A Review on Current Therapies of Alzheimer's Disease and Prospects on Novel Potential Therapies

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Abstract: Alzheimer's Disease (AD) is a severe neurodegenerative disease that can cause dementia in mainly elderlies, afflicting millions of patients around the world (Merriam, 1988). Exact causations of AD are still unknown. However, numerous different therapies are proposed, and they show different therapeutic effects towards the disease. In this paper, current main therapies of AD are examined, and future potential therapies are proposed and discussed. Traditional pharmacy therapies, surgery, and other mature methods are listed and examined. Potential therapies like dietary therapy, neuroglia-related therapy, and gene therapy are discussed, and new research orientations are introduced as well.

1. Introduction

Alzheimer's Disease (also known as AD) is first discovered by and named after a German doctor Alzheimer. AD is one of the most common progressive neurodegenerative diseases around the world. AD is normally found in aged people and rarely in young. Typical symptoms of AD include dementia, which is the most common type. Severe AD is able to induce strong cognitive disorder that may jeopardize patients' life. Therefore, causations of AD and therapies to cure AD has long been a focus in medical field.

However, due to the complexity of AD, exact causations of it still remain unknown. But through long time of research, several theories have been proposed to partially explain the origination of AD. Prevalent theories include Aβ oligomers aggregation theory, Tau protein hyperphosphorylation theory, neuroinflammation theory, etc. These theories provide guidelines for researchers to develop possible therapies of this disease.

Unfortunately, up to now, only limited types of therapies are proved to be effective in relieving AD symptoms such as dementia. However, none of them can totally cure the disease. This is partially due to the uncertified mechanism of this disease. With more and more mechanisms of AD being discovered, new therapies are proposed as well. Total cure of AD is still distant, but recent discoveries open up new prospects.

In this passage, current therapies are reviewed. Then, based on current cutting-edge progress in therapeutic research, new orientations are proposed and examines.

2. Literature Review

2.1. Current Therapies

Current therapies to AD are still limited. Most of them can only alleviate the cognitive dysfunction symptoms to a certain degree. It is currently impossible to totally cure Alzheimer's Disease. Traditional therapies basically include different kinds of drugs to decrease the negative effects of neuropathology, and novel therapies take more approaches, including diet, genetics, and so on, to increase the effectiveness and efficiency. We can gain plenty of insights from the novel therapies and find possible ways to figure out a better way to cope with AD.

Traditional therapies of AD mainly focus on the use of pharmaceutical drugs. Because AD pathology is mainly physiological, physical treatments do not play an important role in AD therapies.

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Based on different theories about AD pathogenesis, a series of drugs are developed to attenuate the cognitive impairs brought by AD.

2.1.1. NMDA Antagonists

Glutamate, as an important neurotransmitter in the formation of memory by initiating LTP, can have a negative effect on cognitive function of CNS when its function is too high. Overstimulated function of glutamate is due to the overactivation of its receptor, NMDARs. Therefore, to lower the excitotoxicity of this neurotransmitter, it is viable to block the overactivation of NMDA receptor. NMDA antagonists can thus be a potential drug for AD treatments. Researchers have developed several kinds of NMDA antagonists, but their clinical effects on alleviating the cognitive impairs are mostly unsatisfactory. One of them, an uncompetitive antagonists called Memantine, is tested to be effective in treating AD. In fact, Memantine is the only approved drug in this category for treatment of moderate to severe AD symptoms (Breiyeh, 2020).

2.1.2. Cholinesterase Inhibitors (AChEIs)

Acetyl choline (ACh) has been recognized as an important neurotransmitter in several cognitive processes. Decrease in ACh level in brain is a factor of dementia. Therefore, increasing the function of ACh in brain is an adoptable method for treating dementia caused by AD to certain extent.

Commonly, after ACh molecules finish binding on the post-synaptic membrane, they will be decomposed by an extracellular enzyme acetylcholinesterase, also known as AChE. In this way, AChE is able to maintain the ACh level in the synapses in an acceptable range.

To increase ACh level in synapses, one method is to inhibit the function of AChE. That is because when these enzymes can no longer function, excess amounts of ACh will not be decomposed and remain in the synapses. In this way, the neurotransmitter molecules can keep binding to the receptors and recreate excitatory potentials. Therefore, although the actual level of ACh in brain is not changed, the function of the neurotransmitter is largely improved during this process. AChE inhibitors (AChEIs) thus became a commonly used drug for treatments of AD. Developed drugs in this category include Donepezil, Rivastigmine, Galantamine (GAL), and so on.

Researchers have also tried to increase ACh functions in other ways, such as activating the synthesis of ACh. However, the usage of AChEIs is still a mainstream in pharmaceutic treatments of AD by cholinergic pathways.

2.1.3. Antioxidants

Oxidative pressure, as explored in previous studies, is an important factor for AD. Free radicals can damage various structures in cell, like the lipid in cell membrane or DNA. Also, mitochondrial dysfunction contributes to oxidation as well. To deal with oxidation process, antioxidant therapies are used.

Vitamins and carotenes are reductive agents that can protect cellular structures from oxidative impairments. Commonly applied species include Vitamin C, Vitamin E, Vitamin B_{12}, β-carotene. Vitamin E is proved to attenuate oxidative toxicity of Aβ, and Vitamin C is able to decrease the high level of isoprostanes and reduce oxidative pressure in vivo (Wang, 2012).

Some other types of antioxidants targets mitochondria. Coenzyme Q10, Mito Q, NADH, and lipoic acid belong to this type. Lipoic acid is able to chelate redox-reactive metals in mitochondria to prevent accumulative of toxic oxidative species. Coenzyme Q10 and NADH, as primary reducing powers in biological oxidation, also function to regulate oxidative level in mitochondria in a normal range. Mito Q is another mitochondria-targeted antioxidant that is reported to reduce free radicals and maintain mitochondrial functions with high efficiency.

Several chemicals produced by our own body have reducing functions as well. Melatonin is a hormone synthesized by pineal gland, and it is able to scavenge oxygen or nitrogen-based oxidative reactants by stimulating several related enzymes (Wang, 2012). Estrogen has a neuroprotective effect by protecting the neurons from damage of Aβ, but evidence does not show that estrogen has a significant improvement to cognitive abilities of the patients.

These antioxidants can be used as drugs or a supplement in diet. Due to its simpleness and

effectiveness, adding antioxidants in diet may be a great method for daily prevention or treatment of oxidation-related neurodegenerative diseases like AD.

2.1.4. Anti-inflammatory Drugs

Neuroinflammation is one of the causes for AD. Thus, anti-inflammatory drugs are used to deal with neuroinflammations. Nowadays, the potential of Non-Steroid Anti-Inflammatory Drugs (NSAID) in treating AD is discovered.

2.2. Novel Therapies

2.2.1. Dietary Therapy

Recently, researchers have found that changing the dietary structure of AD patients can also prevent or slow down the progression of the dementia symptoms. One of the diets that is proved to be functional is the Mediterranean Diet. Mediterranean Diet is characterized by high intake of vegetables, legumes, fruits, and cereals; high intake of unsaturated fatty acids, like olive oil; but low intake of saturated fatty acids (Scarmeas, 2006). In prevention of AD, research has shown that higher adherence to Mediterranean Diet is associated with a reduction in risk for AD (Scarmeas, 2006). The specific mechanisms are being investigated. The functioning of Mediterranean Diet might be related to content of antioxidants within the food.

A number of natural substances are also integrated into diet for AD treatment, such as tea or other herbal medicine. However, not enough evidence has shown that they can overturn the AD symptoms. But dietary therapy is still considered as a promising approach due to its convenience and lack of side effects.

2.2.2. Novel Drug Therapy

Apart from the traditional drugs that focus on only a few targets, novel drugs are developed to address more pathways. Currently, there are already drugs developed based on microbiome in human gut, such as GV-971.

Also, natural extracts show their strong potentials for being new targets for developing new drugs. Traditional herbal medicines are widely researched on nowadays. Some fruitful results are already obtained. For example, green tea, a common beverage in China, has a wide range of chemicals that function as antioxidants, like different kinds of catechins including ECG, EGCG, etc. (Lim, 2012). Another example come from Magnolia Officinalis, which is a type of Traditional Chinese Medicine. An important compound in Magnolia Officinalis, Magnolol, plays a role in antioxidation, antiinflammation, etc. More interestingly, a novel pathway is discovered, which is to increase phagocytosis of microglia cells by activating a specific protein PPAR-γ (Xie, 2020). All these examples show the huge potential of finding functional chemicals in natural extracts, which could be developed as novel drugs in the future.

3. Research Proposal

Natural extracts refer to chemicals extracted from natural components. For example, plants, animals, or microorganisms. Generally, most common natural extracts that can be used as medicine come from plants. From ancient times, people were using plant material to produce effective therapies. In Traditional Chinese Medicine or Traditional Tibetan Medicine, herbs are the primary material for making different decoctions. Those decoctions, which are essentially the mixture of herbal soup, are proved to be effective in treating a lot of diseases. Therefore, finding possible therapies in those natural extracts is a viable method. Previous research has suggested that there is huge potential in discovering new drugs within natural material. For example, in 1972, Chinese female scientist Tu Youyou extracted a chemical called Artemisinin in *Artemisia apiacea*, a commonly used species in Traditional Chinese Medicine. Artemisinin was later discovered to have great treatment effects to malaria (Tu, 2011). This discovery definitely provides support for the viability of developing new therapies for AD in natural extracts.

Examining the natural extracts can contribute to AD therapies in two ways. For the first, similar

to the discovery of Artemisinin, we are able to target new chemical molecules that have therapeutic effects for AD. These compounds have the potential to be developed as new drugs for AD treatments. As mentioned in previous part, researchers have already found effective chemicals in a wide range of natural materials, mainly plants, such as catechins in green tea, magnolol in Official Magnolia Bark, and several other compounds in Ginkgo. Still, secondary metabolism of plants is a huge resource waiting for us to discover. Through screening potentially effective natural extracts in animal models, useful natural components will be found, and specific chemical compounds can be certified, too. Finally, these chemicals will become candidates for clinical drug development.

In addition, apart from natural extracts' possible use in pharmaceutic therapies, they can also contribute to dietary treatments. A lot of these natural components are actually edible. Therefore, adding them into the diet of patients can probably alleviate the symptoms without the necessity to take drugs. However, having certain chemical compounds within the edible natural extracts does not necessarily mean that they are competent for dietary therapies. After the discovery of their therapeutic effects in animal models, further research should be conducted to test their viabilities in human diets in order to draw a convincing conclusion.

3.1. Screening for Potentially Effective Natural Extracts in Nematode Model

Up to now, a lot of effort has been made to screen for possible drugs in natural extracts, especially herbal medicine. A great portion of plant species in traditional medicine has been tested. Therefore, in order to seek for novel findings, confining the research field in herbal medicine may not be a sustainable approach. Instead, it would be a good choice to enlarge the range into other plant materials that are used in human life, such as spice, essential oil, or incense.

These three targets have the similarity that they are used for specific aromatic chemical substance. This indicates their abundant secondary metabolites, which set up a basis for effective screening. Also, as their secondary metabolic products can directly be ingested or smell by human beings, their toxicity is relatively low. In addition, a lot of spices and plant species used for essential oil or incenses are also found in the list of traditional herbal medicines. Although they may not be mainstream medicines in traditional therapies, they are still recognized to be effective in some treatments. This suggests that using them for drug screening has support from previous medical experience. Finally, in some cases, scents or flavors produced by them are thought to provide "calming" or "healing" effect to the nervous system. Several studies did prove that these herbal products had neuroprotective effects. Considering all points above, herbal materials in species, essential oil, or incenses can indeed be an ideal starting point for novel drug screening. Fragrant resin from trees (like colophony or myrrh) or essential oil from herbal medicinal plants can be suitable materials for further research. Evidence from previous research also did try several scented plants and got desired results. For example, valerian, an herb that is usually used in essential oil, has been researched on and proved to have neuroprotective effects and be able to alleviate the cognitive impairments in nematodes AD model (Mungali, 2021). All of these provide great rationale for future research direction in drug screening.

In the screening process, nematodes, to be more specific, *Caenorhabditis elegans* (referred to as *C. elegans* in the following passage) are ideal animal models. First of all, nematodes are tiny organisms that grow and reproduce fast. This means that natural extracts can be tested in a large quantity of samples. Also, due to their fast growth and reproduction rate, the whole process of screening can be completed within a short period of time. Secondly, genomic analysis of *C. elegans* shows that the resemblance of AD-related genes in *C. elegans* and human is approximately 80%. In this way, natural extracts that are effective in nematodes AD models have higher chances to be effective as well in humans. Molecular mechanisms explored in *C. elegans* are also likely to be valid in humans. At last, *C. elegans* has long been the most commonly used experimental material in developmental biology. Therefore, a great amount of experience has been accumulated in research of *C. elegans.* It is a mature animal model for research use. Previous research has produced full information about its genome, and its developmental process is clear, so exploring molecular mechanisms after screening for drugs will be much more convenient.

For research in finding new effective natural extracts for AD, *C. elegans* mode GMC101 is an

ideal choice. GMC101 strain overexpresses $A\beta_{1-42}$ protein, main toxic Aβ protein in human AD pathogenesis, in muscle cells, which leads to paralysis as an indicator of AD symptoms (McColl, 2012). GMC101 nematodes can be grown in NGM medium with *E. coli* OP50 strain as feed. In the bacterial culture of *E. coli* OP50 added onto NGM plate, solutions of selected natural extracts can be added into certain concentrations (commonly used concentrations are 10mM or 100mM). After growing GMC101 nematodes on the plates with natural extracts under 20℃, a certain number of L4 larvae will be collected and given heat shock under 25℃ for 24h, and paralysis rate in the population can be calculated. In comparison to the paralysis rate of population grown in plate without the natural extract, the significance of effects of natural extracts to alleviate paralysis rate can be obtained through Fischer's exact test. In this way, natural extracts that can significantly lower the paralysis rate of GMC101 nematode will be selected for further research.

3.2. Determining the Molecular or Cellular Mechanisms of the Natural Extracts' Alleviation Effects towards AD Symptoms in Nematodes Model

After certifying the alleviation effects of natural extracts on AD nematode model GMC101, it is important to determine the exact molecular or cellular mechanisms of these functions in order to provide a perspective on drug development.

The specific protocols for exploring the molecular or cellular mechanisms will not be specified here, but some general ideas or suggestions are presented.

First of all, exploration on genetic level can be done by using genetically modified nematode models. A lot of functions of drugs are related to several genes that are mentioned before, like APOE, PSEN1, APP, etc. Thus, genetic engineering tools such as CRISPR/Cas9 can be utilized by plasmid or viral vector to knockout target gene in GMC101 nematodes. After the target gene are successfully knocked out from genome, a steadily inherited strain will be selected and cultured. Then, this new strain with a gene knocked out will be employed in the same experimental process in screening for effective natural extracts. If the alleviation effect proved in GMC101 no longer works, there are chances that the function of the specific type of natural extract is related to the knockout gene. If the alleviation process still remains in the new strain, other strains with different genes knocked out can be tested.

When none of the commonly investigated genes do not participate in the molecular mechanism, there are chances that natural extracts function in a new pathway. Therefore, a transcription-level test can be conducted. After processed with the specific type of natural extract, nematodes are collected from the plate, and for each of them, total mRNA is extracted, and transcriptome will be analyzed. If one or more mRNAs are transcribed at a significantly higher level than the normal state, RNAi can be conducted in nematodes to block the expression of the specific genes. By doing this, the genes are silenced, which achieves a similar effect of gene knockout by gene editing. When the genes are silenced, if the alleviation effects of natural extracts disappear, a new gene is proved to be related to the mechanism and the new pathway can be investigated in further research.

It is worth mentioning that it will be fruitful to focus on the mechanisms regarding neuroglia cells, mainly astroglia cells and microglia cells. Currently, more and more attention in neurobiological studies is attracted to the field of neuroglia cells. Apart from neurons, neuroglia cells are responsible for regulating a wide range of different functions in the brain. The pathogenesis of AD related to neuroglia cells in different ways, which mainly have to do with immune responses. Natural extracts may have functional components with respect to neuroglia cells. If this kind of components are found, probably new molecular or cellular pathways involving neuroglia cells will be discovered, based on which huge potentials of developing novel drugs can be developed. Previous research has already set up foundation for this. As mentioned in previous passage, Magnolol discovered in Magnolia Officinalis is involved in a pathway of stimulating phagocytosis of microglia cells, by which Aβ senile plaques are cleared and AD symptoms are alleviated. Knowing the huge potential of neuroglia cells, we can draw our attention to explore natural extracts' mechanisms this aspect.

3.3. Testing the Effectiveness of Selected Natural Extracts in Mammal Models

After the natural extracts are proved to be effect, there is still a long way to go to be implemented

in real therapies. A primary concern is that even if extracts can effectively treat AD symptoms in nematode model, it does not mean that the extracts will definitely work in human. Although human beings and nematodes share great similarity on the genes and proteins related to AD, far more complex regulatory mechanisms in humans, such as blood-brain barrier (BBB), should be taken into account. Therefore, further test is surely necessary for verifying the treatment effects. However, directly testing in humans is risky and is a violation of medical ethics. Therefore, it is important to conduct further test first in mammal AD models, such as mice or monkeys. If in these animals, the selected natural extracts also show strong effectiveness and little side-effect, considering clinical trials of the selected natural extracts will be appropriate.

4. Discussion

From the literature review part, we are able to see that current therapies are still limited. Pharmaceutical treatments can only to some extent slow down the progression of AD dementia or alleviate the symptoms partially. The fundamental reason is that AD mechanisms are not understood thoroughly yet. Recently, the emergence of several novel therapeutic methods cast a light on the future of AD treatments, including dietary therapy, developing novel drugs, and so on. Among them, selecting natural extracts for potential drug development and dietary therapies becomes a focus of research proposal.

In the research proposal, nematode AD model, *C.elegans* GMC101 strain, is used as a primary material for screening for effective natural extracts. The experimental procedure advances gradually into test in mammal models like mice or monkeys, and finally the extracts can probably be implemented in clinical drugs or diets in humans. The whole process follows makes sense theoretically. Following this procedure, natural extracts effective for humans can be found, but in a really small number. This proposal has several advantages. Nematode model can be easily required, and the costs for culturing it is low. The screening process is economically inexpensive. Life cycle for nematode only lasts for 3 days. Experimental results can be acquired really quickly. Nematode's genome is already sequenced, and its physiology and developmental biology are all clear. It will be a huge convenience for the investigation of functioning mechanisms of natural extracts. However, limitations do exist: Nematode experiments are conducted in a large number, normally more than hundreds of individuals for each plate. This can post large workload to the researchers. Differences between nematodes and mammals can lead to the ineffectiveness of a lot of natural extracts in mammal models, although they may play a role in alleviating AD symptoms in nematode model. There are rigorous ethical considerations to conduct trials in humans. If the natural extracts are only tested in nematodes or mammal models, a lot of other procedures should be taken to test natural extracts in human beings.

Overall, based on current situations in AD treatment, the proposed research can cast light on the future of dietary therapy and novel drug development. Despite that there are some drawbacks, if the procedure is implemented in the reality, the results may be fruitful.

5. Conclusion

Alzheimer's Disease (AD) is a widespread neurodegenerative disease that causes dementia in patients who are mainly elderlies. Its pathogenesis is still unclear till today, but a lot of valuable theories, such as Aβ aggregation and tau hyperphosphorylation, are proposed. Pharmaceutical drugs, like Memantine and Donepezil, are developed as NMDA antagonists, AChEIs, antioxidants, anti-inflammatory drugs, and so on. Some novel treatment approaches are also proposed, such as dietary therapy, novel drug development, etc. The potential of finding possible drugs in natural extracts or using natural extracts in diets is recognized. A wholistic research proposal based on nematode AD model, *C.elegans* GMC101 strain, to screen for possible effective natural extracts in spice is made. Some suggestions to investigate mechanisms regarding neuroglia cells and to test the effectiveness of selected extracts in mammal model are brought up, too. Following this experimental procedure, hopefully some functional components can be successfully screened out, which will be used for drug

development or dietary therapies for the next step. AD treatments might have a breakthrough in the progress of these meaningful attempts. In the near future, we may have a more effective therapeutic plan for Alzheimer's Disease.

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