmen hızla büyüyen bir halk sağlığı sorunudur (Küçük ve Yıbar, 2021). Dünya Sağlık Örgütü (WHO), obezitenin küresel prevalansının 1975 ile 2016 yılları arasında nerdeyse üç katına çıkmış olduğunu belirtmiştir (WHO, 2021). Dünya çapında 650 milyonu obez olmak üzere 1,9 milyardan fazla yetişkinin aşırı kilolu olduğu bildirilmiştir (Rosa ve diğerleri, 2020). “Türkiye Beslenme ve Sağlık Araştırması-2019” raporuna göre Türkiye’de obezite prevalansı ise; 15 yaş ve üstü obez bireylerin oranı 2016 yılında %19,6 iken, 2019 yılında %21,1 olarak bulunmuştur (TÜİK, 2020).

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