Hypothesis

Yokukan-San and Tetracycline Treatment for Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a progressive neurological disorder that causes memory loss, cognitive decline, and behavioral changes. AD pathologies involve different factors, including damage of cholinergic neurons, extracellular deposition of β-amyloid (Aβ) into senile plaques, intracellular accumulation of hyperphosphorylated tau protein, microglia-related neuroinflammation, and oxidative stress. Several medications, such as **cholinesterase inhibitors, N-Methyl-D-aspartate receptor antagonists, and immunotherapy drugs, are administered for AD treatment. Along with AD-related neurological disorders, b**ehavioral and psychological symptoms of dementia (BPSD) are also prevalent in individuals with AD. Pharmacological treatments for BPSD include **antipsychotics**, memantine, and others. **Yokukan-san (YKS)** is a traditional Japanese Kampo medicine. YKS contains a blend of several herbs, including *Uncaria uncis cum ramulus, Angelicae radix, Bupleurum radix*, **and others**. **It has been efficacious against BPSD; thus, it was** officially approved for BPSD treatment in Japan. Recently, the anti-AD effects of YKS have attracted considerable attention. *Uncaria uncis cum ramulus* managed AD by reducing Aβ accumulation, decreasing abnormally hyperphosphorylated tau protein, and inhibiting acetylcholinesterase. Similarly, *Angelicae radix* has improved memory deficits in a rat AD model by reducing Aβ levels, promoting cholinergic function, and decreasing oxidative stress and neuroinflammation. Tetracyclines (i.e., minocycline and doxycycline) popularly exhibit anti-inflammatory effects by inhibiting microglia. Moreover, minocycline has reduced Aβ production and hyperphosphorylation of tau protein. Experimental AD models demonstrated that minocycline and doxycycline improved cognitive/learning, and memory deficits, respectively. Therefore, minocycline and doxycycline are efficacious against AD. Multidrug treatment is more effective than single-drug treatment because of the synergistic effects associated with the different mechanisms of action of involved drugs. In the absence of currently effective and low-priced treatments, YKS and tetracycline are proposed for AD treatment.

Keywords: Alzheimer's disease; Kampo; Yokukan-san; tetracycline

Alzheimer's disease (AD) is a progressive neurological disorder that causes memory loss, cognitive decline, and changes in behavior. Pathologies of AD involve various factors such as cholinergic neuron damage, extracellular deposition of β-amyloid (Aβ) into senile plaques, intracellular accumulation of hyperphosphorylated tau protein as neurofibrillary tangles, microglia-related neuroinflammation, oxidative stress, inappropriate deposition or misdistribution of metal ion, glutamate excitotoxicity, microbiota-gut-brain axis dysfunction, and abnormal autophagy [1,2]. Several drugs, such as **cholinesterase inhibitors (i.e., donepezil, galantamine, and rivastigmine), N-Methyl-D-aspartate receptor antagonists (i.e., memantine) that suppress** glutamate excitotoxicity**, and immunotherapy drugs (i.e., lecanemab, and aducanumab) that improve** Aβ **clearance, are administered for AD treatment [3]. Along with AD-related neurological disorders, b**ehavioral and psychological symptoms of dementia (BPSD), such as agitation, psychosis, depression, apathy, aggression, and hallucinations, are prevalent among individuals with AD.

Pharmacological treatments for BPSD include **antipsychotics (i.e., risperidone, olanzapine, and haloperidol), antidepressants (i.e., citalopram, and sertraline), benzodiazepines, cholinesterase inhibitors (i.e., donepezil, galantamine, and rivastigmine), anticonvulsants (i.e.,** valproic acid, gabapentin, lamotrigine, topiramate, and carbamazepine), and memantine [4]**.**

Kampo medicine is a traditional Japanese medicine developed based on unique theories and therapeutic methods of traditional Chinese medicine. **Yokukan-san (YKS)**, also known as **Yi-Gan San** in China, is a type of Kampo medicine that contains a blend of several herbs, including *Atractylodes lanceae rhizome*, *Poria, Cnidium rhizome, Uncaria uncis cum ramulus* **(UUCR)**, *Angelicae radix* **(AR)**, *Bupleurum radix*, **and** *Glycyrrhiza radix*. Clinical studies have shown that YKS helped improve **BPSD** without significant side effects. Consequently, the Japanese Ministry of Health approved YKS, whereas the Japanese Society of Neurology in 2010 recommended it for BPSD treatment [5,6]. The mechanism underlying the effects of YKS on BPSD remained unclear. Recently, regulatory effects on neurotransmitter systems by UUCR and AR may have contributed to the improvement in various psychiatric and behavioral symptoms [7]. Recently, the anti-AD effects of YKS have gained considerable attention [8]. UUCR, a component of YKS, has been proven to treat AD by reducing the accumulation of Aβ (especially oligomers of the amyloid-β42), decreasing abnormally hyperphosphorylated tau protein, and inhibiting acetylcholinesterase [9]. AR, which is another component of YKS, has significantly improved memory deficits in a rat AD model induced by Aβ protein. It helped reduce Aβ levels, promote cholinergic function, and decrease oxidative stress and neuroinflammation [10].

Regarding aforementioned microglia-related neuroinflammation, Aβ is a typical trigger for microglial activation. Activated microglia migrate towards senile plaques, engulf Aβ, and release enzymes to digest Aβ. However, microglia become less efficient at handling Aβ over prolonged periods. Moreover, microglia continue to generate proinflammatory cytokines and induce neurotoxicity, causing neurodegeneration, which is also induced by amyloid plaque accumulation at synapses [2,3]. Tetracyclines (i.e., minocycline (MIN), and doxycycline (DOX)) are known to cross the blood–brain barrier and exhibit anti-inflammatory effects by inhibiting microglia. Moreover, MIN has reduced Aβ production and tau protein hyperphosphorylation in the hippocampus. These results indicate that MIN and DOX could naturally improve cognitive/learning and memory deficits, respectively, in experimental AD models [11].

Multidrug treatment is more effective than single-drug treatment because of the synergistic effects associated with the different mechanisms of action of involved drugs. The combination of YKS and tetracycline is recommended as one of the transitional treatments in the absence of currently effective and low-priced treatments.

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