The Potential Effects of Resveratrol Against Alzheimer’s Disease

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Abstract

There is not yet a known cure for Alzheimer’s disease, but research has provided many possible therapeutic agents; one of these agents is the polyphenol known as resveratrol that is found most commonly in grapes and wine. Studies have indicated that a moderate consumption of red wine has been associated with lower occurrences of Alzheimer’s disease as well as other types of dementia. Such a correlation could be caused by the presence of the antioxidant resveratrol. Recently, numerous studies have cited the beneficial effects of resveratrol that may prove successful in fighting the symptoms and slowing the progression of Alzheimer’s disease in the brain. In addition to the characteristics of resveratrol that allow it to combat the physical manifestation of Alzheimer’s in the brain, the bioavailability of the polyphenol as well as its possible co-administration with melatonin to create a synergistic effect will be discussed in this review.

Introduction

Alzheimer’s disease (AD) is a very common neurodegenerative disease that is most often associated with the elderly. AD is typified by synaptic failure in the brain that occurs because of plaques and tangles that prohibit the transmittance of information and kill brain cells. The tangles are made up of clumps of rogue tau proteins that disrupt a cell’s transport system and the plaques are comprised of amyloid beta oligomers that build up in synapses throughout the brain. AD causes large amounts of oxidative damage
and as a result of neuronal death, the brain shrinks and loses function, causing memory
loss, confusion, difficulty completing or learning new tasks, social withdrawal, and
personality changes. AD eventually results in death.

There are two forms of AD: early-onset and late-onset. Late-onset is by far the
most common, occurring in over 95% of cases. The greatest risk factor for this type of
AD is age, beginning at sixty-five, and the risk doubles every five years thereafter. The
other form is early-onset, which is very rare in comparison. The age of onset ranges
between forty and sixty, although there have been patients whose symptoms began even
earlier. Early-onset often follows a clear pattern of inheritance and is caused by a genetic
mutation; however, there are only 200-300 known families in the world that have the
mutation that causes familial early-onset AD.

Both forms of AD cause the same damage to the brain; early-onset AD simply
begins its destruction at an earlier age. There is currently no cure for AD and although
there are treatments to slow or delay progression, they are effective for only a given
amount of time. In the search for a cure, any treatment that slows or delays progression of
AD is beneficial. Antioxidants as therapeutics have the potential to reduce the oxidative
stress that is a trademark of AD. In addition, any substance that would reduce amyloid
beta deposition or that displays neuroprotective effects to strengthen the brain may prove
helpful in weakening symptoms. Recently, resveratrol has gained recognition as a
substance that fits these characteristics and could thus be used as at least a temporary
therapeutic to fight against AD.

Resveratrol is a polyphenolic compound that is produced in plants mostly as a
reaction against fungal infection. It is found in grapes, peanuts, and some berries, and
because of its presence in grape skins, resveratrol is also found in wine. The concentration of resveratrol in wine is dependent upon the amount of time during the fermentation process when there is contact with the grape skins, so red wine has a higher content than white wine. Resveratrol is an antioxidant, and it has been found to have numerous health benefits, including characteristics that may help to prevent cancer and cardiovascular disease in addition to AD, while also having no known adverse side effects.

**Neuroprotective Effects and Antioxidant Properties**

Any substance with neuroprotective effects acts to shield neurons from degeneration or apoptosis – cell death. This neurodegeneration is a major characteristic of AD, as is oxidative damage, which creates toxic effects in the brain and is partly responsible for cell deterioration. Therefore, in order to be effective and to slow the progression of the disease throughout the brain, any potential treatment for AD is expected to combat this oxidative imbalance.\(^2\) Resveratrol is often identified as an antioxidant and has proved just as, if not more, efficient in the protection against oxidative damage as other antioxidants such as vitamins C and E.\(^3\) In addition, resveratrol has been known to display neuroprotective actions that benefit various neurodegenerative disorders, not solely AD, and it is believed that the polyphenol has potential as a neuroprotective biofactor. Studies have indicated that in certain animal models, resveratrol has proven its ability to prevent cognitive decline and to provide neuroprotection.\(^4\)
Reduction of Amyloid Beta

Because amyloid beta plaques are one of the hallmark features of AD, any potential therapeutic would have to prove effective in reducing or eliminating these harmful build-ups. While resveratrol has not been found to completely inhibit amyloid beta production, it has been shown to reduce the levels of amyloid beta produced from cell lines. Fibril formation and cytotoxicity of amyloid beta can be inhibited by resveratrol, but oligomer formation continues despite the presence of the polyphenol. Rather than targeting the source of amyloid beta production, resveratrol promotes the clearance of amyloid beta; this reduction is a result of intracellular degradation of the amyloid peptide acted upon by resveratrol. However, the exact process enacted by resveratrol to cause this decrease of amyloid beta in cell lines is not yet known. Despite this lack of complete understanding, studies have shown that the AMP-activated protein kinase that is activated by resveratrol plays a role in amyloid beta metabolism, contributing to lower amyloid beta levels in the brain.

To be more specific, it is known that while resveratrol promotes the reduction of the amyloid beta plaques in the brain, only certain regions experience this decrease and of those regions, the percentage area of amyloid beta plaques that are reduced varies. Studies have shown that the medial cortex, striatum, and hypothalamus experienced the largest decrease. Reduction of amyloid beta plaques in any capacity is beneficial to slowing the progression of AD; however, these findings indicate that resveratrol is not an effective enough therapeutic to completely eliminate amyloid beta production or to decrease plaques throughout the entire brain.
Activation of SIRT1

Sirtuin 1 is part of the sirtuin family of proteins. Although very little is currently understood about sirtuins in humans, SIRT1 is known to be involved in various cell signaling pathways and in many important body processes, including apoptosis, autophagy, cardiovascular disorders, and neurodegeneration. The latter makes SIRT1 relevant to AD.

Resveratrol has been found to bind to and activate SIRT1, resulting in an imitation of the possible benefits of caloric restriction. Caloric restriction is the drastic reduction of calorie intake and is believed to lengthen lifespan, specifically by encouraging the survival of those irreplaceable cells that are often affected by the neurodegeneration that accompanies aging. In addition, SIRT1 activation is believed to play a role in the deterrence of amyloid beta generation; caloric restriction can also influence typical AD neuropathology. Besides indicating caloric restriction as another possible treatment for AD, the benefits of increased levels of SIRT1 activity as induced by promote imply the escalating potential of the polyphenol as a therapeutic agent for AD.

However, other studies have concluded that resveratrol is incapable of activating SIRT1. If this is true, resveratrol would of course become seemingly less beneficial as an AD treatment, but it is important to keep in mind its many other valuable attributes and neuroprotective qualities.
Co-administration with Melatonin

Melatonin is a naturally occurring compound that is most often associated with circadian rhythms. It is a hormone secreted by the pineal gland in the brain, but it is found in other peripheral cells, like bone marrow cells, as well. Often, AD patients experience circadian rhythm disorders and have trouble sleeping, which is most likely because their melatonin levels are much lower in comparison to people of the same age who do not suffer from AD. Melatonin has been used successfully to improve the sleeping problems of AD patients. In addition, melatonin is an antioxidant like resveratrol, and it thus has distinctive properties that could prove useful in the treatment of AD. For example, melatonin has been found to lessen oxidative damage in a mouse model of AD. Melatonin has similar neuroprotective effects as well, and it has demonstrated its efficiency in prohibiting cell death as well as in protecting against amyloid beta cytotoxicity.

Because melatonin and resveratrol seem beneficial thus far and retain an enormous amount of potential in the search for a truly effective therapeutic for AD, there have been recent studies that examine the possible synergistic effects of the two compounds when co-administered. Studies have proposed that melatonin acts to potentiate resveratrol’s neuroprotective effect on oxidative damage. As previously discussed, resveratrol activates the AMP-activated protein kinase, which allows for a reduction of amyloid beta buildup. However, when co-administered, resveratrol and melatonin were found to inhibit AMPK activation and thus were able to prevent neuronal death. In addition, this same study speculated that melatonin, also a SIRT1 activator,
could be combined with resveratrol to create a synergistic effect involving SIRT1 activity for neuroprotection.

**Bioavailability and Consumption**

As mentioned, resveratrol is found in high levels in grapes and wine, with the highest concentrations typically in red wine. However, resveratrol is quickly absorbed and metabolized after oral consumption by humans, making its oral bioavailability close to zero. Only metabolites of resveratrol enter the bloodstream and come into contact with target organs. Because of this rapid excretion of resveratrol in its pure form, it is uncertain at this point what constitutes the most effective dose as a treatment. Stabilization of resveratrol is therefore necessary to allow for the greatest possible bioavailability. Studies have shown that lipid-core nanocapsules containing resveratrol allow for higher concentrations of the polyphenol in the brain and other organs than an equivalent dose of free resveratrol. These nanocapsules may have potential as an effective way to maintain higher levels of bioavailability.

It should also be noted that resveratrol has been found to cause hormetic dose responses in animal models; that is, low doses may cause protective effects, but higher doses may cause adverse effects, aggravating AD and other diseases. With this exception, resveratrol remains an attractive potential therapeutic for AD patients because of its lack of proven harmful side effects. When compared to other pharmaceutical agents, such as cholinesterase inhibitors, that have been approved for use yet cause side effects and result in little success, the easily accessible and beneficial resveratrol appears as a viable and preferable option. However, any side effects that may occur as a
result of consumption of resveratrol over a significant time period remain unknown, in both animals and humans. The safety of resveratrol as an AD treatment can therefore not be guaranteed until long-term studies of possible side effects have been performed.\textsuperscript{23}

**Conclusion**

The potential for resveratrol as an effective therapeutic for AD has been clearly demonstrated. Its antioxidant characteristics and neuroprotective properties can fight against the neurodegeneration and oxidative damage experienced by an AD-ravaged brain. Studies have shown resveratrol to have an effect on the reduction of amyloid beta, and the activation of SIRT1 by the polyphenol can imitate the benefits of caloric restriction, including longevity. Co-administration with the important hormone melatonin has been found to create a more powerful neuroprotective effect.

It is, of course, important to keep in mind that a majority of these studies were performed on animal models, cultures, cell lines, and the like rather than humans, so it is possible that human AD patients may not experience the exact same effects after the consumption of resveratrol. Furthermore, the bioavailability of resveratrol remains low, and although the lipid-core nanocapsules could prove successful in the future, there is no current method to ensure anything more than the fact that metabolites of resveratrol remain in a human body after consumption. However, there is no reason to believe that the idea of resveratrol as a therapeutic for AD should not continue to be pursued, especially because the cure remains elusive while the disease is being diagnosed in a continually increasing percentage of the elderly.
Literature Cited


