International Journal of Research Publication and Reviews, Vol 3, no 1, pp 623-630, January 2022

WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Discovering Periwinkle: A Potential Memory Enhancer for Alzheimer's Disease

Angel Jules Galo,[1] Joshua Rexter Inutan,[1] Jan Claude Masmodi,[1] Weizz Negrido,[1] Sybil Rose Rama[1], Carina Shayne Yabut,[1] and Jacqueline Abiso-Padilla[2]

1,2 San Pedro College, Davao City, Philippines

A B S T R A C T

Memory is likely the most important feature that distinguishes humans from other animals. Drugs and natural remedies have been used to improve people's memories for centuries. Periwinkle is a type of plant that comes from the Apocynaceae family and has been used to treat a range of illnesses in the past. Vinpocetine is a compound produced from vincamine, a component present in common periwinkle leaves. This paper reviews the periwinkle plant and we found out that vinpocetine is being used to treat a wide range of neurological illnesses, as well as Alzheimer's disease. Alzheimer's disease (AD) is a neurological illness that affects people as they get older. It is characterized by the progressive loss of memory and cognition, the development of mental symptoms and behavioral abnormalities, and the deterioration of daily duties.

Keywords: Alzheimer's Disease (AD), Periwinkle, Vinpocetine

1. Introduction

In the United States, the sixth leading risk factor for anyone's death in any age group is Alzheimer's disease, with a 5% increase in deaths from 2015 to 2016. Alzheimer's disease claims the lives of a large number of people each year and has risen by 139% between 2000 and 2016, while deaths attributable to the leading cause of mortality, cardiovascular disease, fell by 6%. This growth refers to the changes in death certificate reporting trends, as well as a rise in Alzheimer's disease rates fatalities [1].

Alzheimer's disease is a brain disorder and it was initially distinguished by a German doctor named Dr. Alois Alzheimer in 1906 [2]. Alzheimer's disease is a developing neurological illness that is distinguished by memory loss, degeneration of nearly all intellectual skills, increasing apathy, disorientation, and gait irregularities [3] that typically affects those over 65 years old, accounting for 50–60% of dementia cases. [4] Alzheimer's disease had the highest incidence rate among men and women where it was discovered that the global prevalence rate was 10 cases per 100,000 people per year. This means that every year, roughly 350,000 people in the world get younger-onset dementia. [3]

Alzheimer's disease occurs when the brain's nerve cells die and it worsens with time. The brain shrinks to some extent but, unexpectedly, does not lose a substantial number of neurons. Neurodegenerative disease, also known as Alzheimer's, impairs critical nerve cell operations and systems. The neurodegenerative disease mainly damages the medial temporal lobe or hippocampal memory systems, such as the entorhinal cortex and hippocampus, containing nerve cells and connections.[5] Later on, it has repercussions essential for language-related parts of the cerebral cortex, logic, and social relation.[6] Degenerative alterations in a range of neurotransmitter systems characterize the disease. Changes in the monoaminergic brain system, which releases norepinephrine, glutamate and serotonin, as well as a little neuropeptide-containing systems, are among them. Degenerative alterations in certain brain regions, such as the temporal and parietal lobes, as well as confined areas of the frontal cortex and cingulate gyrus, are also hallmarks of Alzheimer's disease. The deterioration of these systems may highlight specific elements of Alzheimer's disease-related dementia [7].

As Alzheimer's illness develops, it produces changes in the brain and forgetting recent incidents or discussions is one of the first indicators [8] but patients that have late-stage Alzheimer's lose their capacity to communicate and adapt to the environment. A person with this condition will suffer from significant memory loss and be unable to complete its daily tasks when the disease progresses. It may also be difficult for people with suspected Alzheimer's symptoms to recognize that they have a problem and aging is the most well-known risk factor, and the majority of patients are 65 years and older. The disease has three stages, ranging from mild to severe. More severe symptoms emerge, such as disorientation and behavior changes, growing confusion about events such as time and place, more serious memory loss, and difficulty speaking, swallowing, and walking [9].

* *Corresponding author.*
E-mail address: sybilr_rama@spcdavao.edu.ph

Periwinkle as a memory enhancer has already been introduced in various clinical studies which suggest that Alzheimer's illness may have a new treatment. Catharanthus roseus or commonly known as periwinkle is an ornamental plant that is grown in the gardens of many households so it is easily cultivated and abundant in the population. It is known to contain many powerful alkaloids that are beneficial to the health and have medicinal properties, it's most notable compound is vincristine and vinblastine which are anticancer substances. It also helps in lowering your hypertension, toothache, and most importantly is memory loss [10].

Periwinkle is a perennial plant with petals that bloom at different times of the year depending on the environment. These are frequently grown for their distinctive hues, which range from white to green-yellow to lavender. Other names of this plant are Lochnera rosea, Vinca rosea, and Ammocallis rosea. These are some illnesses that are being treated with periwinkle (edema): diarrhea, throat infections, vaginal discharge, chest discomfort, tonsillitis, intestinal pain, high blood pressure, toothache, water retention and swelling (inflammation) [11]. This plant can also be used for "brain health," which includes improving brain blood circulation, metabolism, and mental productivity, as well as improving memory and cognitive skills, reducing senility, and also delaying the aging of brain cells [12].

The objectives of this review are (1) to explore the effectiveness of Periwinkle to treat Alzheimer's disease, (2) to identify the constituents of Periwinkle that is beneficial in the treatment of Alzheimer's disease, and lastly (3) to describe the full potential of periwinkle as a medicinal plant.

2. Methods

Articles concerning the effectiveness of periwinkle in enhancing memory and curing the Alzheimer's disease that are publicly published and free to be cited were searched and compiled through Google scholar and Google docs. There were no criteria in picking the articles but are made sure that it is relevant to the topic and timely, so articles used in this peer review are factual and reliable.

3. Prevalence of Alzheimer's Disease

As the global population ages, massive resources will be critical as it is necessary to adequately care for those who are afflicted by Alzheimer's disease. Research is currently undertaken to discover interventions that would both postpone the development of the disease and reduce its progression. Effective therapies have the potential to drastically reduce Alzheimer's disease prevalence and incidence. [13,14] Alzheimer's disease (AD) is a disorder in the nervous system that particularly affects the neurons in the brain, and age is the well-known risk factor in this condition. [15] It is clinically marked by the gradual onset of memory and cognition impairment, the emergence of psychiatric symptoms, behavioral disorder, and independence in personal daily activities that significantly interferes with social and occupational functioning. [13]

This condition is the frequent type of dementia (senile) [15] where it is thought to begin 20 years or more before symptoms appear, with slight changes in the person's brain. Individuals only start to notice signs like memory loss and language problems after years of brain changes. [14] Additionally, based on the study, several risk factors are determined with this condition such as infections, genetic factors, vascular diseases, increasing age, head injuries, and environmental factors that contribute to the disease's progression. [16]

The number of people living with this disease is rapidly increasing, and it was found that around 44 million people worldwide are thought to be having Alzheimer's disease and Alzheimer's disease is the sixth largest cause of death in the US. where only around one out of every four persons with the disease is diagnosed worldwide. [14] Fatalities from stroke, HIV, and heart disease dropped between 2000 and 2018, but recorded deaths from Alzheimer's grew by 146.2 percent. [17] Furthermore, over the age of 85, the prevalence of the condition is thought to be as high as 25% to 50%, and it is gradually being recognized as one of the most serious medical problems among the elderly.[15]

4. Pathogenesis of Alzheimer's disease

Amyloid-beta peptide(Aβ), a 39-43 long amino acid peptide, is made from its precursor, the amyloid precursor protein, through proteolytic processing (APP). The buildup deposition of Amyloid-beta (Aβ) in the cerebrum may come from oversupply due to APP isis-metabolism or/and a failure in clearance, which is fundamental to the pathophysiology of AD [18] The amyloid-β peptide (Aβ) aggregates and accumulates. Neuron's activity has increased Amyloid-beta (Aβ) synthesis, reduced Amyloid-beta-degrading enzymes, or changed to convey mechanisms that transport Amyloid-beta over a barrier amid the blood and the brain could all cause Amyloid-beta to accumulate in the brain.

The fibrillar amyloid plaques dislocate and deform neuronal functions, whereas Amyloid-beta oligomers (AβOs) impair synaptic functions. An oligomer interacts with membranes and receptors on the cell surface, causing signaling action of cascades to be disrupted, neuron activity to be altered, and microglia (resident immune cells) to release neurotoxic mediators. Cerebral microinfarcts with the stimulation of astrocytic glial cells and macrophages are caused by vascular anomalies that limit the nutritional availability also by-products of metabolism. ApoE4, a lipid-carrier protein, enhances Aβ synthesis while decreasing clearance. When ApoE4 is generated in under stress neurons, it is disassembled into neurotoxin-producing components that disrupt the anatomical structure and chondriosome function, similar to intracellular Aβ.[19]

5. Physical manifestations of patients with Alzheimer's disease

Alzheimer's disease causes damage to a person's brain, which reveals itself in early clinical signs and symptoms. The majority of patients with Alzheimer's disease, especially those with the late-onset variety, begin to show symptoms in their mid-60s. Between the ages of 30 and 60, early-onset Alzheimer's disease appears. The early signs and symptoms of Alzheimer's disease differ from person to person. Memory issues are part of the early indicators of Alzheimer's disease-related cognitive loss. Word searching, vision/spatial problems, and slower thinking or judgment, are all examples of non-memory cognitive domains which can also be signs of Alzheimer's disease in its early stages. Some patients may also show signs of modest cognitive impairment. People with Alzheimer's disease experience more memory loss and other cognitive issues as the disease advances [20]. Alzheimer's disease is a disease that progresses over time and can be moderate to severe. Before reaching severe cognitive impairment, the scale starts with mild impairment and advances to moderate impairment.

5.1. Mild Alzheimer's disease

An individual with mild Alzheimer's illness may appear normal in appearance, but he or she is losing their ability to perceive the world around them [20]. In many ways, individuals can function independently, but they will almost certainly require assistance with other things in order to retain their independence and safety. They can still manage driving, working and engage in recreational pastime [21]. Some of the signs of mild Alzheimer's Disease are poor judgment leading to bad decisions, repeating questions, mood and personality changes, memory loss, requiring more time to execute routine everyday tasks, increased anxiety and aggression, wandering and getting lost, loss of spontaneity, and sense of initiative [20].

5.2. Moderate Alzheimer's disease

Moderate Alzheimer's disease requires more stringent care and assistance, which can be difficult for many family members [20]. The patient may have trouble speaking and doing repetitive chores, become incontinent at times, and behavioral changes, such as distrust and irritation [21]. Some of the symptoms are have trouble logically thinking and structuring thoughts, having difficulty distinguishing family and friends, irrational outbreaks of rage, repetitious utterances or movements, muscular twitches, problems coping with new situations, shortened attention span, increased uncertainty and cognitive loss, shortened attention span, language difficulties, as well as troubles with reading and writing, difficulties coping with new surroundings, impulsive conduct such as getting undressed at random moments or locations or using swear words, failure to learn new things, hallucinations, delusions, and paranoia, difficulty carrying out multi-step tasks [20].

5.3. Severe Alzheimer's disease

People with severe Alzheimer's disease seek assistance with regular tasks and are indeed likely to demand 24-hour care. The impacts of Alzheimer's disease on people's overall well-being become increasingly apparent at this stage. As a result of injury to movement-related parts of the brain, people become bedridden. Patients who are confined to their beds are vulnerable to ailments like sepsis, skin infections, and blood clots, which can induce severe infection and organ damage. Eating and drinking become difficult as an effect of damage to the brain's location that controls swallowing. As a result, food could end up in the trachea rather than the esophagus. As a result, particles of food may build up within the lungs causing illness. Aspiration pneumonia is a type of infection that is a leading cause of mortality in Alzheimer's patients [21]. The most common symptoms are weight loss, swallowing difficulties, sleepiness, incontinence control issues, seizures, groaning, moaning, or grunting, skin infections, and inability to communicate [20].

6. Factors and causes of the high incidence rate of Alzheimer's disease

An international population has observed trends of increasing longevity and aging of the world's population in most developed and developing countries [22]. The demographics can be interpreted as a milestone of humanity and a new and impending challenge to the healthcare system. Since old age is a well-known determinant in the proliferation of common chronic diseases, these noncommunicable diseases would become an additional responsibility for healthcare professionals.

In every five years, the prevalence of dementia nearly approaches double its past number where the number of people living with dementia was greater in women than in men [23]. The result of their systematic review and meta-analysis showed that global prevalence of Alzheimer's disease per 10,000 persons from age groups of 60 to 69, 70 to 79, 80 to 89, and 90 years and older were 183, 514, 1,510, and 3,572 that variates with different geographic location. A research article [24], states that a model based on a global prevalence of 27.7 million people affected by dementia could cost an estimate of 156 billion USD.

Since aging is an imminent fact, the means to decrease the burden and the costs it accompanies is to prepare and advocate for preventive treatment stratagem while researchers find ways to create effective treatment. For an efficacious treatment to be developed, proper analysis of the disease pathway and risk factors must be done but the process of their mechanisms are diverse and the possibility that a few or many of these processes may be wrong [25]. While the prospects for the total prevention of Alzheimer's disease may still be difficult, the goal for the short term is to delay disability and create progress in preventive treatments in the hope of lessening the burden on health systems [26].

Time trends in a study in US states [27] suggest that a decline in incidence rates of cognitive impairment over time can be expected given the current inclination of potential risk factors and protective factors. But in spite of that, trends in cardiovascular risk and prevalence could also indicate an increase. 41.5% of the US population had been calculated to have various manifestations of CVD in 2015 and is forecasted to rise to about 45.1% in 2035 [28].

There are multiple approaches in minimizing the risk factors of dementia and Alzheimer's disease that can be classified into two groups: lifestyle practices which include physical exercise and cognitive activities and the other which is collateral benefits that are health interventions that are meant to treat conditions aside from Alzheimer's disease and dementia although causality in the collateral benefits is not yet established [29]. The most conspicuous out of them are hypertension, type 2 diabetes, and hyperinsulinemia [30].

7. Mechanism of Action of the Periwinkle Plant

Periwinkle improves the brain's capacity to use oxygen and as a result, glucose enhances brain activity. The most important component that causes the action is the vincamine chemical and vinpocetine, a chemically modified derivative. Vincamine is a vinca minor alkaloid that is considered to improve cerebral circulation and brain function. Vinpocetine has been shown in several trials to improve cerebral blood flow without influencing peripheral blood flow [31]. Increased brain tissue tolerance, anticonvulsant action, phosphodiesterase (PDE) inhibitory effects, hypoxia, ischemic damages and inhibition of thrombocyte aggregation are all recognized as biochemical and pharmacologic activities of this substance. Blocking voltage-dependent neuronal sodium channels, indirect suppression of several metabolic pathways triggered by a rise in intracellular calcium concentration, to a limited extent and adenosine absorption inhibition seem to be relevant to these effects..[32].

For more than 30 years, vinpocetine has been used in clinical trials to treat cerebrovascular illnesses such as stroke and dementia in several countries. Vinpocetine is already marketed as a nutritional supplement to aid in aspects of memory. This chemical is being studied for its unique therapeutic benefits and mechanisms of action in a variety of cell types and disease models, thanks to its outstanding safety profile. Vinpocetine has been found to have a number of unique effects according to recent research. These new discoveries could help vinpocetine be repositioned in humans for the treatment and prevention of related disorders [33].

Vinpocetine comprises a range of properties that may be beneficial to those suffering from Alzheimer's disease. Vinpocetine was really well controlled at doses into 60 mg/d in human research for dementia and stroke, with no significant adverse effects reported.[34].

8. Discussion

8.1. Alzheimer's Disease Statistics

According to the Alzheimer's Association, as of 2020, 5.8 million Americans that are aged 65 and higher have the disease. By 2025, when more members of the generation, baby boomers, reach that age, the number of individuals suffering with Alzheimer's disease in the United States is anticipated to climb to 7.1 million, a nearly 22 percent increase. Nevertheless, this development will not be maintained throughout the country. In some areas, the number of elderly persons with Alzheimer's disease is predicted to rise below 10% and in others, it will rise by more than 30%. [35].

8.2. Significant factors lead to the increase of the cases

8.2.1. Aging

Alzheimer's disease is not caused by getting older alone but it is indeed the most well-known risk factor. Every five years, the amount of patients with Alzheimer's disease increases among those over the age of 65. Around one-third of all individuals aged 85 and above suffer from Alzheimer's disease. Researchers are exploring how age affects the brain and how it might injure neurons as well as other several types of brain cells that will cause the disease. Age-related adjustments include shrinking of specific regions of the brain, infection, vascular injury, the formation of dangerous particles known as free radicals, as well as the disintegration of energy production inside cells [36].

Early-onset alzheimer's: A case study. (n.d.). from https://www.physio-pedia.com/Early-Onset_Alzheimer%27s:_A_Case_Study

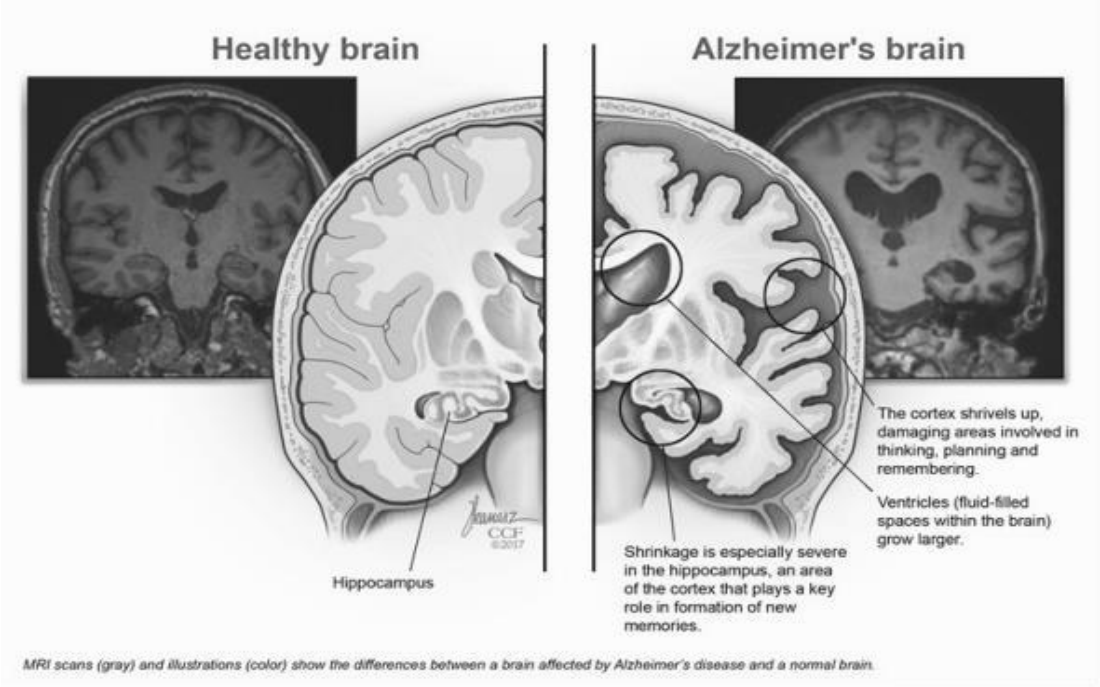


Figure 1. Comparison of a Healthy Brain and Alzheimer's Brain

The structure of an Alzheimer's disease-affected brain differs significantly from a healthy brain. When the cerebral cortex begins to deteriorate it implies that this portion of the brain shrinks and the shrinkage differs substantially from a normal brain's cerebral cortex. The cerebral cortex is the brain's outermost layer and it is in charge of whatever you're thinking about [37] And also, Alzheimer's disease causes the brain to deteriorate tissue in a continuous way. The hippocampus, specifically, is a region of the brain that has the most significant tissue loss early in the disease. The responsible for the formation of new memories is hippocampus and its increasing shrinking causes short-term loss of memory [38]

8.2.2. Genetics

If you have a family history of the condition, it does not mean you will acquire it. Even so, this could mean that you're more likely to get it. Every individual's chance of inheriting Alzheimer's disease is influenced by the genes they receive from their birth parents. Genetic risk factors are alterations or variations in genes that can lead to the development of a disease. With these risk factors, some diseases run in families [36]

8.2.3. Health, Environmental, and Lifestyle

People's health has been related to a nutritious diet, physical activity, community interactions, relaxation, and mentally challenging interests as they age. These qualities may also reduce the risk of Alzheimer's disease and cognitive decline [36]

8.2.4. Down's Syndrome

Alzheimer's disease is more likely to affect people with Down's syndrome. Another reason for that is due to the genetic mutations that result in Down's syndrome have the ability to increase the risk of amyloid plaque formation, leading to Alzheimer's disease in certain people [39].

8.2.5. Cardiovascular Diseases

Several lifestyle variables and disorders linked to cardiovascular illness have been shown to raise the risk of Alzheimer's disease, according to research. Smoking, being overweight, high blood pressure, diabetes, and high cholesterol are among them. [39].

8.3. Periwinkle plant as a memory enhancer

Periwinkle's active constituent vinpocetine is a synthetic ethyl ester of apovincamine,[3] and is the most clinically promising treatment for vascular dysfunction in the brain. It is actively distributed as an effective "memory booster". Since it is widely marketed, it has already undergone clinical trials. The result of such trials exhibited and illustrated the benefits of the plant-based supplement in its active constituent which is the Vinpocetine. Based on studies, this active constituent of the periwinkle increases the circulation of blood in the brain.[40]

In a clinical trial, a double-blind method was performed and the result shows it has a significant reaction as an outcome for the enhancement of geriatric patients with chronic cerebral dysfunction. During the trial, 42 patients in a 90 days period who have been given placebo tablets. And there are also 42 patients who have been given vinpocetine 10 mg three (3) times a day for thirty (30) days and then 5 mg three (3) times a day for sixty (60) days paralleling the period of 90 days for patients to participate in trial that are given with placebo.

Balestreri, R., Fontana, L., & Astengo, F. (1987). A Double-Blind Placebo-Controlled Evaluation of the Safety and Efficacy of Vinpocetine in the Treatment of Patients with Chronic Vascular Senile Cerebral Dysfunction. Journal of the American Geriatrics Society, 35(5), 425–430

TABLE 3. SUMMARY OF RESULTS OF MINI-MENTAL STATUS QUESTIONNAIRE PARTS A AND B (RANGE, 0 TO 39)

Drug	Baseline (Day 1)	Day 30	Day 30 minus Day 1	Day 90	Day 90 minus Day 1
Vinpocetine					
Mean	17.40	18.60	1.30*†	20.50	3.10*†
Median	17.00	20.00	0.0	21.00	4.00
SD	7.12	7.99	3.15	8.52	3.88
Minimum	6.00	5.00	−4.0	5.00	−6.0
Maximum	32.00	35.00	7.00	36.00	12.00
N	42.00	41.00	41.00	41.00	41.00
Placebo					
Mean	16.20	16.30	−0.1	16.90	0.4
Median	16.00	17.00	0.0	18.00	1.00
SD	6.57	7.81	2.84	8.40	3.63
Minimum	6.00	5.00	−7.0	2.00	−10.0
Maximum	29.00	31.00	6.00	30.00	8.00
N	42.00	41.00	41.00	39.00	39.00

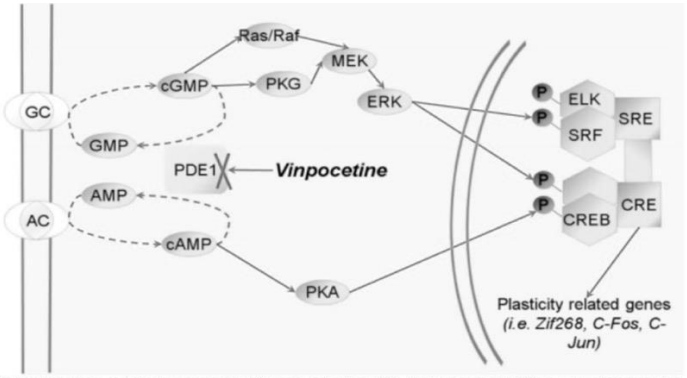
**Significant change from baseline (P < 0.01).*
†Significantly different from placebo (P < 0.01).

Figure 2.
Mini-Mental Status Questionnaire Result (Double-Blind: Vinpocetine as the treatment in Chronic Vascular Senile Cerebral Dysfunction)

The evaluation of the effectiveness of this clinical study is measured by *CGI (Clinical Global Impression) scal*e; the measurement of the severity of the illness was lessened by 44% of the vinpocetine-treated patients compared with the percentage outcome of the placebo group which is 13%, *SCAG (Sandoz Clinical Assessment-Geriatric) scale*; in this study, the cognition and the psychological state of the vinpocetine-treated patients were improved by 26% by 90 days and MMSQ (*Mini-Mental Status Questionnaire);* the score patients whose treated with vinpocetine is improved and more effective compared to the placebo group in 30 and 90 days period of trial.[41]

The periwinkle plant has a vinpocetine alkaloid which has been utilized for long-term potentiation, enhancing your spatial memory in experimental animals, and improving performance on cognitive examinations in humans. The reason for vinpocetine's cognitive-enhancing action is when the PDE type 1 decreases, which results in an increase in cAMP and cGMP levels. Phosphorylation of the transcriptional factors cAMP response element binding protein (CREB) and serum response factor (SRF) is caused by cyclic nucleotides that subsequently activate a cascade of kinases and therefore activate plasticity-related genes. [42].

Medina, A. (2010, June 01). Vinpocetine as a potent anti-inflammatory agent. from https://www.pnas.org/content/107/22/9921



Adenylyl cyclase activity increases cAMP levels, activating PKA. Active forms of PKA may translocate to the nucleus and phosphorylate CREB. Similarly, guanylyl cyclase activity increases cGMP levels, activating the Ras/Raf pathway either directly or through PKG. This leads to the activation of ERK and the phosphorylation of both CREB and SRF. Because PDE1 catalyzes the hydrolysis of cAMP and cGMP, its inhibition by vinpocetine increases the level of these cyclic nucleotides, ultimately leading to the expression of plasticity-related genes.

Figure 3. Vinpocetine Mechanism of Action

9. Conclusion

The principal aim of this review article was to discuss and know the memory enhancement properties of the periwinkle plant, to combat or prevent Alzheimer's disease. However, the treatment of Alzheimer's disease is still in process. Various factors related to dementia play vital roles in developing AD. According to the study, aging is not a cause of AD. It is shown in the study that every five years, the number of patients with Alzheimer's disease doubles among those over the age of 65. Periwinkle active constituent vinpocetine, a synthetic ethyl ester of apovincamine, was claimed to promote brain metabolism, boost glucose and oxygen intake in the hippocampus, and make improvements of brain resilience to a state of anoxia. Immunomodulatory effects have occurred suggested by obstructing the Nav channel, regulating chemical transmitters allowed to leave, as well as raising the impact about Adenoscan in antileukemic anoxia.

Acknowledgement

The completion of this paper could never be accomplished without the wisdom and gifts given to us by our almighty God, the knowledge and skills he provided helped us to do and finish the paper on time. We also give our sincere thanks to Mrs. Jacqueline Padilla for guiding, lending and giving her precious time in order for us to have correct and well written paper review that would help not only us but other researchers to gain knowledge unto the benefits of periwinkle. A special thanks to our friends and family who supported and encouraged us to finish this study, and provided us with our emotional and physical stability as well as food, shelter and internet service that we could use to communicate with ourselves in the crisis of C19 pandemic. Lastly, we express our deepest gratitude to the Pharmacy Department Faculty of San Pedro College that allowed us to conduct this research and helped gain strength and wisdom to accomplish the paper as it is now

REFERENCES

1. Alzheimer's disease: Facts & figures. (n.d.). Retrieved December 30, 2021, from https://www.brightfocus.org/alzheimers/article/alzheimers-disease-facts-figures
2. Alzheimer's disease fact sheet. (n.d.). National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet
3. Stevie Hendriks, M.Sc., et al. The incidence of young onset dementia: a systematic review and meta-analysis.(Funder(s): Alzheimer Nederland; Gieskes-Strijbis Foundation; Dutch Knowledge Center on Young-Onset Dementia)
4. Singhal, A., Bangar, O., & Naithani, V. (2012). Medicinal plants with a potential to treat Alzheimer's and associated symptoms. International Journal of Nutrition, Pharmacology, Neurological Diseases, 2(2), 84.
5. What happens to the brain in alzheimer's disease? [Internet]. National Institute on Aging. U.S. Department of Health and Human Services; [cited 2021Dec2]. Available from: https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease
6. Kocahan S, Doğan Z. Mechanisms of alzheimer's disease pathogenesis and prevention: The brain, neural pathology, N-methyl-D-aspartate receptors, tau protein and other risk factors. Clinical Psychopharmacology and Neuroscience. 2017;15(1):1–8.
7. Wenk, G. L. (2003). Neuropathologic changes in Alzheimer's disease. Journal of Clinical Psychiatry, 64, 7-10.
8. What is Alzheimer's? (n.d.). Alzheimer's Disease and Dementia. https://www.alz.org/alzheimers-dementia/what-is-alzheimers
9. Alzheimer's disease - Symptoms and causes. (2020, December 29). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms- causes/syc-20350447
10. HealthBenefitstimes.com. (2018). Retrieved December 3, 2021, from Health benefits of MadagascarPeriwinkle:https://www.healthbenefitstimes.com/madagascar- periwinkle/#:~:text=Health benefits of Madagascar periwinkle Madag ascar periwinkle contains,also helps in managing your blood sugar levels
11. Periwinkle uses, benefits & side effects - drugs.com herbal database. (n.d.). Retrieved December 03, 2021, from https://www.drugs.com/npc/periwinkle.html
12. Periwinkle: Health benefits, uses, side effects, dosage & interactions. (n.d.). RxList. https://www.rxlist.com/periwinkle/supplements.htm
13. Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. (n.d.). PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181909/
14. Naqvi, E. (2017, June 30). Alzheimer's disease statistics. Alzheimer's News Today. https://alzheimersnewstoday.com/alzheimers-disease-statistics/
15. Traditional Chinese medicine: A promising candidate for the treatment of Alzheimer's disease. (n.d.). CyberLeninka. https://cyberleninka.org/article/n/1309898
16. Causes and risk factors for Alzheimer's disease. (n.d.). Alzheimer's Disease and Dementia. https://www.alz.org/alzheimers-dementia/what-is-alzheimers/causes-and-risk- factors
17. 2020 Alzheimer's disease facts and figures. (2020, March 10). Alzheimer's Association. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.120
18. Yan, Z., & Feng, J. (2004). Alzheimer's disease: Interactions between cholinergic functions and β- amyloid. Current Alzheimer Research, 1(4), 241–248. https://doi.org/10.2174/1567205043331992
19. Selkoe, D. J. (2008). Biochemistry and molecular biology of amyloid β- protein and the mechanism of alzheimer's disease. Dementias, 245–260. https://doi.org/10.1016/s0072- 9752(07)01223-7
20. What are the signs of Alzheimer's disease? (n.d.). National Institute on Aging. https://www.nia.nih.gov/health/what-are-signs-alzheimers-disease
21. (Alzheimer's Association | Alzheimer's Disease & Dementia Help. https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf
22. Kinsella, K., & He, W. (2009). an aging world: 2008. US Census Bureau, international population reports. Washington, DC: US Government Printing Office
23. Cao, Q., Tan, C. C., Xu, W., Hu, H., Cao, X. P., Dong, Q., ... & Yu, J. T. (2020). The prevalence of dementia: A systematic review and meta-analysis. Journal of Alzheimer's Disease, 73(3), 1157-1166.
24. Kinsella, K., & He, W. (2009). an aging world: 2008. US Census Bureau, international population reports. Washington, DC: US Government Printing Office
25. Querfurth, H. W., & LaFerla, F. M. (2010). Mechanisms of disease. N Engl J Med, 362(4), 329-344.
26. Brookmeyer, R., Johnson, E., Ziegler- Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. Alzheimer's & dementia, 3(3), 186-191.

27. Rocca, W. A., Petersen, R. C., Knopman, D. S., Hebert, L. E., Evans, D. A., Hall, K. S., ... & White, L. R. (2011). Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. Alzheimer's & Dementia, 7(1), 80-93.
28. Nelson, S., Whitsel, L., Khavjou, O., Phelps, D., & Leib, A. (2016). Projections of cardiovascular disease prevalence and costs. RTI Int., Res. Triangle Park, NC, USA, Tech. Rep, 214680(001.001).
29. Jedrziewski, M. K., Lee, V. M. Y., & Trojanowski, J. Q. (2005). Lowering the risk of Alzheimer's disease: evidence-based practices emerge from new research. Alzheimer's & Dementia, 1(2), 152-160.
30. Grodstein, F. (2007). Cardiovascular risk factors and cognitive function. Alzheimer's & Dementia, 3(2), S16-S22.
31. Rathee, P., Chaudhary, H., Rathee, S., & Rathee, D. (2008). Natural memory boosters. Pharmacognosy Reviews, 2(4), 249.
32. Jha, M. K., Rahman, M. H., & Sheikh, H. (2012). Vinpocetine: a smart drug and a smart nutrient: a review. International Journal of Pharmaceutical Sciences and Research, 3(2), 346.
33. An update on Vinpocetine: New discoveries and clinical implications. (15, January). PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5766389/
34. Alternative medicine and Alzheimer's disease. (n.d.). PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2731997/
35. Suneson, G., Byrnes, H., & TODAY, U. (2020, August 10). Alzheimer's disease to affect 7.1 million Americans by 2025. Here's the expected increase by state. WLST. https://www.usatoday.com/story/money/2020/08/10/alzheimers-disease-states-where- cases-will-rise-most-by-2025/42187567/
36. What causes alzheimer's disease? (n.d.). Retrieved December 30, 2021, from https://www.nia.nih.gov/health/what-causes-alzheimers-disease
37. Kennard, C. (2021, December 06). The effects of alzheimer's on the brain. Retrieved December 25, 2021, from https://www.verywellhealth.com/the-alzheimers-brain-97675
38. 2015, A. (2015, October 15). Alzheimer's and a shrinking hippocampus. Retrieved December 25, 2021, from https://blogs.biomedcentral.com/on-medicine/2015/10/15/alzheimers-shrinking-hippocampus/
39. Alzheimer's disease - Causes. nhs.uk. (2021). Retrieved 29 December 2021, from https://www.nhs.uk/conditions/alzheimers-disease/causes/.
40. Vinpocetine: Uses, benefits, side effects, warnings | NutrientJournal. (2020, March 8). Nutrient Journal. https://nutrientjournal.com/vinpocetine-enhances-cognition-vasodilator/
41. Balestreri, R., Fontana, L., & Astengo, F. (1987). A Double-Blind Placebo Controlled Evaluation of the Safety and Efficacy of Vinpocetine in the Treatment of Patients with Chronic Vascular Senile Cerebral Dysfunction. Journal of the American Geriatrics Society, 35(5), 425–430. doi:10.1111/j.1532-5415.1987.tb04664.x
42. Medina, A. (2010, June 01). Vinpocetine as a potent antiinflammatory agent. Retrieved December 29, 2021, from https://www.pnas.org/content/107/22/9921