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THE DYNAMIC NATURE OF ALZHEIMER'S DISEASE AND A STRATEGIC TREATMENT PLAN BASED ON TRADITIONAL CHINESE MEDICINE (TCM)

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ABSTRACT

Current treatment of Alzheimer's disease with acetylcholinesterase inhibitors or NMDA receptor antagonists is unsatisfactory. The reason for this may lie in the changing nature of the disease, which has received little attention. This paper examines scientific studies of the disease from a yin-yang perspective, and presents an entirely new mechanism in which the disease changes from a "hot" or "yin-deficient" state to a "cold" or "yang-deficient" state, or vice versa. Therefore, treatment of the disease needs to be adjusted accordingly. Furthermore, this paper identifies a drug lead based on the "hot" and "cold" properties of some well-known memory-enhancing herbs.

KEYWORDS

Alzheimer's disease; Yin-deficient; Yang-deficient; Medical mechanism; Treatment; Memory-enhancing herbs; Traditional Chinese medicine

ACRONYM

HDL	High-density lipoprotein
LDL	Low-density lipoprotein
NMDA	N-methyl-D-aspartate
TCM	Traditional Chinese medicine
TSH	Thyroid stimulating hormone

AUTHOR'S INTRODUCTION

Nai-Yi Wang is a Ph.D. organic chemist with a 40-year career in teaching and research at universities and in the pharmaceutical industry. He holds more than 20 patents in synthetic organic chemistry, natural product synthesis, and biotechnologies. His research has focused on cardiovascular drugs discovery, anticancer compounds syntheses, and the development of immunoassays. As an organic chemist specializing in natural products synthesis, Wang has accomplished the first total synthesis of compactin (an analog of the Merck cholesterol-lowering drug Zocor). He is also an expert in the chemistry of Traditional Chinese Medicine.

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1. INTRODUCTION

Despite tremendous efforts, the treatment of Alzheimer's disease, characterized by the extracellular formation of beta amyloid plaques and/or the appearance of tangled tau proteins in brain cells, remains ineffective.

It is unclear what causes Alzheimer's disease, but researchers have linked the disease to a deficiency of brain acetylcholine, which has led to the development of many acetylcholinesterase inhibitors. However, for the less than 50% of patients who respond to the treatment during the early stages of the disease, these drugs not only lose effectiveness as the disease progresses, but also have serious side effects.

NMDA (N-methyl-D-aspartate) receptor antagonists are another type of drug approved by the U.S. Food & Drug Administration. But they can only alleviate symptoms, not reverse or halt the progression of the disease. In addition, in past studies, the participants' gender, their age, and/or the stage of the disease were not well defined. Consequently, the results were often inconsistent.

An alternative approach to the treatment of Alzheimer's disease is desperately needed. I propose a new treatment approach based on the yin-yang theory. Yin and yang are relative terms and

occur in pairs (e.g. night and day, small and large, cold and hot, etc.). They antagonize each other, but under specific conditions, they are interchangeable (reminiscent of the interconversion of kinetic and potential energies). The theory is universally true. In a healthy individual, yin and yang are in harmony, but the balance is shifted when a person becomes ill. The sum of the two forces constitutes the vital energy (Qi) of the individual. Determination of yin or yang deficiency has traditionally been accomplished by non-scientific methods, but these methods lack accuracy. Modern analytical techniques, such as the measurement of thyroid stimulating hormone (TSH) levels or other substances (e.g. cytokines) in the blood, can be a more accurate predictor of yin and yang deficiency.

It is well known that most diseases have yin- and/or yang-deficient states. In the case of Alzheimer's disease, at the onset, a person may be in either a yin- or yang-deficient state, depending on his/her age or other pathological conditions. If left untreated, or treated incorrectly (as the current practice does), both yin and yang may become deficient, and the vital energy controlled by the kidney begins to dwindle (i.e. Qi deficiency). At the final stage of the disease, the vital energy is further depleted until the end of life.

2. SCIENTIFIC STUDIES

The following scientific studies support my proposal:

- Butterfield and Pocernich mentioned in their 2003 review [1a] that, in contrast with theories describing the pathogenesis of early-stage Alzheimer's disease, late-stage pathogenesis is thought to be attributed to the loss of NMDA receptors culminating in hypofunction. In addition, the activities of NMDA receptors are bi-directional and age-related [1b]. Hence, it appears that two opposing mechanisms (yin-deficiency and yang-deficiency) interact throughout the development of the disease.

- In a study of middle-aged people conducted at the University of Pittsburgh [2], those with Type 1 diabetes had significantly more brain lesions and slower cognitive function than people without the disease. Because Type 1 diabetes is a yin-deficient disease, it is conceivable that Alzheimer's disease is also a yin-deficient disease among younger people.

- Another study led by Bruce Reed, professor of neurology at the University of California, Davis [3], showed that, for people over the age of 70, both higher levels of high-density lipoprotein (HDL) and lower levels of low-density lipoprotein (LDL) in the bloodstream were associated with lower levels of amyloid plaques in the brain. Put differently, at this age, the disease is most likely in a yang-deficient or yin and yang both deficient state, which is consistent with the manifestation of lower HDL levels or higher LDL levels, a consequence of yang-deficiency.

- It was discovered that very few people with rheumatoid arthritis developed Alzheimer's disease. In an effort to unlock the mystery, Huntington Potter and coworkers [4] found that injection of a protein (GM-CSF), upregulated in rheumatoid arthritis, into aged Alzheimer's disease mice significantly reduced brain amyloidosis and completely reversed cognitive impairment. But a more recent study [5] claimed that rheumatoid arthritis increased the risk of

developing Alzheimer's disease. The seemingly contradictory results can be easily reconciled with the aid of Traditional Chinese Medicine (TCM), because the predominance of yin-deficiency or yang-deficiency is, among other things, age dependent.

- Vitamin D deficiency increases the risk of Alzheimer's disease [6]. The study was done on 1,658 men and women with an average age of 73. The link between vitamin D and Alzheimer's disease among the elderly is expected, because a lack of the former (a "hot" substance) allows the latter (a yang-deficient or "cold" disease) to more easily occur [7].

3. CONCLUSIONS

Since acetylcholinesterase inhibitors and NMDA receptor antagonists are “cold” drugs, they are only effective for Alzheimer’s disease of the yin-deficient type. When the disease progresses to the advanced stage where yin and yang are both deficient, the drugs are no longer effective and may even be harmful. However, prescription drugs for the yang-deficient type of Alzheimer’s disease are lacking. A few herbal formulas used for enhancing memory are available. The general guideline in using herbal medicine is that for yin-deficient (“hot”) disease, a yin-nourishing (“cold”) remedy must be used, and for yang-deficient (“cold”) disease, a yang-fortifying (“hot”) remedy is required. But currently, the TCM classification of the types of Alzheimer’s disease is non-systematic and does not take into account the age of the patients or the stage of the disease.

Nevertheless, once the correct diagnosis is made in the context of the new proposal, the following protocol may be used: For yin-deficient Alzheimer’s disease, “Zhi bai rehmannia capsule” (it is interesting that the active compounds isolated from the ingredients of the formula—such as catalpol, mangiferin, berberine, paeoniflorin, and loganin, are known acetylcholinesterase inhibitors), or its equivalent may be employed initially. The formula must be “warmed up” (replacing the cold ingredients with warmer substances) gradually to prevent the body from becoming too “chilly.” For yang-deficient Alzheimer’s disease, on the other hand, the hot formula, such as “Yang xin tang” or “Gui pi tang,” or both (the active compounds in the formula, e.g. tenuifolin, cinnamaldehyde, epicatchin(ox), jujuboside A, ginsenoside Rg1, etc., either prevent the formation of beta amyloid plaques or keep the tau proteins from aggregation), may be prescribed, but adequate cooling (by adjusting the ingredients in the formula) must be

applied to avoid “over-heating.” Finally, for patients at the yin and yang both deficient stages, “Dihuang yin zi” (a blend of yin-deficient and yang-deficient herbs), plus or minus, coupled with Qi enhancement, may serve as the last resort.

After detailed examination of the constituents of a large number of memory-enhancing herbs. I noticed that a common structural feature (3-phenyl-2- propenoic acid or analogs) is present in most of the molecules. For example, ferulic acid (in danggui and chuanxiong), tenuifolin (in tianma), cinnamaldehyde (in rougui), curcumin (in jianghuang), rosmarinic acid (in rosemary and jingjie), acteoside (in roucongong), safranal (in honghua), caffeic acid and chlorogenic acid (the last two compounds are found in coffee) are all derived from 3-phenyl-2-propenoic acid or aryl alpha, beta- unsaturated carbonyl compounds. Scientific studies showed that these molecules are indeed capable of improving memory. One of the plausible mechanisms is the protection of the Tau or beta-amyloid proteins from misfolding by a reversible Michael addition reaction, which prevents the formation of aggregates or insoluble plaques [8]. Most surprisingly, the herbs which contain these active components are generally considered as “hot” substances in TCM. This discovery may help design new types of drugs for the treatment of Alzheimer’s disease.

4. RECOMMENDATIONS

For a thorough review of the concept of “hot” and “cold“ substances and diseases in TCM, please read the author's book [7]. For a specific example, please read the scientific publication of George et al. [8].

5. SPECIAL NOTE

This paper is for research purposes only. Readers should consult a qualified herbal medical doctor for any therapeutic questions.

6. GLOSSARY

Acetylcholinesterase inhibitors:

Substances that inhibit the activity of acetylcholinesterase, resulting in increased availability of acetylcholine.

Cold herbs:

Herbs that possess anti-inflammatory, vasoconstriction, diuretic, activities, etc. Rehmannia root is a typical example.

Hot herbs:

Herbs that display pro-inflammatory, vasodilation, anti-allergic effects, etc. Cinnamon is a typical example.

Memory-enhancing formulas:

Herbal formulas that enhance memory.

Memory-enhancing herbs:

Herbs that enhance memory.

NMDA receptor antagonists:

Drugs that block the biological response of NMDA when binding to the latter's receptor.

3-Phenyl-2-propenoic acid derivatives: Compounds derived from 3-Phenyl-2-propenoic acid.

Tau or beta-amyloid proteins:

Neural proteins in the brain. Aggregation (denaturation) of these proteins is associated with the etiology of Alzheimer's disease.

Traditional Chinese medicine:

A theory-guided medical practice composed of a set of diagnostic methods and the systematic use of herbal materials as the major tool of treatment.

Yang-deficiency:

Pale face, cold extremities and fatigue due to insufficient supply of energy.

Yin-deficiency:

Producing excessive internal heat characterized by evening fever, night-sweats or weight loss as a result of insufficient cooling

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Editors of
"EVOLUTIONARY PROGRESS IN SCIENCE, TECHNOLOGY, ENGINEERING,
ARTS AND MATHEMATICS (STEAM)"

1. Dr. Lawrence K. Wang (王抗曝)

Editor Lawrence K. Wang has served the society as a professor, inventor, chief engineer, chief editor and public servant (UN, USEPA, NY, Albany) for 30+ years, with experience in entire field of environmental science, technology, engineering, arts and mathematics (STEAM). He is a licensed NY-MA-NJ-PA-OH Professional Engineer, a certified NY-MA-RI Laboratory Director, a MA-NY Water Operator, and an OSHA Train-the-Trainer Instructor.

He has special passion, and expertise in developing various innovative technologies, educational programs, licensing courses, international projects, academic publications, and humanitarian organizations, all for his dream goal of promoting world peace. He is a retired Acting President/Professor of the Lenox Institute of Water Technology (LIWT), USA, a United Nations Industrial and Development Organization (UNIDO) Senior Advisor in Vienna, Austria, and a former professor/visiting professor of Rensselaer Polytechnic Institute, Stevens Institute of Technology, University of Illinois, National Cheng Kung University, Zhejiang University, and Tongji University.

Dr. Wang is the author of 750+ papers and 50+ books, and is credited with 29 invention patents. He holds a BSCE degree from National Cheng Kung University, a MSCE degree from the University of Missouri, a MS degree from the University of Rhode Island and a PhD degree from Rutgers University, USA. Currently he is the book series editor of CRC Press, Springer Nature Switzerland, Lenox Institute Press, World Scientific Singapore, and John Wiley.

Dr. Wang has been a Delegate of the People to People International Foundation, an American Academy of Environmental Engineers (AAEE) Diplomate, a member of WEF, AWWA, ASCE, AIChE, ASPE, CIE and OCEESA, and a recipient of WEF Kenneth Research Award (NY), Five-Star Innovative Engineering Award, and Korean Pollution Control Association Award (for developing flotation technology in South Korea).

2. Dr. Hung-ping Tsao (曹恆平)

Editor Hung-ping Tsao has been a mathematician, a university professor, and an assistant actuary, serving private firms and universities in the United States and Taiwan for 30+ years. Dr. Tsao has been an Associate Member of the Society of Actuaries and a Member of the American Mathematical Society.

His research have been in the areas of college mathematics, actuarial mathematics, management mathematics, classic number theory and Sudoku puzzle solving. In particular, bikini and open top problems are presented to share some intuitive insights and some type of optimization problems can be solved more efficiently and categorically by using the idea of the boundary being the marginal change of a well-rounded region with respect to its inradius; theory of interest, life contingency functions and pension funding are presented in more simplified and generalized fashions; the new way of the simplex method using cross-multiplication substantially simplified the process of finding the solutions of optimization problems; the generalization of triangular arrays of numbers from the natural sequence based to arithmetically progressive sequences based opens up the dimension of explorations; the introduction of an innovative way to solve Sudoku puzzles makes everybody's life so much easier and other STEAM project development.

Dr. Tsao is the author of 10+ books and over 40 academic publications. Among all of the above accomplishments, he is most proud of solving manually in the total of ten hours the hardest Sudoku posted online by Arto Inkala in early July of 2012 and introducing an easy way to play Sudoku in 2019.

He earned his high school diploma from the High School of National Taiwan Normal University, his BS and MS degrees from National Taiwan Normal University, Taipei, Taiwan, his second MS degree from the UWM in USA, and a PhD degree from the University of Illinois, USA.



Editors of the eBook Series of the *"EVOLUTIONARY PROGRESS IN SCIENCE, TECHNOLOGY, ENGINEERING, ARTS AND MATHEMATICS (STEAM)"*

Dr. Lawrence K. Wang (王抗曝) -- left

Dr. Hung-ping Tsao (曹恆平) -- right

INTRODUCTON TO THE E-BOOK SERIES OF

"EVOLUTIONARY PROGRESS IN SCIENCE, TECHNOLOGY, ENGINEERING, ARTS AND MATHEMATICS (STEAM)"

The acronym STEM stands for “science, technology, engineering and mathematics”. In accordance with the National Science Teachers Association (NSTA), “A common definition of STEM education is an interdisciplinary approach to learning where rigorous academic concepts are coupled with real-world lessons as students apply science, technology, engineering, and mathematics in contexts that make connections between school, community, work, and the global enterprise enabling the development of STEM literacy and with it the ability to compete in the new economy”.

The problem of this country has been pointed out by the US Department of Education that “All young people should be prepared to think deeply and to think well so that they have the chance to become the innovators, educators, researchers, and leaders who can solve the most pressing challenges facing our nation and our world, both today and tomorrow. But, right now, not enough of our youth have access to quality STEM learning opportunities and too few students see these disciplines as springboards for their careers.” STEM learning and applications are very popular topics at present, and STEM related careers are in great demand.

According to the US Department of Education reports that the number of STEM jobs in the United States will grow by 14% from 2010 to 2020, which is much faster than the national average of 5-8 % across all job sectors. Computer programming and IT jobs top the list of the hardest to fill jobs.

Despite this, the most popular college majors are business, law, etc., not STEM related. For this reason, the US government has just extended a provision allowing foreign students that are earning degrees in STEM fields a seven month visa extension, now allowing them to stay for up to three years of “on the job training”. So, at present STEM is a legal term.

The acronym STEAM stands for “science, technology, engineering, arts and mathematics”. As one can see, STEAM (adds “arts”) is simply a variation of STEM. The word of “arts” means application, creation, ingenuity, and integration, for enhancing STEM inside, or exploring of STEM outside.

It may also mean that the word of “arts” connects all of the humanities through an idea that a person is looking for a solution to a very specific problem which comes out of the original inquiry process. STEAM is an academic term in the field of education. The University of San Diego and Concordia University offer a college degree with a STEAM focus.

Basically STEAM is a framework for teaching or R&D, which is customizable and functional, thence the “fun” in functional. As a typical example, if STEM represents a normal cell phone communication tower looking like a steel truss or concrete column, STEAM will be an artificial green tree with all devices hided, but still with all cell phone communication functions. This e-book series presents the recent evolutionary progress in STEAM with many innovative chapters contributed by academic and professional experts.