Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 105 (2018) 40-50 EISSN 2392-2192

Use of Traditional Japanese Medicine Kampo in course of Alzheimer's Disease

Maria Gołębiowska[1,]*, Beata Gołębiowska[2]

[1] Student, I Faculty of Medicine, Medical University of Lublin, Al. Raclawickie 1, 20-059 Lublin, Poland

[2] Pediatric Neurology Department, III Chair of Pediatrics, Medical University of Lublin, ul.Prof. A. Gebali 6, 20-093 Lublin, Poland

*E-mail address: golebiowska.maria8@gmail.com

ABSTRACT

Dementia, the plague of the aging populations, is highly prevalent in East Asia, with currently over 9,8 million dementia patients. Alzheimer's disease (AD), the most common cause of dementia, awaits for more detailed research in terms of understanding patomechanism of the disease, but more importantly, in supporting the treatment of this incurable disease in modern medicine. Therefore, alternative therapies assisting traditional therapeutic options become more popular, with the comeback of traditional medications, such as Traditional Japnese Medicine (TJM) - Kampo. The aim of this study was to present the use and effectiveness of TJM in treatment of symptoms of AD. Among articles in PubMed Medline database in years 2008-2018, 8 articles were selected for further analysis. Most of the research (38%) consisted of observational studies using different neuropsychiatric scales and methods of assessment of dementia. Studies presented significant improvements of behavioral symptoms with additional therapy with Yokukansan, Orengedoku-to, Ninjin'yoeito and other Kampo formulas in AD patients. Reviewed research presents effectiveness of Kampo treatment in supporting of cognitive and behavioral symptoms reduction, as well as protection of beta-amyloid induced toxicity. However, more research involving bigger cohorts is needed in order to confirm results on the larger scale, in order to introduce the beneficial aspects of Kampo in AD populations worldwide.

***Keywords*:** dementia, Alzheimer's disease, kampo, traditional medicine

(Received 05 July 2018; Accepted 19 July 2018; Date of Publication 21 July 2018)

1. INTRODUCTION

1. 1 Dementia - disease of the aging world

Dementia, a long term gradual decrease in ability to think and remember, affecting greatly person's functioning, is one of most common diseases of the aging populations. The most frequent type of dementia is Alzheimer's disease, which equals 50-70% of all its cases. Alzheimer's disease (AD), a disorder of a pathomechanism poorly understood by modern medicine, greatly affects the patients quality of life and includes support of many caregivers. It is not only one of the most costly diseases of financial aspects, but more importantly, on individual level a huge burden associated with stigma and social challenges. [1, 2]

Among many hypotheses on origin of the AD, the genetic causes are believed to be the most frequently involved in pathogenesis in between 49 to 79% of cases. Most of genetic mutations do not present autosomal correlation and happen with influence of environmental and genetic alterations. [3] The main genetic risk factor is the inheritance of ε4 allele of the apolipoprotein E (APOE), primarily known for role in catabolism of trigliceryde-rich lipoproteins, in CNS is responsible for transport of cholesterol and hypothetically takes part in cognitive processes and immunoregulation. The higher risk of 10 to 30 times of developing AD is confirmed among Caucasian and Japanese carriers of 2 E4 alleles. [4] Around 0,1% of cases are early onset familial Alzheimer's disease, connected to autosomal inheritance of mutations of genes encoding amyloid precursor protein (APP) and presenilins 1 and 2. [5]

With this genetic predisposition another hypothesis is connected -the accumulation of amyloid β (Aβ) derived from amyloid precursor protein (APP) resulting in formation of amyloid plaques. [6] Lastly, tau hypothesis involves hyperphosphorylated tau proteins which form neurofibrillary tangles inside the neurons, leading to destruction of the cytoskeleton of the cell and its apoptosis. [7] The environmental risk factors which may contribute to development of AD include obesity, hypertension, mental health disorders such as depression, and head trauma. [8]

Ten main early signs of Alzheimer's and other types of dementia include:

- *memory loss which disrupts daily life,*
- *challenges in planning or solving problems,*
- *difficulty in completing familiar tasks,*
- *confusion with time and place,*
- *trouble with understanding visual images, spacial relationships,*
- *new problems with speaking or writing*
- *misplacing things*
- *decreased or poor judgment,*
- *withdrawal from work or social activities,*
- *changed in mood or personality.* [9]

These symptoms occur in AD earlier than in the regular course of aging. The usual onset of Alzheimer's is about 65 years old, and progresses to the late stages, when the patient needs assistance in most all of the personal care as well as 24h supervision. Later symptoms of the disease are classified into core symptoms (loss of cognitive functions) and behavioral and psychological symptoms (eg. aggression, hallucinations). [1]

Nowadays over 46 million people live with dementia worldwide. According to 2015 World Alzheimer Report, East Asia is the world region highest number of population living with dementia - 9,8 million. Japan is in the fourth place of all of the countries - 3,1 million living with dementia - preceded by China, USA and India. Within the possible treatment options only symptoms-related treatment is available and can be differentiated mainly to preservation of cognitive functions, reduction of behavioral changes and restoration of sleep cycle. Memory loss, problems in thinking, reasoning and other cognitive impairments are treated mainly with cholinesterase inhibitors (rivastigmine, donepezil) and memantine; behavioral symptoms, such as aggression, anxiety, depression, hallucinations and sleeping deprivation with antipsychotic and antidepressant drugs. Most of those medications have several side effects, which along with common polypharmacy in geriatric patients may lead to iatrogenic adverse events, lack of patients compliance and lower quality of life. Higher mortality among patients using antipsychotic drugs was also proved by several studies. [8;10-11]

1. 2. Traditional Japanese Medicine

Kampo is a study of Chinese medicine and its further vast development on Japanese soil. The Traditional Chinese Medicine (TCM) originated from the wisdom of three sovereigns - Fuxi, the creator of humanity, Shennong, master of plants, the attributed author of The Classic of Herbal Medicine and Yellow Emperor - the creator of Yellow Emperor's Inner Cannon - the fundamental doctrinal source of TCM - source of Yin and Yang, Qi flow and Five Elements. [12, 13] Chinese medicine was introduced in Japan in early 6th century and later adapted to Japanese reality, which we can nowadays study in the oldest surviving Japanese medical document, Ishinpo. Despite years of globalization of Western medicine, Japanese traditional medicine is still actively present in the modern medical treatment options. Among some groups in the population it is considered sometimes as the primary way of treatment, in some cases, especially in diseases not conquered by Western medicine, used as alternative or complementary way of treatment. 14th edition of Japanese Pharmacopeia includes 165 herbal ingredients listed as Kampo medication. Ministry of Health in Japan approved 148 of traditional herbs for National Health Insurance reimbursement until now. [14] In year 2000, it was discovered that 72% of physicians prescribed known Kampo medicine, and simultaneously both new and already known plants are evaluated to measure their effectiveness in treatment of known and yet not defeated diseases. [15]

2. AIM

The aim of this study is to present the use and effectiveness of Traditional Japanese Medicine Kampo in treatment of Alzheimer's disease.

3. METHODS

Substantial articles on use of Kampo in treatment of Alzheimer's disease symptoms have been analyzed. Among articles in PubMed Medline database from years 2008-2018, 8 articles were selected for analysis.

4. RESULTS

Most of the presented research was observational studies (38%), using different neuropsychiatric scales and methods of assessment of dementia in patients. 25% of the research was case reports and evenly 25% of research was biochemistry studies on kampo properties in preventing Alzheimer's Disease. One study (12%) was an animal- AD model mice study.

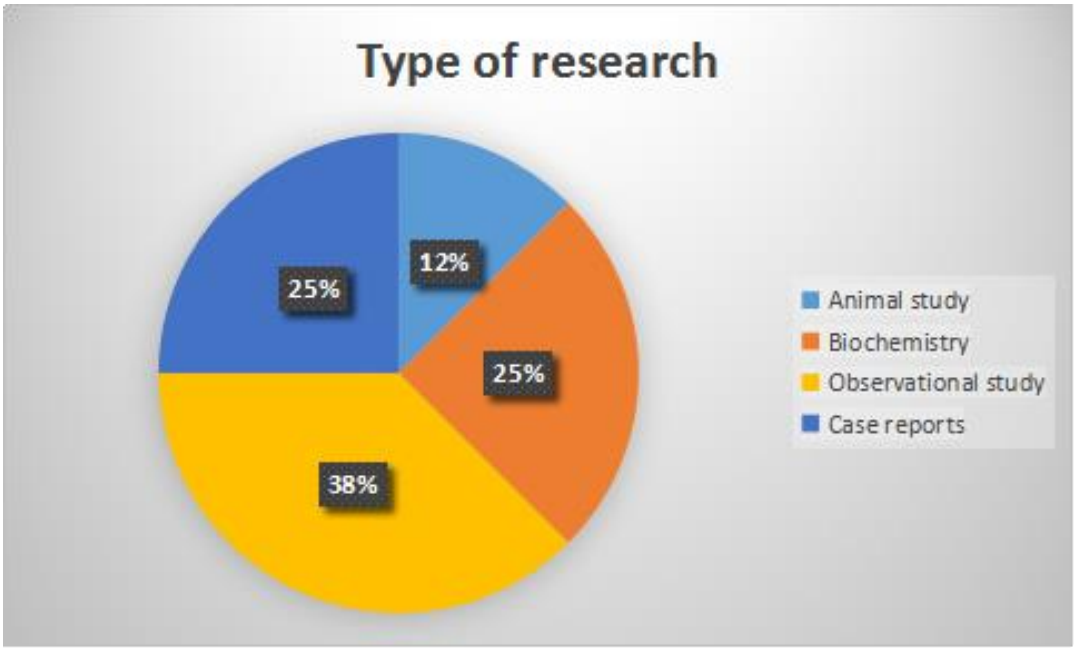

Chart 1. Type of research reviewed. Prepared by authors.

Among presented research, 6 Kampo formulas were investigated, with Yokukansan being researched by 2 independent studies. Table below presents the compounds of all formulas as well as their primary medical indication in TJM.

Table 1. Kampo medicine used in AD research, the compounds and primary medical indication. Prepared by authors.

Name of the Kampo medicine	Compounds of the formula	Primary medical indication
Yokukansan (YKS)	Atractylodes lancea rhizome, Poria sclerotium, Cnidium rhizome, Uncaria thorn, Japanese angelica root, Bupleurum root, Glycyrrhiza	infantile agitation and irritability, also spasms, feverishness, intolerance to heath and cold due to hyperfunction of the liver and loss of appetite

Orengedoku-to	Coptidis Rhizoma, Scutellariae Radix, Phellodendri Cortex, and Gardeniae Fructus	excessive body heat, thirst, nausea, mental confusion
Ninjin'yoeito (NYT)	Ginseng, Japanese angelica root, peony root, rehmannia root, atractylodes rhizome, poria sclerotium, cinnamon bark, astragalus root, Citrus unshiu peel, polygala root, schisandra fruit, and Glycyrrhiza	anorexia, fatigue, cold extremities,night sweats and anaemia
Keishi-ka-ryukotsu-borei-to (KRBT)	cinnamon bark, peony root, jujube fruit, oyster shell, fossilized bone, glycyrrhiza, and ginger rhizome	neurasthenia, impotence and nocturnal enuresis in children
Kamikihi-to (KKT)	Astragali Radix, Bupleuri Radix, Zizyphi Spinosi Semen, Atractylodis Rhizoma, Ginseng Radix, Holen, Longanae Arillus, Polygalae Radix, Gardeniae Fructus, Zizyphi Fructus, Angelicae Radix, Glycyrrhizae Radix, Zingiberis Rhizoma, and Saussureae Radix	insomnia, depression, neurosis and anemia
Chotosan	Uncariae cum Uncis Ramulus, Citri Reticulatae Pericarpium, PinelliaeTuber, Ophiopogonis Radix, Poria, GinsengRadix, Saposhnikoviae Radix, Chrysanthemi Flos, Glycyrrhizae Radix, Zingiberis Rhizoma, Gypsum fibrosum	chronic headaches and hypertension

4. 1. Yokukansan influence on behavioral and psychological symptoms

Yokukansan (YKS) is one of Kampo mixtures primarily used for infantile agitation and irritability, therefore its effectiveness towards reduction of behavioral and psychological symptoms such as aggression, agitation, hallucinations in Alzheimer's disease patients has been investigated. [16] Originally according to Chinese traditional indications, YKS - "medicine suppressing the liver" treated spasms, feverishness, intolerance to heath and cold due to hyperfunction of the liver and loss of appetite. Liver, the organ which stabilizes mental

functions and produces anger if impaired according to TCM principles, has been treated with YKS for over 400 years in Japan for the irritability, aggression and insomnia symptoms. [17]

In the first study from 2010 by Hayashi et al, 26 patients with AD under 85 years, previously receiving regular the treatment of BPSD, with no change in previous dosage regimens of the drugs, received additionally Yokukasan in order to measure improvement in the behavioral and psychological symptoms. The primary outcome measure was evaluated by the changes in Neuropsychiatric Inventory (NPI-Q) total score, secondary outcomes included changes in the NPI-Q subscales, cognitive functions were measures with Mini-Mental State Examination (MMSE), activities of daily living with Disability Assessment of Dementia (DAD). Additionally, burden of caregivers was surveyed with Zarit burden interview and Self-Rating Depression Scale (SDS). Within 4 weeks treatment with YKS, the NPI total score decreased significantly (baseline: 26.8±11.5, after 4 weeks: 17.2±12.9), among NPI subscales the decrease was seen only in hallucinations, anxiety, agitation, abnormal behaviour or irritability aspects. Within MMSE no significant changes were observed (baseline: 11.9±8.6, after 4 weeks: 11.3±8.6), within DAD, the increase of the score was observed (baseline: 29.6±34.0, after 4 weeks: 35.8±36.0). Burden of caregivers did not change significantly, with the main reason for this result - the short duration of the study (4 weeks). Presented research proved the efficacy of YKS, increase of the effect of standard treatment either due to additive/synergistic effect or due to the use of YKS alone, most importantly without elevation of the adverse events of psychotropic drugs. [16]

In next Yokukansan study from 2017 by Furukawa et al., total 145 patients with AD of 22 sites participated in the first randomized double-blind placebo controlled study. Participants groups of 75 (YKS) and 70 (placebo) cases received active YKS (7.5 g/day) and placebo respectively. Within 4 weeks duration the primary outcome was measured with NPI-Q total score, and secondary outcome measurement included 12-week changes in NPI-Q score, changes in NPI-Q subcategories and total score in MMSE. In this study, both 4 week and 12 week NPI-Q scores did not show statistically significant differences between the YKS and placebo groups, also within NPI-Q subcategory scores and MMSE scores, no chages have been noted. Within YKS subgroup of participants with MMSE < 20points received greater decrease of agitation/aggression and hallucination symptoms within NPI-Q subgroups comparing to the placebo group ($P = 0.007$). No adverse events have been noted during the study. [18]

4. 2. Orengedoku-to in strengthening YKS effect

Orengedoku-to, ancient remedy to reduce anger and prevent excessive bleeding in soldiers before the battle, has been known in Chinese medical books from 752 AD. This four herbs formula treated patients of excessive body heat, thirst, nausea, mental confusion. [19] In 2013 study by Okamoto et al. the augmentation of orengedoku-to to YKS and regular psychotic medication was implemented in order to reduce the behavioral and psychological symptoms of AD and other psychiatric disorders. Within three presented cases, one case related to Alzheimer's disease symptoms, with most important the aggressive behaviour. The treatment of aripiprazole had to be withdrawn due to extrapyramidal symptoms such as moderate tremor, mild goitre and steppage gait. As a substitution, YKS has been prescribed, with significant improvement within first 16 weeks. Later the patient became mildly aggressive again which is why orengedoku-to (5 g/day) was added to the current treatment of YKS. The combination showed efficacy equal of aripiprazole without adverse events. In other

two cases, both tardive dyskinesia in course of methamphetamine-induced psychosis and aggressive impulses of intermittent explosive disorder were suppressed, proving the empirical effectiveness of augmentation of orengedoku-to to yokukansan treatment in reducing aggression and impulsivity. [17]

4. 3. Ninjin'yoeito and improvement of cognitive and behavioral functions

Ninjin'yoeito (NYT, Ren-Shen-Yang-Rong-Tang), a multicomponent formula extracted from 12 natural herbs, is a drug approved for treatment of anorexia, fatigue, cold extremities,night sweats and anaemia. It was also proved to be effective in promotion of remyelination as a possible medication strategy in treating demyelinating diseases. In 2016 study by Kudoh et al. its effect on improvement of cognitive and behavioral functions in AD has been evaluated in a two-years trial. 23 patients diagnosed with AD in age between 65-85 years, with MMSE score between 15-23 points and after insufficient response to treatment with donepezil alone were divided into two groups: group with NYT and control group (donepezil only). Within exclusion criteria, treatment with other Kampo medicine or other acetylcholinesterase inhibitor than donepezil, other neurological, psychiatric diseases causing dementia and other serious uncontrolled disease, were considered. The assessment of the improvement was made as a primary outcome with MMSE and Alzheimer's Disease Assessment Scale-cognitive component (ADAS-J cog), for the secondary outcome the behavioral changes were assessed with NPI-Q depression scores. The assessment was performed every 6 months within 2 years trial period. Primary outcome measurement with MMSE showed no differences between two groups, however within the ADAS-J cog the significant improvements in the NYT group has been observed, the median score at baseline was higher than scores at further periods of assessment (baseline–6 months: $P < 0.01$; baseline–12 months: $P < 0.01$; baseline–18 months: $P < 0.01$; baseline–24 months: $P < 0.01$). the NPI-Q depression, delusions and elation scores in secondary outcome measure were noted in the NYT group (delusions: $P < 0.01$; depression: $P < 0.01$; elation: $P < 0.05$). Study proved the effectiveness of joint donepezil and NYT treatment for improvement of cognitive functions and reduction of the depressive, delusional and elation symptoms of AD patients. [20]

4. 4. Use of Keishi-ka-ryukotsu-borei-to (KRBT) for BPSD

Next study from 2013 by Niitsu et al. discussed the use of Keishi-ka-ryukotsu-borei-to (KRBT) in treatment of Alzheimer related BPSD. KRBT, 7 crude drugs formula, is primarily used in treatment of neurasthenia, impotence and nocturnal enuresis in children. The case report of 80 year old male who developed delusions of robbery and cognitive dysfunction, as well as aggressive behaviour. MRI examination proved the diagnosis of AD (moderate enlargement of the cerebral ventricles, sulci as well as atrophy of the left hippocampus and cerebral cortex. The aggressive behaviour and cognitive dysfunctions slightly improved with treatment of donepezil, tiapride and yokukansan within 9 months, however delusions still appeared with additional development of sexual delusions (change of sex). It was decided to change YKS medication with KRBT at 7.5 g per day, which resulted in improvement of BPSD in form of sexual delusions, agitation, insomnia within 4 days after introduction of the regimen, also with improvements in NPI-Q total score (76 before, 35 after the implementation of treatment. Additionally, during KRBT treatment the elevation of FSH (40.0 mIU/mL) and

LH (7.8 mIU/mL) with normal testosterone level (7.1 ng/mL). In order to assess the connection between BPSD and hormone levels, the treatment was interrupted for 2 weeks period. The interruption resulted in increase of the behavioral symptoms, NPI score (from 35 to 64 in the end of 2 weeks), within hormonal level changes, normalized LH level (4.8 mIU/mL), decreased testosterone levels in serum (5.7 ng/mL), and FSH levels (37.4 mIU/mL) remained increased. KRBT treatment was repeated, and after 4 weeks the BPSD decreased again along with the NPI score (64 to 29), however the LH level in serum increased again (8.4 mIU/mL). Presented research proved effectiveness of the KRBT treatment, as well as showed positive correlation with increase of LH level in serum and reduction of sexual delusions. [21]

4. 5. Kamikihi-to (KKT) in treatment of memory impairment and changes in axonal and synaptic degeneration

Kamikihi-to (KKT), approved combination of 14 Kampo herbs, has been used as treatment for insomnia, depression, neurosis and anemia. Some of its components, eg. Ginseng Radix, Astragali Radix were described in research with neurite extension characteristics. [22] In 2011 research by Tohda et al., the influence of KKT on memory impairment in AD mice model has been evaluated. 5XFAD mice models tend to develop visible amyloid deposits within 2 months of age, which is consistent with acceleration of Aβ42 generation. 4-7 months old mice received 200mg/kg p.o. KKT or vehicle solution (physiological saline) for 15 days. Last day of the trial the novel object recognition test has been performed, where the KKT-treated mice showed improvement of object recognition memory, but no differences in locomotion test were found. Within performed immunohistochemistry tests of the brains in later stages of the research, it was found that KKT treatment reduced amount of amyloid plaques in hippocampus and prefrontal cortex, as well as the number of degenerated axons and presynaptic terminals in frontal cortex. The length of axons also increased in KKT group after the progression of the axonal atrophy. Taking all findings into consideration, the memory recovery in AD mice model can be associated with regenerative functions of KKT on axons and synapses of 5XFAD mice. [23]

4. 6. Protection against beta-amyloid toxicity with chotosan components

Chotosan (CTS), another traditional 10 herbs - Kampo prescription used for treatment of chronic headaches and hypertension in China, Japan, and Korea, has been proven to be effective in treatment of AD dementia since 1997 [24] 2016 study by Wei et al. decided to focus on anti-Alzheimer components in CTS. Research used model system of PC12 clonal cell line derived from adrenal gland pheochromocytoma of neuronal characteristics of a rat. Chotosan formula was separated depending on the differences in polarity with a solvent extraction system, later taken under a qualitative analysis with high-performance liquid chromatography with quadrupole time-of-flight mass spectrometry (HPLC-QTOFMS) method. 10 compounds of CTS were evaluated in its neuroprotective effects against Aβ 25-35 induced cytotoxicity (with MTT assay) and inhibition of self-induced Aβ 1-42 aggregation (wht Thioflavin T-binding assay). CTS-E fraction showed protective effects on induced neurotoxicity, especially phenolic acids from Chrysanthemi Flos and flavonoids from Citri Reticulatae Pericarpium. Within particular molecules caffeic acid, chlorogenic acid, 1,5-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid and 4,5-dicaffeoylquinic acid had neuroprotective effects on Aβ25-35-induced neurotoxicity, and phenolic acids, nobiletin and

hesperidin inhibited Aβ1-42 self-induced aggregation. The research proved the effectiveness of CTS-E fraction in protection of PC12 cells from the neurotoxicity induced by beta-amyloid. [25]

4. 7. Anti-Aβ-42 aggregation compounds of Uncaria rhynchophylla

Last research is combining the achievements of traditional medicine in search for molecular targeted therapy treatment options. Senile plaques, causes of dementia in AD are composed mainly from Aβ40 and Aβ42. Aβ42 monomer shows more rapid aggregation as well as neurotoxic potential comparing to Aβ40. The polymerization consists of 2 phases - nucleation and elongation phase, where each nuclei reacts with monomers and enables their polymerization and creation of the fibrils. Uncaria rhynchophylla, the component of Yokukansan was confirmed to reduce the aggregation of Aβ42. In recent study by Yoshioka et al. From 2016, the active anti-aggregative component, uncarinic acid C was identified, along with compound 3 (saponin A from purified Uncaria elliptica) - specific inhibitor of nucleation phase. With these findings, researchers hope for the oligomer-specific inhibitors therapy for AD.

4. CONCLUSIONS

In the rapid increase of aging populations, and consequently - the increase of populations living with dementia and Alzheimer's disease, modern medicine is currently in need of new approaches and all possible therapeutic options available. Kampo medicine, nourished for centuries by Japanese scholars, remains still a mysterious treasure of Japanese civilization, unknown to the Western world and practiced only in Japan, and in some cases, in North America. Presented research shows more natural therapeutic ways of treatment of cognitive and behavioral symptoms of AD, greatly affecting patient's quality of life. Kampo medicines cause very few adverse events and are especially safe for elderly patients, in comparison to psychotic drugs used in Western settings, associated additionally with higher mortality rates, which additionally speaks as a significant advantage and requests further research of Traditional Japanese Medicine in Western settings. Authors hope that with the presented review the knowledge on beneficial aspects of Kampo in Alzheimer's disease, TJM will be further investigated and better understood, which will lead to broadening of the therapeutic specters for AD.

References

[1] Cunningham EL, McGuinness B, Herron B, Passmore AP. Dementia. *Ulster Med J.* (2015) May; 84(2): 79-87.

[2] Ferencz B, Gerritsen L. Genetics and Underlying Pathology of Dementia. *Neuropsychol Rev.* (2015); 25(1): 113–24.

[3] Duyckaerts C, Delatour B, Potier M. Classification and basic pathology of Alzheimer disease. *Acta Neuropathol.* (2009) Jul; 118(1): 5-36.

[4] Wisniewski T, Frangione B Apolipoprotein E: a pathological chaperone protein in patients with cerebral and systemic amyloid. *Neurosci Lett.* (1992) 135 (2): 235–8.

[5] Chouraki V, Seshadri S. Genetics of Alzheimer's Disease. *Adv Genet.* (2014) 87: 245–94.

[6] Reitz C., Brayne C., Mayeux R. Epidemiology of Alzheimer disease. *Nat. Rev. Neurol.* (2011) 7, 137–152.

[7] Goedert M. NEURODEGENERATION. Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein. *Science.* (2015) Aug 7; 349(6248): 1255555.

[8] Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement.* (2016) Apr; 12(4): 459-509.

[9] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Demen.* (2011) 7(3): 263–9

[10] Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* (2005) 353(22): 2335–41.

[11] Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* (2005) 294(15): 1934–43.

[12] Randel S, Soong LL. Traditional Chinese medicine in China. *West J Med.* (1983) Aug; 139(2): 236–238

[13] Latif A. Traditional Chinese medicine. *J Pak Med Assoc.* (1979) Feb;29(2):41-3.

[14] Katayama K, Yoshino T, Munakata K, Yamaguchi R, Imoto S et al. Prescription of Kampo Drugs in the Japanese Health Care Insurance Program. *J Evid Based Complementary Altern Med* (2013): 576973.

[15] *Nikkei Medical*, October 2000 (Supplement) (original in Japanese)

[16] Hayashi Y, Ishida Y, Inoue T, Udagawa M, Takeuchi K et al. Treatment of behavioral and psychological symptoms of Alzheimer-type dementia with Yokukansan in clinical practice. *Prog Neuropsychopharmacol Biol Psychiatry* (2010) 34: 541–545

[17] Okamoto H, Chino A, Hirasaki Y, Ueda K, Iyo M. et al. Orengedoku-to augmentation in cases showing partial response to yokukan-san treatment: a case report and literature review of the evidence for use of these Kampo herbal formulae. *Neuropsychiatr Dis Treat* (2013) :9 151–155

[18] Furukawa K, Tomita N, Uematsu D, Okahara K, Shimada H et al. Randomized double-blind placebo-controlled multicenter trial of Yokukansan for neuropsychiatric symptoms in Alzheimer's disease. *Geriatr Gerontol Int.* (2017) Feb; 17(2): 211-218.

[19] Okamoto H. Reconsideration of Japanese traditional herbal medicine: new field of research and clinical medicine. *Mini Rev Med Chem.* (2006) 6(5): 543–547.

[20] Kudoh C, Arita R, Honda M, Kishi T, Komatsu Y et al. Effect of ninjin'yoeito, a Kampo (traditional Japanese) medicine, on cognitive impairment and depression in patients with Alzheimer's disease: 2 years of observation. *Psychogeriatrics.* (2016) 16: 85–92

[21] Niitsu T, Okamoto H, Iyo M. Behavioural and psychological symptoms of dementia in an Alzheimer's disease case successfully treated with natural medicine: association with gonadotropins. *Psychogeriatrics.* (2013) 13: 124–127

[22] Tohda, C., Naito, R., and Joyashiki, E. Kihi-to, a herbal traditional medicine, improves Abeta(25–35)- induced memory impairment and losses of neurites and synapses. *BMC Complement. Altern. Med.* (2008). 8, 49. doi: 10.1186/1472-6882-8-49.

[23] Tohda C, Nakada R, Urano T, Okonogi A, Kuboyama T. Kamikihi-to (KKT) Rescues Axonal and Synaptic Degeneration Associated with Memory Impairment in a Mouse Model of Alzheimer's Disease, 5XFAD. *Int J Neurosci* (2011) 121: 641–648

[24] Terasawa K, Shimada Y, Kita T, Yamamoto T, Tosa H. Choto-san in the treatment of vascular dementia: a double-blindplacebo-controlled study. *Phytomedicine* (1997) 4: 15–22.

[25] Wei M,, Chen L, Liu J, Zhao J, Liu W. et al. Protective effects of a Chotosan Fraction and its active components on beta-amyloid-induced neurotoxicity. *Neurosci Lett* (2016) 617: 143–149

[26] Yoshioka T, Murakami K, Ido K, Hanaki M, Yamaguchi K. et al. Semisynthesis and Structure−Activity Studies of Uncarinic Acid C Isolated from Uncaria rhynchophylla as a Specific Inhibitor of the Nucleation Phase in Amyloid β42. *Aggregation J. Nat. Prod.* (2016) 79: 2521−2529