**Garlic Acid and GABRB3 gene Role in Epileptic Seizure Manifestation**

.

ABSTRACT

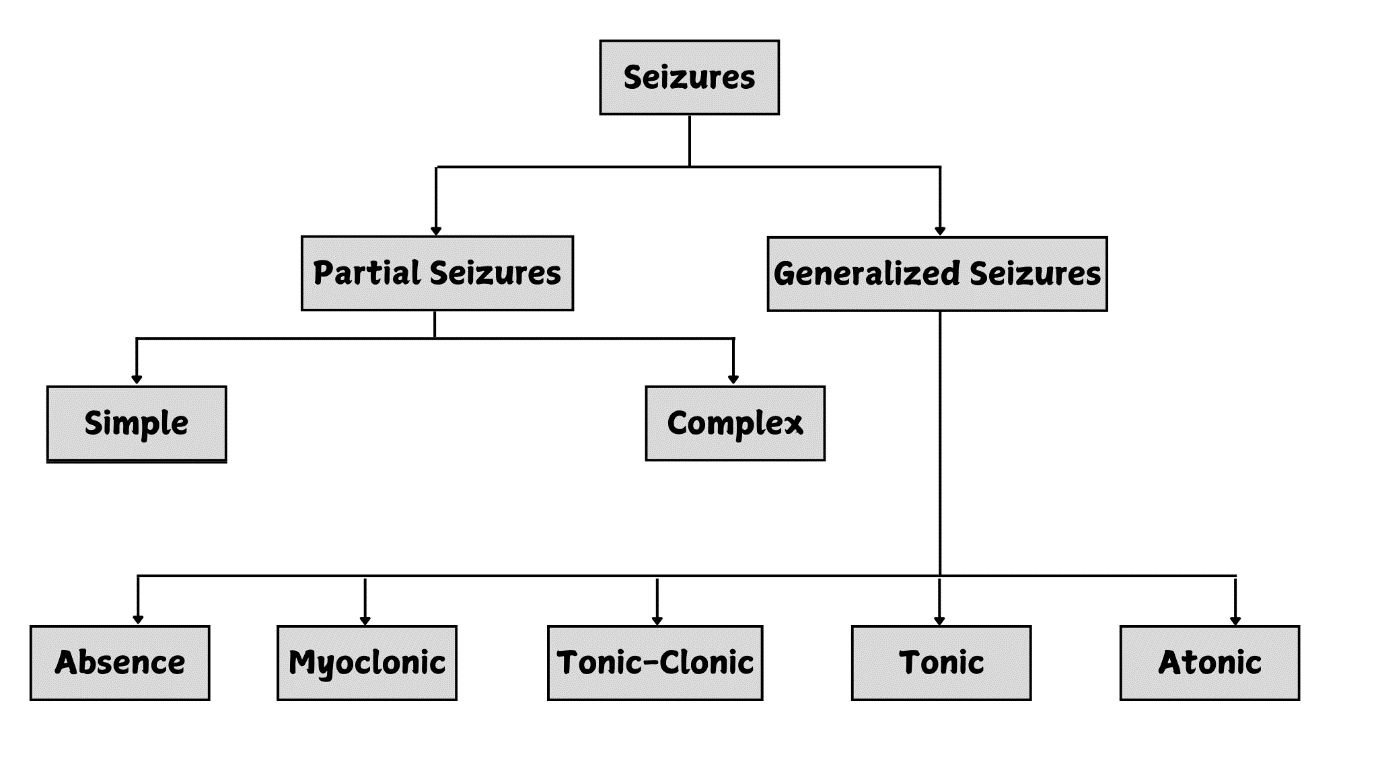
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| Epilepsy is a chronic neurological disorder characterized by recurrent unprovoked seizures, which result from abnormal excessive or synchronous neuronal activity in the brain. Alterations in GABAergic signaling can significantly contribute to seizure susceptibility and propagation. Studies have shown that genetic mutations affecting GABA\_A receptor subunits, such as those in the GABRB3 gene, are linked to various forms of epilepsy. These mutations can lead to a loss of function or altered receptor expression, resulting in reduced GABAergic inhibition and increased excitability within neural circuits. The interplay between excitatory and inhibitory neurotransmission is critical; a deficiency in GABAergic signaling can lead to hyperexcitability and ultimately contribute to the onset of seizures. Therapeutic modulation of the GABAergic system has been a cornerstone in the treatment of epilepsy. Many antiseizure medications (ASMs) enhance GABAergic transmission either by increasing GABA availability or by directly acting on GABA\_A receptors. Garlic acid is notable for its potential health benefits, particularly in neuroprotection and anti-inflammatory effects. Garlic contains a variety of organosulfur compounds, including allicin, alliin, and diallyl sulfides, which contribute to its characteristic flavor and therapeutic properties. The primary objective of this review is to explore the relationship between garlic acid and the GABRB3 gene in the context of epilepsy. Given the increasing interest in natural compounds as adjunctive treatments for neurological disorders, this review aims to synthesize current literature on the neuroprotective effects of garlic acid, particularly its potential influence on GABAergic neurotransmission and seizure regulation. |

*Keywords: (*Garlic acid, GABAergic, GABRB3, Epilepsy, Seizure, Neurotransmission*)*

1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent unprovoked seizures, which result from abnormal excessive or synchronous neuronal activity in the brain (1). According to the International League Against Epilepsy (ILAE), epilepsy is defined as a condition that predisposes individuals to recurrent seizures, with the diagnosis requiring at least two unprovoked seizures occurring more than 24 hours apart (2, 3). The disorder affects approximately 50 million people worldwide, one in three people worldwide, making it one of the most common neurological conditions globally (4, 5).

The classification of seizures and epilepsies has evolved significantly over the years, with the most recent update provided by the ILAE in 2017. This classification system categorizes seizures primarily based on their onset—focal or generalized—and further distinguishes them according to clinical features such as awareness and motor activity (6, 7). Focal seizures, which begin in one hemisphere of the brain, can be further classified based on whether consciousness is impaired. Conversely, generalized seizures involve both hemispheres and can manifest as tonic-clonic or absence seizures (8, 9). The updated classification also recognizes combined generalized and focal epilepsies and emphasizes the importance of understanding the etiology of each seizure type (2).



**Figure 1:** Overview of epilepsy classification (*Designed on Canva by authors*)

This comprehensive classification framework is crucial for clinicians and researchers as it aids in accurate diagnosis, treatment planning, and understanding the epidemiology of epilepsy. It also facilitates communication among healthcare providers and improves patient education regarding their condition. By categorizing epilepsies into distinct syndromes that incorporate clinical features, EEG findings, and genetic information, this system enhances our ability to tailor therapeutic interventions to individual patient needs (3, 6, 10).

The γ-aminobutyric acid (GABA)ergic system plays a crucial role in maintaining the balance between excitation and inhibition in the central nervous system (CNS). GABA is the primary inhibitory neurotransmitter in the mammalian brain, and its actions are mediated predominantly through GABA\_A receptors, which are chloride ion channels that hyperpolarize neurons upon activation (11, 12). This hyperpolarization is essential for preventing excessive neuronal firing, which can lead to seizures (13, 14).

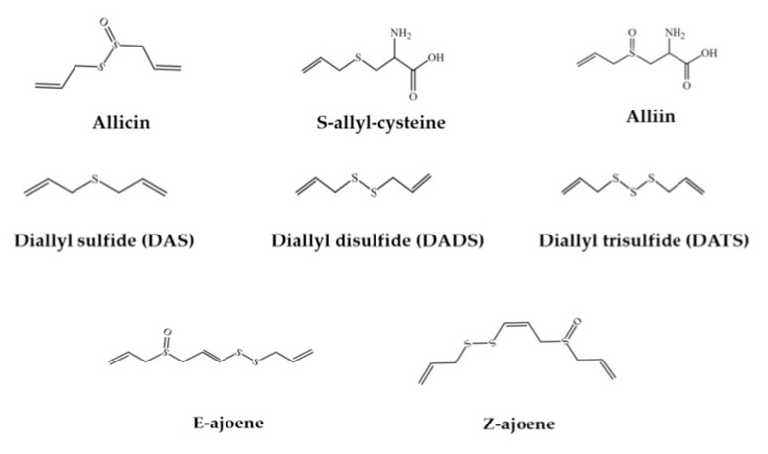
In the context of epilepsy, alterations in GABAergic signaling can significantly contribute to seizure susceptibility and propagation (15). In healthy neurons, GABA\_A receptor activation typically results in an influx of chloride ions (Cl⁻), leading to a hyperpolarizing effect that inhibits neuronal excitability (14, 15). However, in certain pathological conditions, such as during the development of epilepsy or in immature brains, the intracellular chloride concentration can be altered. This shift may cause GABA to produce a depolarizing effect instead, which can facilitate seizure activity (16, 17).

Research has shown that genetic mutations affecting GABA\_A receptor subunits, such as those in the GABRB3 gene, are linked to various forms of epilepsy. These mutations can lead to a loss of function or altered receptor expression, resulting in reduced GABAergic inhibition and increased excitability within neural circuits (18, 19). The interplay between excitatory and inhibitory neurotransmission is critical; a deficiency in GABAergic signaling can lead to hyperexcitability and ultimately contribute to the onset of seizures (20). The therapeutic modulation of the GABAergic system has been a cornerstone in the treatment of epilepsy. Many antiseizure medications (ASMs) enhance GABAergic transmission either by increasing GABA availability or by directly acting on GABA\_A receptors. For instance, benzodiazepines and barbiturates potentiate GABA's effects, thereby enhancing inhibitory signaling and reducing seizure frequency (21, 22). Recent advancements have led to the development of new ASMs that specifically target GABAergic mechanisms, aiming to provide more effective and better-tolerated treatment options for patients with epilepsy (23, 24).

**Garlic Acid: Neuroprotective Effects**

Garlic, scientifically known as Allium sativum, has been recognized for its culinary and medicinal properties for thousands of years. Among its many bioactive compounds, garlic acid is notable for its potential health benefits, particularly in neuroprotection and anti-inflammatory effects. Garlic contains a variety of organosulfur compounds, including allicin, alliin, and diallyl sulfides, which contribute to its characteristic flavor and therapeutic properties (25, 26). Garlic acid is derived from the enzymatic breakdown of alliin when garlic is crushed or chopped. This process generates allicin, which is the most biologically active compound in garlic. Allicin exhibits a range of pharmacological activities, including antioxidant, anti-inflammatory, and antimicrobial effects (27, 28). Additionally, garlic acid has been shown to enhance GABAergic neurotransmission, which may play a role in seizure regulation (23). This interaction suggests that garlic acid could be beneficial in managing conditions such as epilepsy, where GABAergic signaling is disrupted.

The chemical structure of garlic acid consists of a sulfur atom bonded to a carbon chain, which contributes to its reactivity and biological activity.



**Figure 2**: illustrates the chemical structure of garlic acid, highlighting its organosulfur nature (29).

Research has demonstrated that garlic and its derivatives possess neuroprotective properties by mitigating oxidative stress and inflammation in neuronal cells. For instance, studies have indicated that garlic extracts can reduce neuronal cell death induced by excitotoxicity and oxidative damage (30). Furthermore, garlic's ability to modulate neurotransmitter systems may provide therapeutic avenues for neurological disorders characterized by excitatory-inhibitory imbalances.

The primary objective of this review is to explore the relationship between garlic acid and the GABRB3 gene in the context of epilepsy. Given the increasing interest in natural compounds as adjunctive treatments for neurological disorders, this review aims to synthesize current literature on the neuroprotective effects of garlic acid, particularly its potential influence on GABAergic neurotransmission and seizure regulation.

**Interaction with GABAergic neurotransmission**

Recent studies have highlighted the significance of the GABAergic system in maintaining neuronal excitability and preventing seizures. As alterations in GABAergic signaling are implicated in various forms of epilepsy, understanding how garlic acid may interact with this system could provide insights into novel therapeutic strategies (23, 31). Additionally, the GABRB3 gene, which encodes a subunit of the GABA\_A receptor, has been associated with epilepsy through genetic mutations that affect receptor function and expression (18, 32, 33). The GABRB3 gene encodes the beta-3 subunit of the gamma-aminobutyric acid type A (GABA\_A) receptor, a critical component in the inhibitory neurotransmission system of the central nervous system. Located on chromosome 15 at the 15q12 region, GABRB3 spans approximately 250 kilobases and consists of 10 exons, with alternative splicing generating multiple isoforms of the protein (34, 10). This gene is part of a gene cluster that includes GABRA5 and GABRG3, which together contribute to the formation of functional GABA\_A receptors composed of various combinations of subunits (35).

The structure of the GABA\_A receptor is characterized by a pentameric arrangement, typically comprising two alpha, two beta, and one gamma subunit. The beta-3 subunit plays a crucial role in receptor function, influencing the receptor's pharmacological properties and its response to GABA, the primary inhibitory neurotransmitter in the brain (13). The receptor's activation leads to an influx of chloride ions (Cl⁻), resulting in hyperpolarization of the neuron and inhibition of neuronal excitability. Disruption in this process can lead to increased seizure susceptibility (36). Expression patterns of GABRB3 are not uniform across different brain regions or developmental stages. It is highly expressed in embryonic brain tissue, where it is regulated by transcription factors such as repressor-element-1-silencing transcription factor (REST) (18). In adults, expression levels are significantly lower but remain elevated in specific areas such as the hippocampus, which is crucial for memory and learning processes. Studies have shown that homozygous disruption of GABRB3 in animal models leads to severe neurological deficits, including myoclonic seizures and impaired cognitive functions (23).

Notably, mutations in GABRB3 have been linked to various neurodevelopmental disorders, including epilepsy. Specific point mutations within this gene have been associated with childhood absence epilepsy (CAE), resulting in decreased GABAergic currents and altered neuronal excitability (18). These findings underscore the importance of GABRB3 not only in normal brain function but also in its role as a significant contributor to epilepsy pathogenesis. The GABRB3 gene, which encodes the beta-3 subunit of the GABA\_A receptor, has been implicated in various seizure disorders due to its critical role in inhibitory neurotransmission. Genetic variants in GABRB3 can lead to both gain-of-function (GOF) and loss-of-function (LOF) effects, contributing to a spectrum of epilepsy phenotypes. Recent studies have identified numerous pathogenic variants associated with epilepsy, highlighting the importance of GABRB3 in the pathophysiology of these disorders. A comprehensive analysis of GABRB3 variants has revealed that many of these mutations are missense changes, which alter amino acid sequences and can affect receptor function. For instance, a study identified 54 epilepsy-associated missense variants and additional truncating or frameshift mutations within the coding region of GABRB3 (37). These variants were classified as pathogenic based on the American College of Medical Genetics and Genomics (ACMG) criteria, with most cases being de novo mutations (34).

Table 1 summarizes known GABRB3 variants and their associations with various seizure disorders. The data indicate that individuals with GABRB3 mutations often present with early-onset seizures, developmental delays, and varying degrees of intellectual disability. Common seizure types associated with these variants include focal seizures, generalized tonic-clonic seizures, and epileptic spasms (34).

Interestingly, while LOF variants have traditionally been associated with decreased GABAergic inhibition leading to increased seizure susceptibility, recent findings have shown that some GOF variants can also contribute to severe epilepsy phenotypes. According to (37), two patients with specific GABRB3 mutations exhibited hypersensitivity to vigabatrin, suggesting that these mutations resulted in enhanced receptor activity rather than diminished function. This challenges the prevailing assumption that all epilepsy-associated GABRB3 variants lead to LOF effects. The clinical implications of these findings are significant. Understanding the specific genetic variants present in patients can inform treatment strategies and improve personalized medicine approaches for epilepsy management. For instance, identifying whether a patient carries a LOF or GOF variant could guide the selection of antiepileptic drugs that target specific receptor functions (38).

**Table 1:** Summary of Known GABRB3 Variants and Their Associations with Seizure Disorders

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variant Type** | **Specific Variant(s)** | **Associated Seizure Disorders** | **Onset Age** | **Notes** |
| Missense (18) | p. (Glu77Lys), p. (Thr287Ile) | Developmental and Epileptic Encephalopathy | Early infancy | Gain-of-function effects observed |
| Truncating (39). | Various | Childhood Absence Epilepsy | 0-14 years | Loss-of-function effects leading to seizures |
| Frameshift (40) | Various | Focal Seizures, Generalized Tonic-Clonic Seizures | 1-21 months | Severe developmental delay common |
| Deletion (41) | Various | Dravet Syndrome, Febrile Seizures Plus | Varies | Often associated with intellectual disability |

Recent research has significantly advanced our understanding of the GABRB3 gene and its role in epilepsy, revealing various genetic mutations associated with different seizure disorders. The GABRB3 gene encodes the beta-3 subunit of the GABA\_A receptor, which is crucial for inhibitory neurotransmission in the central nervous system. Mutations in this gene have been linked to a range of neurodevelopmental disorders, including epilepsy, autism spectrum disorders (ASD), and Angelman syndrome (42, 18).

Several studies have identified specific mutations within the GABRB3 gene that correlate with early-onset epilepsy syndromes (42, 37, 43). For example (18) reported that three different point mutations in exons 1A and 2 of GABRB3 segregated with childhood absence epilepsy (CAE), resulting in decreased GABAergic currents. These mutations can lead to significant alterations in receptor function, contributing to increased neuronal excitability and seizure susceptibility.

Furthermore, GABRB3 mutations have been implicated in more severe forms of epilepsy, such as Lennox-Gastaut syndrome and infantile spasms. A recent case study highlighted a patient with a novel GABRB3 mutation who presented with neonatal hypotonia and developed pharmacoresistant epileptic encephalopathy characterized by multiple seizure types beginning at three months of age (10). Electroencephalographic findings revealed generalized and multifocal epileptiform abnormalities, underscoring the critical role of GABRB3 in early-onset seizure disorders.

In addition to direct mutations, epigenetic factors also influence GABRB3 expression and function. Research indicates that alterations in the regulatory regions of GABRB3 can lead to changes in its expression levels, which may contribute to the pathogenesis of ASD and other neurodevelopmental disorders (23). Notably, increased expression of GABRB3 has been associated with certain ASD phenotypes, suggesting a complex interplay between genetic variants and environmental factors in the development of these conditions (44, 34). Table 1 summarizes key findings from current research on GABRB3 variants and their associations with various seizure disorders. The data indicate that both gain-of-function and loss-of-function mutations can lead to distinct clinical presentations, emphasizing the need for personalized approaches to treatment based on specific genetic profiles.

**Garlic Acid: Neuroprotective Effects**

Garlic acid, a prominent bioactive compound derived from Allium sativum, has garnered significant attention due to its diverse therapeutic properties, particularly in neuroprotection and modulation of oxidative stress. The primary bioactive constituents of garlic include allicin, alliin, diallyl sulfide, and various organosulfur compounds, which contribute to its health benefits (44). These compounds exhibit a range of biological activities that make garlic acid a valuable candidate for the prevention and management of various diseases, including neurological disorders. One of the key mechanisms by which garlic acid exerts its neuroprotective effects is through its antioxidant properties. Research indicates that garlic acid can enhance the expression of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, thereby reducing oxidative stress in neuronal cells (45). This reduction in oxidative stress is crucial because excessive oxidative damage is a significant contributor to neuronal injury and is implicated in the pathogenesis of epilepsy and other neurodegenerative diseases (47).

In addition to its antioxidant capabilities, garlic acid has been shown to possess anti-inflammatory properties. It can inhibit the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are often elevated in neurological conditions and contribute to neuroinflammation (48). By modulating inflammatory pathways, garlic acid may help protect against neuronal damage and improve overall brain health. Furthermore, garlic acid has been reported to enhance GABAergic neurotransmission, which is particularly relevant in the context of epilepsy. Studies suggest that garlic-derived compounds can increase GABA levels in the brain, thereby promoting inhibitory signaling and potentially reducing seizure frequency (47, 31). This interaction with the GABAergic system underscores the potential of garlic acid as an adjunctive treatment for epilepsy, especially in patients with disrupted GABAergic signaling. Garlic acid's bioactivity is also influenced by its method of preparation and consumption. Raw garlic typically contains higher concentrations of bioactive compounds; however, certain processing methods can enhance the availability of these compounds. For instance, fermentation has been shown to increase the levels of beneficial sulfur-containing compounds while reducing pungency (45). This suggests that dietary choices regarding garlic consumption may impact its therapeutic efficacy.

One notable study utilized a rat model to investigate the effects of garlic extract on oxidative stress-induced neuronal injury. The results indicated that garlic extract significantly reduced levels of malondialdehyde (MDA), a marker of lipid peroxidation, while increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) (48, 49). This suggests that garlic acid can effectively counteract oxidative damage in neuronal tissues, which is particularly relevant in conditions characterized by increased oxidative stress, such as epilepsy. Another preclinical investigation focused on the anti-inflammatory properties of garlic acid. In a mouse model of neuroinflammation induced by lipopolysaccharide (LPS), treatment with garlic extract resulted in a significant reduction in pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (32, 33). This anti-inflammatory effect is crucial as neuroinflammation is known to exacerbate neuronal excitability and contribute to seizure propagation.

Furthermore, studies have explored the impact of garlic acid on GABAergic signaling. In an animal model of epilepsy induced by pentylenetetrazol (PTZ), administration of garlic extract was found to enhance GABA levels in the brain, leading to a significant reduction in seizure frequency and duration (47, 50). This finding highlights the potential of garlic acid as a natural adjunctive therapy for epilepsy by modulating inhibitory neurotransmission.

**Table 2**: Summary of Animal Models Used in Garlic Acid Research

|  |  |  |  |
| --- | --- | --- | --- |
| **Animal Model** | **Treatment** | **Outcomes** | **Mechanism of Action** |
| Rat (51) | Garlic extract | Reduced oxidative stress markers | Increased SOD and CAT activity |
| Mouse (52) | Garlic extract | Decreased levels of TNF-α and IL-6 | Anti-inflammatory effects |
| PTZ-induced seizure model (53) | Garlic extract | Reduced seizure frequency and duration | Enhanced GABA levels |
| LPS-induced neuroinflammation (32) | Garlic acid | Lowered pro-inflammatory cytokines | Inhibition of neuroinflammation |
| Chronic renal failure model (54) | Garlic extract | Improved renal function and reduced oxidative stress | Antioxidant activity |

Table 2 summarizes various animal models used in garlic acid research, detailing the specific outcomes observed and mechanisms involved. These studies collectively underscore the multifaceted bioactivity of garlic acid, supporting its role as a neuroprotective agent with potential therapeutic applications in epilepsy and related disorders.

**Potential Mechanisms of Action**

Garlic acid and its bioactive compounds exhibit a range of pharmacological activities that contribute to their neuroprotective effects, particularly in the context of epilepsy and other neurological disorders. The mechanisms through which garlic acid exerts its beneficial effects can be broadly categorized into antioxidant, anti-inflammatory, and neurochemical pathways. Antioxidant Activity, one of the primary mechanisms of action attributed to garlic acid is its potent antioxidant activity. Garlic acid has been shown to enhance the expression of various antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), thereby reducing oxidative stress within neuronal cells (47). This reduction in oxidative stress is crucial, as excessive reactive oxygen species (ROS) can lead to neuronal damage and contribute to the pathogenesis of epilepsy (54). Garlic-derived compounds like allicin are particularly effective at scavenging free radicals, which helps protect neurons from oxidative injury (55). Garlic acid also exhibits significant anti-inflammatory properties, which are vital for protecting neuronal health. It has been demonstrated that garlic extracts can inhibit the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in various models of neuroinflammation (32, 33). By modulating inflammatory pathways, garlic acid can reduce neuroinflammation, a known contributor to increased seizure susceptibility and severity (48). The inhibition of nuclear factor kappa B (NF-κB) signaling is one mechanism through which garlic acid exerts its anti-inflammatory effects, leading to decreased expression of inflammatory mediators in the brain (56).

Another critical mechanism by which garlic acid may exert its neuroprotective effects is through the enhancement of GABAergic neurotransmission. Research indicates that garlic acid can increase GABA levels in the brain, promoting inhibitory signaling and potentially reducing seizure frequency (47). This interaction with the GABAergic system is particularly relevant for individuals with epilepsy, where GABAergic dysfunction is often observed. By enhancing GABAergic activity, garlic acid may help restore balance within excitatory-inhibitory networks in the brain.

Garlic acid has also been shown to influence nitric oxide (NO) production, which plays a role in vasodilation and neurotransmission. Increased NO levels can enhance blood flow to the brain and improve overall neuronal function (55). The modulation of NO production by garlic compounds may contribute to their neuroprotective effects by promoting better oxygenation and nutrient delivery to brain tissues.

**Interplay Between Garlic Acid and GABRB3 in Epileptic Seizures**

Garlic acid, a bioactive compound derived from Allium sativum, has shown promising potential in modulating the GABAergic system, which is critical for maintaining inhibitory neurotransmission in the brain. The GABRB3 gene encodes the beta-3 subunit of the GABA\_A receptor, and mutations in this gene can lead to various forms of epilepsy characterized by impaired GABAergic signaling (18). Understanding the interplay between garlic acid and GABRB3 is essential for exploring novel therapeutic strategies for epilepsy.

Research indicates that garlic acid may enhance GABAergic function through several mechanisms. One of the primary ways garlic acid exerts its effects is by increasing the levels of GABA in the brain. Studies have demonstrated that garlic extracts can elevate GABA concentrations, thereby promoting inhibitory signaling and potentially reducing seizure activity (47). This is particularly relevant for individuals with GABRB3 mutations, where GABA\_A receptor function is compromised, leading to increased neuronal excitability and seizure susceptibility.

In a study examining the effects of garlic-derived compounds on GABA\_A receptor activity, it was found that these compounds could potentiate GABA-induced currents. Specifically, garlic acid was shown to enhance chloride ion influx through GABA\_A receptors, thereby increasing inhibitory neurotransmission (18). This synergistic effect suggests that garlic acid could serve as an adjunctive treatment for patients with epilepsy associated with GABRB3 mutations, particularly those exhibiting loss-of-function variants (57).

Moreover, the potential for garlic acid to modulate the activity of GABA\_A receptors could have significant implications for therapeutic strategies involving drugs like vigabatrin. Vigabatrin is a medication that increases GABA levels by inhibiting its breakdown; however, its efficacy can vary depending on the specific genetic variant present in patients (18). For individuals with certain gain-of-function variants of GABRB3, vigabatrin may exacerbate symptoms due to increased tonic currents mediated by these receptors. In contrast, garlic acid's ability to enhance GABAergic signaling without causing adverse effects may provide a safer alternative or complementary approach for managing seizures in this population (18).

Furthermore, garlic acid's antioxidant and anti-inflammatory properties may also contribute to its neuroprotective effects. By reducing oxidative stress and inflammation in neuronal tissues, garlic acid can create a more favorable environment for effective GABAergic signaling (47, 58). This multifaceted approach underscores the potential of garlic acid not only as a modulator of neurotransmission but also as a protective agent against the pathological processes that contribute to epilepsy.

**Clinical Observations**

Clinical observations and studies have increasingly highlighted the potential benefits of garlic and its derivatives in managing epilepsy. Garlic, particularly in the form of aged garlic extract (AGE), has been recognized for its neuroprotective properties, which may contribute to seizure reduction and improved neurological function in individuals with epilepsy. One notable study examined the protective effects of AGE against pentylenetetrazole (PTZ)-induced seizures in a rat model. The results demonstrated that pretreatment with AGE significantly decreased the incidence of seizures, with an 80% reduction observed at a dose of 400 mg/kg (51). Furthermore, AGE administration elevated the median convulsive dose (CD50) of PTZ, indicating a protective effect against seizure induction. This study also reported a significant increase in brain GABA levels following AGE treatment, suggesting that garlic may enhance inhibitory neurotransmission, which is crucial for seizure control.

In another clinical observation involving children with epilepsy, garlic consumption was associated with improved seizure control and reduced frequency of episodes. Parents reported that regular intake of garlic led to fewer seizures and better overall management of their children's condition (59). This anecdotal evidence supports the notion that dietary interventions, including garlic supplementation, may serve as a complementary approach to conventional antiepileptic medications. A comprehensive review of natural products in epilepsy also noted that garlic has been used traditionally for its anticonvulsant properties. Although specific clinical trials are limited, many patients have reported subjective improvements in seizure frequency and severity when incorporating garlic into their diet (60, 61). The review emphasized the need for further research to substantiate these claims and explore the underlying mechanisms by which garlic exerts its effects on seizure activity.

**Table 3:** Overview of Clinical Studies Linking Garlic Consumption to Epilepsy Outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study Reference** | **Population** | **Intervention** | **Key Findings** | **Conclusion** |
| Thabet et al. (2016) | Rat model | Aged garlic extract (AGE) | 80% reduction in seizure incidence; increased GABA levels | AGE shows potential as a neuroprotective agent against seizures. |
| He et al., (2021) | Children with epilepsy | Garlic consumption | Reports of reduced seizure frequency | Regular intake may help manage epilepsy symptoms. |
| Bayan et al. (2014) | General population | Garlic supplementation | Anecdotal improvements in seizure control | Further research needed to confirm benefits. |

Table 3 provides an overview of clinical studies linking garlic consumption to epilepsy outcomes, summarizing key findings and implications for future research.

**Potential for Therapeutic Use**

Garlic (Allium sativum) has long been recognized for its medicinal properties, and recent research has reinforced its potential therapeutic applications, particularly in the context of neurological disorders such as epilepsy (26, 62). The bioactive compounds in garlic, including allicin and garlic acid, exhibit a range of pharmacological effects that may contribute to seizure management and overall brain health (45, 47). One of the primary therapeutic potentials of garlic lies in its ability to enhance GABAergic neurotransmission. As discussed previously, garlic acid has been shown to increase GABA levels in the brain, which is crucial for maintaining inhibitory control over neuronal excitability (47, 20). This mechanism is particularly relevant for patients with epilepsy, where GABAergic dysfunction is often a contributing factor to seizure activity. By promoting GABAergic signaling, garlic may serve as an effective adjunctive treatment alongside conventional antiepileptic medication (63).

Clinical studies have also suggested that garlic consumption can lead to improved seizure control and reduced frequency of episodes in individuals with epilepsy (64). For instance, a systematic review indicated that patients who incorporated garlic into their diets reported subjective improvements in seizure management (60). Although these findings are primarily anecdotal, they underscore the need for further clinical trials to explore the efficacy and safety of garlic as a complementary therapy in epilepsy.

In addition to its effects on GABAergic function, garlic's antioxidant and anti-inflammatory properties may further enhance its therapeutic potential. Garlic has been shown to reduce oxidative stress and inflammation in various models of neurological disorders (51, 65). This is particularly significant given that oxidative stress and neuroinflammation are implicated in the pathophysiology of epilepsy. By mitigating these factors, garlic could help protect neuronal integrity and improve outcomes for individuals with seizure disorders (32).

Moreover, the potential for garlic to influence other signaling pathways related to neuronal health cannot be overlooked. Research indicates that garlic compounds can modulate pathways associated with neuroprotection, such as the Nrf2/Keap1 signaling pathway, which plays a role in cellular defense against oxidative stress (54, 32). This multifaceted approach positions garlic as a promising candidate for drug development aimed at treating epilepsy and other neurological conditions.

Despite the promising findings, it is essential to conduct more rigorous clinical trials to establish standardized dosages, formulations, and long-term safety profiles of garlic as a therapeutic agent. Current evidence suggests that while garlic is generally safe for consumption, potential adverse effects from high doses or long-term use need to be evaluated, especially in vulnerable populations such as pregnant women or children (60, 66).

**FUTURE DIRECTION**

Despite the promising findings regarding the potential therapeutic applications of garlic acid in epilepsy, particularly in relation to the GABRB3 gene, there are still several gaps in current researches that need to be addressed:

1. Lack of mechanistic understanding: Although several potential mechanisms of action have been proposed, such as antioxidant activity, anti-inflammatory effects, and enhancement of GABAergic neurotransmission, the precise mechanisms by which garlic acid interacts with the GABRB3 gene and influences seizure susceptibility are not fully elucidated. Further research is needed to elucidate the molecular pathways involved in this interplay.
2. Unexplored areas of GABRB3 function: While the role of GABRB3 in epilepsy has been well-established, there are still many unexplored areas regarding its function in the brain. For instance, the potential influence of GABRB3 on other neurotransmitter systems, such as glutamatergic signalling, and its implications for seizure regulation have not been extensively studied. Investigating these unexplored areas could provide valuable insights into the pathophysiology of epilepsy and guide the development of targeted therapies.
3. Lack of standardized formulations and dosages: There is a lack of standardization in the preparation and dosing of garlic-derived compounds, which can lead to inconsistencies in research findings and make it challenging to translate results into clinical practice. Establishing standardized formulations and determining optimal dosages for therapeutic efficacy are crucial steps in advancing the use of garlic acid as a potential treatment for epilepsy.
4. Underrepresentation of diverse populations: Most of the current research on garlic acid and epilepsy has been conducted in Western populations. There is a need for more studies involving diverse ethnic and socioeconomic backgrounds to ensure that the potential benefits of garlic acid are accessible to all individuals with epilepsy, regardless of their geographic location or cultural background.
5. Limited clinical evidence: While preclinical studies have demonstrated the neuroprotective effects of garlic acid and its ability to modulate GABAergic function, there is a paucity of well-designed clinical trials investigating its efficacy and safety in patients with epilepsy. More robust clinical data is needed to establish the therapeutic potential of garlic acid and its derivatives in the management of seizure disorders.

To address these gaps, future research should focus on conducting well-designed clinical trials, elucidating the precise mechanisms of action, exploring unexplored areas of GABRB3 function, standardizing formulations and dosages, and including diverse populations in research studies. Interdisciplinary collaborations between researchers, clinicians, and patient advocates will be crucial in driving this research forward and ultimately improving the lives of individuals with epilepsy.

**Recommendations for future studies**

As research into the therapeutic potential of garlic acid and its relationship with the GABRB3 gene progresses, several key recommendations can be made to guide future studies in this area. Addressing these recommendations will help to fill existing gaps in knowledge and enhance the understanding of garlic's role in epilepsy management.

1. Conduct Rigorous Clinical Trials: There is a pressing need for well-designed clinical trials to evaluate the efficacy and safety of garlic acid in patients with epilepsy. These studies should focus on various populations, including those with specific genetic variants like GABRB3 mutations, to assess how garlic acid may influence seizure frequency and severity
2. Explore Mechanistic Pathways: Future research should delve deeper into the molecular mechanisms by which garlic acid interacts with GABAergic signaling and other neurotransmitter systems. Understanding how garlic acid modulates GABRB3 function and its downstream effects on neuronal excitability could elucidate its potential as a therapeutic agent. Investigating these pathways will also help identify biomarkers that could predict patient responses to garlic-based treatments.
3. Standardize Dosage and Formulation: Research should aim to establish standardized dosages and formulations of garlic-derived compounds for therapeutic use. Establishing optimal dosing regimens based on pharmacokinetic studies will be crucial for translating findings into clinical practice.
4. Investigate Long-term Effects: Longitudinal studies are needed to assess the long-term effects of garlic consumption on seizure control and overall neurological health. Understanding the chronic effects of garlic acid, including potential side effects or interactions with conventional antiepileptic drugs, will be essential for determining its
5. Utilize Advanced Technologies: The integration of advanced technologies such as machine learning and neuroimaging can enhance research methodologies. These technologies can help identify specific patient subgroups that may benefit most from garlic-based therapies and monitor changes in brain activity associated with treatment.

By addressing these recommendations, future research can significantly advance the understanding of garlic acid's role in epilepsy treatment and contribute to developing effective, personalized therapies for patients suffering from this complex neurological disorder.

**Conclusion**

This review has explored the potential relationship between garlic acid and the GABRB3 gene in the context of epilepsy. The GABRB3 gene encodes a subunit of the GABA\_A receptor, and mutations in this gene have been linked to various forms of epilepsy characterized by impaired GABAergic. Garlic acid exhibits neuroprotective effects through its antioxidant, anti-inflammatory, and GABAergic modulatory properties, which may contribute to its potential therapeutic applications in epilepsy. The interplay between garlic acid and the GABRB3 gene highlights a promising avenue for developing novel therapies for epilepsy. By enhancing GABAergic function and providing neuroprotection through its antioxidant properties, garlic acid may serve as an effective adjunctive treatment for patients with epilepsy linked to GABRB3 mutations. However, more rigorous research needs to be carried out followed by clinical trials to establish the efficacy and safety of garlic-based treatments.

While this review has synthesized current research on the potential therapeutic applications of garlic acid in epilepsy, several gaps remain. Future studies should focus on conducting well-designed clinical trials, elucidating the precise mechanisms of action, exploring unexplored areas of GABRB3 function, standardizing formulations and dosages, and including diverse populations in research studies. Interdisciplinary collaborations between researchers, clinicians, and patient advocates will be crucial in driving this research forward and ultimately improving the lives of individuals with epilepsy.

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