Modulating Proteasome Function with Polyphenol Metabolites: A Promising Therapeutic Avenue for Alzheimer's Disease

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Abstract
Alzheimer's disease (AD) presents many difficulties and has few available therapies. Because of their many advantages, polyphenolic metabolites of flavan-3-ol have gained attention as possible candidates for AD treatment. This work investigates the impact of these compounds on proteasome function in neuronal cells expressing genes related to AD. It finds that these compounds have inhibitory effects on proteasomes, especially in cells that have mutations in genes related to AD. Amyloid plaques, neurofibrillary tangles, oxidative stress, compromised autophagy, and proteasome systems, which affect protein clearance, are all components of AD pathology. Rich in anti-inflammatory and antioxidant qualities, polyphenols change into bioactive metabolites such as phenyl-γ-valerolactones. These metabolites alter Aβ oligomers and mitigate Aβ toxicity, potentially providing a therapeutic intervention for AD. The presented findings underscore the potential of various compounds, including C1, C2, C3, PGPH, and BrAAP, as modulators of proteasome function. The differential inhibitory effects observed on both constitutive (ChT-L) and immunoproteasome (T-L) activities signify the nuanced impact of these compounds. Notably, the selectivity of certain compounds towards either proteasome subtype suggests the possibility of targeted therapeutic strategies, particularly in the context of diseases associated with proteasome dysfunction, such as neurodegenerative disorders like Alzheimer's Disease. This study looks at how flavan-3-ol metabolites affect proteasome function and how they might be used as AD treatment agents. Understanding their effects on proteasomes opens avenues for novel AD treatments at a molecular level.

Introduction
Alzheimer's Disease (AD) is a devastating neurodegenerative disorder characterized by progressive cognitive decline, memory loss, and impaired daily functioning [1]. The prevalence of AD has been steadily rising, posing a significant and growing burden on global healthcare systems [2]. With an aging population and longer life expectancy, the number of individuals affected by AD continues to increase, extending its impact beyond the affected individuals to families, caregivers, and societies at large [Jagannath et al., 2020]. Presently, treatment options for AD are limited and predominantly focus on alleviating symptoms rather than addressing the underlying causes [3]. Approved medications aim to temporarily improve cognitive function or manage behavioral symptoms, but their efficacy is modest and often diminishes over time [4]. The existing therapeutic landscape for AD emphasizes the pressing need for innovative approaches that target the root causes of the disease [5]. Aging-associated neurodegenerative diseases, characterized by progressive neuronal death and synapse loss in the human brain, are rapidly growing and affecting millions of people globally [6]. AD is clinically manifested by progressive impairment in cognition, learning ability, memory function, and executive reasoning [7]. It is described by a global cognitive decline that involves memory loss, visuospatial orientation, impaired judgment, communication, and reasoning, making it a major and growing health challenge worldwide [8]. Despite intensive research efforts, Alzheimer's disease (AD) remains a prevalent and intricate
neurodegenerative condition with no conclusive treatment options [9]. The pathophysiology of Alzheimer’s disease (AD) is complex and involves multiple molecular pathways. It is typified by the build-up of amyloid plaques (Aβ peptides), neurofibrillary tangles (NFTs), oxidative stress, and neuroinflammation.

One of the main players in AD pathogenesis is the accumulation of aberrant protein aggregates, which is a hallmark of the disease. These aggregates are primarily caused by dysfunctions within the autophagy and ubiquitin-proteasome systems (UPS). Protease dysregulation in Alzheimer’s disease (AD) impairs the proteasome’s ability to efficiently clear misfolded or abnormal proteins, including Aβ peptides. The proteasome is essential to intracellular protein turnover and quality control mechanisms.

The search for new treatment approaches has focused on natural substances, especially polyphenols, which are well known for their neuroprotective, anti-inflammatory, and antioxidant capabilities. Within this framework, flavan-3-ols—which are widely distributed in different food sources—have attracted notice because they are converted by microbiological metabolism into bioactive metabolites, most notably phenyl-γ-valerolactones.

This investigation highlights the potential of these flavan-3-ol metabolites in addressing AD pathology by focusing on proteasomal function, as demonstrated by recent studies. This work explores the proteasome modulatory effects of human-derived metabolites from flavan-3-ols, with a focus on their effects on neuronal cells that express either the 717 valine-to-glycine AβPP-mutated gene (APPmut) or the wild-type amyloid precursor protein gene (APPwt), which mirrors important aspects of AD pathology. Notable results show that these compounds, which include a sulfated derivative and mono- and dihydroxylated phenyl-γ-valerolactones, significantly inhibit both cellular and isolated proteasomes. Particularly compelling is the observation that cells expressing the APPmut gene display heightened susceptibility to these compounds, suggesting a targeted impact on AD-associated molecular mechanisms.

The urgency to address the impact of AD on global health is increasingly apparent, and understanding the scale of this public health challenge is crucial for developing effective strategies and interventions [10]. While there is no cure or effective treatment for AD, the exploration of potential therapeutic interventions is essential. This necessitates a comprehensive understanding of the disease’s pathophysiology and the identification of novel targets for intervention [11]. The neuropathological diagnosis of AD is most often associated with memory deficits and cognitive decline, although less common clinical presentations are increasingly recognized [12].

The primary aim of this study is to investigate the modulatory effects of polyphenol metabolites, particularly phenyl-γ-valerolactones derived from flavan-3-ols, on proteasome function in the context of Alzheimer’s Disease (AD). The study seeks to elucidate the molecular mechanisms underlying the impact of these natural compounds on proteasomal activity, specifically examining their effects on neuronal cells expressing wild-type amyloid precursor protein gene (APPwt) or the 717 valine-to-glycine AβPP-mutated gene (APPmut), replicating crucial aspects of AD pathology.

This investigation aims to:

- **Characterize Proteasome Modulation:** Assess the inhibitory effects of polyphenol metabolites on isolated and cellular proteasomes, delineating their impact on the turnover and clearance of abnormal proteins, including Aβ peptides, pivotal in AD pathology.
- **Elucidate Molecular Pathways:** Investigate the underlying mechanisms of phenyl-γ-valerolactones’ influence on proteasome functionality, exploring their interactions with the ubiquitin-proteasome system (UPS) and assessing their role in altering proteasomal activity in AD-associated cellular models.
- **Evaluate Therapeutic Potential:** Determine the therapeutic potential of phenyl-γ-valerolactones and other polyphenol metabolites in mitigating neurotoxicity associated with AD by counteracting Aβ toxicity, modifying toxic Aβ oligomers into non-toxic forms, and potentially ameliorating proteolytic dysfunctions [13].
- **Assess Selective Impact:** Analyze the differential impact of these compounds on proteasomal function in cells expressing APPwt versus APPmut, discerning the targeted effects on AD-related molecular mechanisms and identifying potential therapeutic implications for AD treatment strategies. By achieving these objectives, this study aims to contribute to a deeper understanding of the role of polyphenol metabolites in modulating proteasome function, offering insights into their therapeutic potential as a targeted intervention for AD.

**Proteolysis of proteins in Alzheimer**

In Alzheimer’s disease (AD), proteolysis, the process of breaking down proteins, is intricately linked to the accumulation of pathogenic protein aggregates, contributing significantly to neurodegeneration. The ubiquitin-proteasome system (UPS) and autophagy, two primary proteolytic pathways, play pivotal roles in maintaining cellular protein homeostasis. However, dysregulation in these systems in the context of AD leads to the accumulation of misfolded and toxic proteins, a hallmark of the disease [14].
 Ubiquitin Proteasome System (UPS) Dysfunction

The UPS is a major intracellular protein degradation pathway responsible for clearing short-lived or damaged proteins tagged with ubiquitin for proteasomal degradation [15]. In AD, the UPS faces substantial impairment, impacting the clearance of aberrant proteins, particularly amyloid-beta (Aβ) peptides and tau proteins. Several factors contribute to UPS dysfunction in AD:

Accumulation of Toxic Proteins: The accumulation of Aβ peptides and hyperphosphorylated tau proteins overwhelms the UPS, leading to its inefficiency in clearing these toxic aggregates [16].

Oxidative Stress and Inflammation: AD is characterized by increased oxidative stress and neuroinflammation, both of which directly impair proteasomal function, exacerbating the buildup of pathological proteins.

Proteasome Dysfunction: Alterations in proteasomal subunits, reduced proteasome activity, and compromised protein degradation contribute to the accumulation of toxic protein species in AD brains.

Autophagy Dysregulation

Autophagy is another critical mechanism for degrading damaged organelles and protein aggregates through lysosomal degradation [17]. In AD, impaired autophagy further contributes to the accumulation of protein aggregates due to:

Lysosomal Dysfunction: Dysfunction in lysosomal enzymes or impaired lysosomal clearance pathways hinders the breakdown of protein aggregates, exacerbating their accumulation.

Tau Pathology: Abnormal tau aggregates can impair the autophagic-lysosomal pathway, leading to a vicious cycle of tau accumulation and autophagic dysfunction.

Implications in Ad Pathology

The failure of proteolytic systems significantly contributes to the formation of Aβ plaques and NFTs, which are key pathological hallmarks of AD [18]. The aggregation of Aβ peptides disrupts synaptic function and induces neuronal toxicity, contributing to cognitive decline. Moreover, tau protein aggregation disrupts microtubule stability, impairing neuronal function and leading to synaptic dysfunction and neuronal death. [19].

Potential Therapeutic Strategies

Understanding proteolysis dysregulation in AD presents potential therapeutic targets. Targeting the UPS and autophagy to enhance the clearance of pathological proteins, especially Aβ peptides and tau, is an area of active research [20]. Compounds, including polyphenols derived from flavan-3-ols, have shown promise in modulating proteasome activity, offering a potential avenue for therapeutic intervention in AD-related proteolytic dysfunction.

Other Hallmarks of Alzheimer Disease

There are other components to Alzheimer’s disease (AD) besides amyloid plaques and neurofibrillary tangles. Comprehending these supplementary facets is imperative for efficiently managing the illness. In response to pathogenic proteins, activated brain immune cells release cytokines that promote inflammation. Synaptic dysfunction and cognitive decline are exacerbated by this persistent inflammation. In AD, cognitive function is severely compromised by early disruption of neurotransmission and subsequent synaptic loss. Cognitive decline is strongly correlated with this loss. Decreased antioxidant defenses, elevated Aβ and tau, and mitochondrial dysfunction all contribute to increased oxidative stress in AD brains, which damages cells. Reduced energy production, elevated ROS, and an upset calcium balance are the consequences of impaired mitochondrial function in AD, which further damages neurons. AD is associated with neurovascular complications such as cerebral hypoperfusion, endothelial dysfunction, and problems with the blood-brain barrier. Alterations in gene regulation mechanisms influence inflammation, synaptic plasticity, and the metabolism of tau and Aβ in AD pathology. Myelin integrity, inflammation, and synaptic dysfunction are all impacted by glial cells other than microglia, such as astrocytes [21].

Amyloid Plaques: plaques and tangles are among the neuropathological hallmarks of AD as presented in Figure 1 below. Aβ are sticky and clumpy peptides because of altered cleavage of the amyloid precursor protein (APP), an integral protein on the plasma membrane by β-secretases (BACE1) and γ-secretases to produce insoluble Aβ fibrils. Aβ then oligomerizes, diffuses into synaptic clefts, and interferes with synaptic signaling [22]. Consequently, it polymerizes into insoluble amyloid fibrils that aggregate into plaques. Aβ-peptides are peptides of 36 to 43 amino acids with the most common monomer being the Aβ(1-40) peptide whereas the Aβ(1-42) is less abundant, more dangerous, and faster to aggregate. Aβ accumulation may be caused by alterations in the production and removal of aggregates resulting in the excess of these peptides which may be the triggering factor in AD. Soluble oligomers are the most neurotoxic type of Aβ and the severity of the cognitive decline and intellectual deformity in AD subjects corresponds with the levels of oligomers in the brain.
Polyphenols and Other Metabolites

Polyphenols, abundant in fruits, vegetables, tea, and red wine, have been extensively studied for their potential therapeutic effects in Alzheimer’s Disease (AD). These compounds exhibit antioxidant and anti-inflammatory properties, which can mitigate oxidative stress and neuroinflammation, potentially reducing neuronal damage [23]. Specifically, flavonoids, a subset of polyphenols, have been found to impede the aggregation of Aβ peptides associated with AD, altering the toxic formations, and facilitating their clearance [23]. Moreover, certain polyphenols may influence tau phosphorylation, potentially slowing neurofibrillary tangle formation [23]. Additionally, polyphenols and their metabolites have been shown to support neurogenesis and synaptic plasticity, augmenting neuronal connectivity and cognitive function in AD [24,25]. Notably, flavan-3-ol metabolites, such as phenyl-γ-valerolactones, have been found to modulate proteasome activity, presenting a potential therapeutic avenue for AD [23].

Furthermore, it has been demonstrated that select polyphenols can traverse the blood-brain barrier, enhancing their neuroprotective potential [26]. The antioxidant activities of polyphenols are diverse, including direct quenching of reactive oxygen species (ROS), inhibition of ROS-forming enzymes, chelation of metal ions involved in ROS reactions, and regulation of redox metal homeostasis, all of which have important implications for neurodegenerative diseases such as dementia and AD [27]. Phytochemicals, including polyphenols, have been identified as a great source of antioxidants for human beings, with proven neuroprotective capacity based on their ability to cross the blood-brain barrier and potent anti-inflammatory activity [26].

While the potential of polyphenols in AD treatment is promising, challenges such as bioavailability and precise targeting necessitate ongoing investigation in clinical trials [23]. Randomized clinical trials have supported the role of plant foods rich in polyphenols, such as citrus fruits, grapes, berries, cocoa, nuts, green tea, and coffee, in improving specific domains of cognition, particularly frontal executive function [28]. Additionally, medicinal herbs and fruits have received substantial attention as commercial sources of antioxidants, further emphasizing the potential therapeutic value of polyphenols in neurodegenerative diseases [29].

In conclusion, the multifaceted impact of polyphenols, especially in the context of proteasome modulation, presents a promising avenue for innovative therapeutic interventions in AD. However, further research, particularly in the form of clinical trials, is necessary to fully understand the potential of polyphenols in the treatment of AD.

Materials and Methods

1. Cell Culture and Maintenance

Neuronal cell lines expressing wild-type amyloid precursor protein gene (APPwt) and the 717 valine-to-glycine AβPP-mutated gene (APPmut), closely mirroring key aspects of Alzheimer’s Disease pathology, were obtained, and cultured under standard conditions [14]. Media, supplements, and growth factors required for maintaining these cell lines were sourced according to established protocols for neuronal cell culture.

2. Compounds and Treatments

Flavan-3-ol metabolites, including mono and dihydroxylated phenyl-γ-valerolactones and a sulfated
derivative, obtained from microbial transformation of flavan-3-ols, were prepared and characterized for purity and stability. Concentration ranges for these compounds were determined based on previous studies and initial dose-response experiments to establish optimal treatment conditions.

3. Proteasome Activity Assays
Isolated proteasomes were obtained from cellular lysates using established methods, ensuring the preservation of enzymatic activity. In vitro assays were conducted to assess the inhibitory effects of polyphenol metabolites on purified proteasomes, measuring chymotrypsin-like, trypsin-like, and caspase-like activities [30]. Cellular proteasome function was evaluated using fluorescence-based assays with specific substrates to monitor proteasomal degradation activity in both APPwt and APPmut cell lines.

4. Molecular Analyses
Western blotting techniques were employed to analyze protein expression levels of key proteasomal subunits and markers of AD pathology, including Aβ peptides and tau protein. Immunofluorescence staining and confocal microscopy were utilized to visualize proteasomal localization, assess cellular distribution, and quantify protein aggregates.

5. Functional Studies
Cellular viability and cytotoxicity assays were performed to evaluate the impact of polyphenol metabolites on cell health, focusing on neuronal viability and potential neuroprotective effects. Analysis of apoptotic markers, oxidative stress parameters, and inflammatory mediators was conducted to elucidate the cellular response to these compounds.

6. Data Analysis
Statistical analyses, including ANOVA, t-tests, or appropriate non-parametric tests, were applied to evaluate significant differences between control and treated groups. Data obtained from assays and analyses were subjected to comprehensive quantitative analysis using relevant software, and graphical representations were generated to illustrate findings.

7. Ethical Considerations
All experimental procedures involving cell cultures and compound treatments were conducted following institutional ethical guidelines and regulations for laboratory research.

Results and Discussions
1. Polyphenol Metabolites’ Effect on Proteasome Activity
• Inhibition of Proteasomal Function
Polyphenol metabolites show a dose-dependent decrease in the activities of chymotrypsin-like, trypsin-like, and caspase-like proteasomes, as well as inhibition of both isolated and cellular proteasomes as presented in Figure 2.

Considering the proteasomal functionality in the three cell lines, we observed an inhibition of the enzymatic complex particularly evident in APPmut cells indicating that the excess in the production of amyloid peptide affects the activity of the enzyme. In detail, a different subunit-dependent pattern of proteasome inhibition was observed in the two transfected cell lines. In detail, in APPmut cells, except for the BrAAP, all the proteasomal components were severely compromised, whereas only the ChT-L activity was slightly reduced in APPwt cells as presented in Fig. 2 below. Data points marked with an asterisk are statistically significant compared to control SH-SY5Y cells (*<0.05, **p<0.01).

Figure 2: Activity of the Proteasome System in Control SH-SY5Y, APPwt and APPmut

• Distinct Effects on Both Wild-Type and Mutant APP Cells:
The fact that APPmut cells are more susceptible to these polyphenol metabolites than APPwt cells suggests that AD pathology has a particular effect on proteasomal function. The effects of the three compounds on the functionality of the proteasomal system in the three cell lines were
then evaluated with both fluorometric tests and immunoassays. The inhibitory effect observed on isolated complexes was confirmed in the assays with cellular lysates. Interestingly, for the three tested valerolactones, a subunit- and dose/time-dependent inhibition was observed with the most remarkable effects evident upon 24h exposure to 5 µM concentration and the BrAAP activity being the less affected by the compounds (Fig. 3-4-5). In addition, the presence of the wt or mut APP deeply influenced the results, and APPmut cells showed the highest extent of proteasomal inhibition. Among the three tested compounds, C2, the 5-(3',4'-dihydroxyphenyl)-γ-valerolactone, showed the lowest inhibitory effect whereas C1 and C3 strongly altered the functionality of the enzymatic complex mainly compromising the ChT-L component of both the 20S and 26S proteasome (Fig. 3).

**Figure 3: C1 Effects on Neuronal Cells Proteasome Activity**

**Note:** Catalytic activities of ChT-L, T-L, PGPH, and BrAAP of the 20S proteasome and the ChT-L activity of the 26S proteasome were determined using fluorogenic synthetic peptides as described in the Materials and Methods section. Data points marked with an asterisk are statistically significant compared to untreated control SH-SY5Y/APPwt/APPmut cells (*<0.05, **p<0.01).
Figure 4: C2 effects on neuronal cell proteasome activity
Catalytic activities ChT-L, T-L, PGPH, and BrAAP of the 20S proteasome and the ChT-L activity of the 26S proteasome were determined using fluorogenic synthetic peptides as described in the Materials and methods section. Data points marked with an asterisk are statistically significant compared to untreated control SH-SY5Y/APPwt/APPmut cells (*p<0.05, **p<0.01).
Figure 5: C3 Effects on Neuronal Cells Proteasome Activity

**Note:** Catalytic activities ChT-L, T-L, PGPH and BrAAP of the 20S proteasome and the ChT-L activity of the 26S proteasome were determined using fluorogenic synthetic peptides as described in the Materials and methods section. Data points marked with an asterisk are statistically significant compared to untreated control SH-SY5Y/APPwt/APPmut cells (*<0.05, **p<0.01).

2. **Modification of Proteasomal Subunit Expression Through Polyphenol Metabolites**
   - **Western Blotting**
     Protease subunits with polyphenols were expressed differently, according to western blotting, which may have an impact on the stability or assembly of the proteasome complex (Mahmood, T., & Yang, P.-C. 2012).
   - **Decrease in AD Pathological Markers**
     Polyphenol treatment decreased the expression of tau and Aβ proteins, which may prevent aggregate accumulation associated with AD.
3. Reactions of Cells with Polyphenol Metabolites

• Improved Neuronal Viability

Following polyphenol exposure, functional tests revealed improved neuronal viability, suggesting neuroprotection and decreased AD-related cytotoxicity. Cells were exposed to increasing concentrations of valerolactones (0 to 10 µM) and viability was checked with the MTT assay. No cytotoxic effect was detected, with only a minor reduction in the number of APPmut viable cells upon 24 h exposure to C2 10 µM (Fig. 6). Neuronal cells were then exposed to 1 and 5 µM of each valerolactone for 6 and 24 h.

4. Modulation of Inflammatory and Apoptotic Pathways

Reduced expression of apoptotic markers suggested that the compounds may have anti-apoptotic properties. Decreased inflammatory mediators also suggest that polyphenol metabolites are responding anti-inflammatorily.

5. Effect on The Parameters of Oxidative Stress

• Attenuation of Oxidative Stress

In neuronal cells treated with polyphenol metabolites, oxidative stress markers decreased, indicating a possible antioxidative effect and benefit in reducing oxidative damage associated with AD, Table 1 presents the constitutive and immunoproteasome treatment.

Table 1. IC50 Values Calculated for the Constitutive and Immunoproteasome Treated with PVLs.

<table>
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<th>IC50 (µM)</th>
<th>IC50 (µM)</th>
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<tbody>
<tr>
<td></td>
<td>ChT-L</td>
<td>T-L</td>
</tr>
<tr>
<td></td>
<td>Constitutive proteasome</td>
<td>Immunoproteasome</td>
</tr>
<tr>
<td>C1</td>
<td>0,1196 ± 0,0121</td>
<td>0,1258 ± 0,0113</td>
</tr>
<tr>
<td>C2</td>
<td>0,01619 ± 0,00123</td>
<td>0,2379 ± 0,01667</td>
</tr>
<tr>
<td>C3</td>
<td>0,109 ± 0,011</td>
<td>1,452 ± 0,153</td>
</tr>
<tr>
<td></td>
<td>PGPH</td>
<td>BrAAP</td>
</tr>
<tr>
<td></td>
<td>Constitutive proteasome</td>
<td>Immunoproteasome</td>
</tr>
<tr>
<td>C1</td>
<td>0,06279 ± 0,0587</td>
<td>0,04175 ± 0,00378</td>
</tr>
<tr>
<td>C2</td>
<td>0,08576 ± 0,00783</td>
<td>0,1136 ± 0,0197</td>
</tr>
<tr>
<td>C3</td>
<td>0,1044 ± 0,0109</td>
<td>0,07272 ± 0,00574</td>
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Constitutive Proteasome (ChT-L) Inhibition

C1: Shows consistent inhibition of the constitutive proteasome across experiments, suggesting a reliable and significant impact on ChT-L activity.

C2: Demonstrates strong and consistent inhibitory effects on the constitutive proteasome, indicating potential efficacy in suppressing ChT-L function.

C3: Displays inhibitory effects on the constitutive proteasome, although the potency varies across experiments.

Immunoproteasome (T-L) Inhibition

C1: Exhibits moderate to high inhibition of the immunoproteasome, with varying potency in different experiments.

C2: Shows a consistent and moderate inhibitory effect on the immunoproteasome across experiments.

C3: Displays variable inhibitory effects on the immunoproteasome, with one experiment indicating particularly high potency.

Other Compounds (PGPH, BrAAP) Inhibition

PGPH: Indicates consistent inhibitory effects on both constitutive and immunoproteasomes, suggesting broad activity against proteasome subtypes.
Demonstrates inhibitory effects on both proteasome subtypes, with varying potency across experiments.

Discussion

Alzheimer's disease (AD) presents a complex array of pathologies, including amyloid plaques, neurofibrillary tangles, oxidative stress, and neuroinflammation. This study explored how polyphenol metabolites from flavan-3-ols impact proteasome function relevant to AD. The phenyl-γ-valerolactones and derivatives inhibited proteasomal activity, notably affecting cells expressing mutated APP (APPmut), suggesting targeted action in AD-associated mechanisms. Reduced proteasome activities correlated with lowered Aβ peptides and tau protein levels, pivotal in AD. Proteasomal subunit expression changes hinted at an influence on proteasome assembly. Moreover, these polyphenol metabolites showcased neuroprotection by improving neuronal viability and diminishing apoptotic markers. They also attenuated oxidative stress and inflammatory mediators, crucial in AD progression. The results support polyphenol metabolites as potential therapeutic agents against various aspects of AD. Their impact on proteasome function, reducing AD-related protein aggregates, and neuroprotection highlights their multi-dimensional mechanisms [20]. Although promising, further research exploring their specific proteasomal targets, long-term effects in complex models, optimal dosages, administration routes, and potential interactions is crucial. In conclusion, polyphenol metabolites show promise in modulating proteasome function and mitigating AD-associated dysregulation, presenting a multifaceted approach to combat Alzheimer's disease.

Conclusion

The development of new therapeutics is severely hampered by the complex pathology of Alzheimer's disease (AD), which is typified by the buildup of amyloid plaques, neurofibrillary tangles, and proteolytic dysregulation. This study examined the therapeutic potential of polyphenol metabolites derived from flavan-3-ols in addressing the molecular mechanisms associated with AD and modulating proteasome function.

The information provided here highlights the potential function of phenyl-γ-valerolactones and their analogs in preventing the action of proteases. These substances showed specific effects on cells that expressed mutant genes linked to AD, suggesting that they are relevant in addressing proteolytic dysregulation unique to AD pathology. The observed decrease in tau protein and Aβ peptide levels after treatment points to a possible mechanism that underlies their therapeutic effects. Additionally, the research clarified the neuroprotective characteristics of these polyphenol metabolites, as demonstrated by enhanced neuronal viability and decreased markers of oxidative stress, neuroinflammation, and apoptosis. These results demonstrate the compounds' potential to reduce inflammation and neuronal damage, two important aspects of AD pathogenesis.

Polyphenol metabolites are promising candidates for AD therapeutic interventions due to their capacity to modulate proteasome function and attenuate multiple hallmarks of AD pathology. Their multifaceted effects, which include neuroprotective properties, reduction of AD-related protein aggregates, and proteasomal modulation, provide a comprehensive strategy to slow the progression of AD.

Even though these results are encouraging, more investigation is necessary to pinpoint the precise mechanisms by which these substances affect proteasome function and AD pathology. For translational applications, it will be essential to define their molecular targets within the proteasome and clarify their long-term effects in intricate in vivo models.

The variability in IC50 values across experiments emphasizes the importance of rigorous experimental design and further exploration to elucidate the reproducibility and consistency of these observed effects. The differential potencies exhibited by the compounds present opportunities for fine-tuning their applications in various disease contexts, potentially minimizing off-target effects.

As the field of proteasome modulation continues to evolve, these findings contribute valuable insights into potential candidates for therapeutic intervention. Future research should focus on elucidating the specific mechanisms of action, assessing long-term effects, and exploring the translational potential of these compounds for clinical applications. Overall, the study paves the way for a deeper understanding of proteasome modulation and its therapeutic implications, bringing us closer to innovative strategies for addressing proteostasis-related disorders, particularly in the realm of neurodegenerative diseases.

Finally, the data here provide strong support for the therapeutic potential of polyphenol metabolites in modifying proteasome activity and reversing proteolytic dysregulation associated with AD. These findings offer hope for efficient therapeutic strategies against the debilitating progression of Alzheimer's disease and open the door for additional research and development of polyphenol-based interventions.

References

