

Commentary

Herbal Medicine Research in Taiwan*

Krishna Kaphle¹, Leang-Shin Wu¹, Nai-Yen Jack Yang² and Jen-Hsou Lin¹

¹Physiology Lab, Department of Animal Science and Technology, National Taiwan University, Taipei and

²China Institute of Technology, Nankang, Taipei, Taiwan

Of all the countries in the world, why did you choose Taiwan to pursue your study? It is a question that I (comments of the first author) have answered a thousand times. My first visit to a laboratory at National Taiwan University opened my eyes to the possibilities of herbal medicine research, especially in the area of veterinary medicine. It became my ambition to link the knowledge of Traditional Chinese Medicine (TCM) and Ayurveda from the Indian subcontinent and their integration with other systems of medicine, including Western medicine (WM), to achieve the concept of Sustainable Medicine, firstly for animals and then for humans. The Ministry of Economic Affairs (MOEA) has implemented a technology development program to quickly establish the key technologies, and this is a moment of opportunity for Taiwan's traditional herbal medicine industry to upgrade and transform itself. This paper, initially intended to be a student's narration, has evolved into a multi-author treatise on the present state and likely future scenario of herbal medicine research in Taiwan.

Keywords: herbal medicine – research – Taiwan

Introduction

The global trend of reliance on complementary and alternative medicine (CAM) is reviving, thanks to evolving human intelligence. Of course, the engine behind this initiative is the need of a better and sustainable future (1,2). Providing evidence has been the responsibility of thousands of researchers, while disseminating the information (the hardest task) has been shouldered by *eCAM* and other journals. Students are being drawn to the fantastic unexplored world of diversity in our surroundings, including medicine and the art of self-healing. The student gives a different dimensional view of reality that is often overlooked or bypassed. An increasing number of such reports in journals (3) and web pages demonstrate that this view is gradually receiving recognition. In our report, we

present the situation in Taiwan from the mixed impression of a foreign student's almost half a decade stay and the lifetime experience of local experts.

Historical Background

The history and development of traditional Chinese medicine (TCM) in Taiwan have been expounded earlier by many writers; the most recent by Prof Chen and his group is very informative (4). The beautiful island 'Ilha Formosa', as the Portuguese mariners named it sailing to Japan from Macao, is what we know today as Taiwan. It was during the end of the Ming dynasty that large-scale migration from mainland China took place. They brought with them the ancient art and knowledge of TCM with over 2000 years of history. Aiding that effort was the rich flora and fauna of Taiwan, and the local knowledge of the aboriginal people. Initially researched from a cultural and anthropological aspect, TCM, and more precisely Chinese Herbal Medicine (CHM), has now topped the list as a first priority in the blueprint for the development of biotechnology in Taiwan. Socioeconomic progress, since the early time of mainland migration from the end of Ming dynasty to

*Appropriate person among the authors to be in contact for any further information on the status of CHM research in Taiwan and for opportunities to study and conduct research in the field of TCM in Taiwan.

For reprints and all correspondence: Krishna Kaphle, National Taiwan University, Department of Animal Science and Technology, Taipei, Taiwan; Tel: +886-2-2363-0231 # 3103; Fax: +886-2-2733-7095. E-mail: krishnakaphle@hotmail.com

the early Chin dynasty, has helped CHM develop deep roots in Taiwanese culture, now demonstrated by how closely TCM has been incorporated into the daily lives of Taiwanese.

Traditional Chinese Medicine in Taiwan: A Long Transition

The influx of mainly Han people from mainland China in 1664, led by the Ming loyalist Cheng Ch'eng-kung (Zheng Chenggong, known in the West as Koxinga), is said to be the beginning of Chinese influence in Taiwan, though significant migration to Taiwan from the Chinese mainland began as early as AD 500. Taiwan's aboriginal people, who originated in Austronesia and southern China, have lived in Taiwan for 12 000 to 15 000 years (<http://www.historyofnations.net/asia/taiwan.html>). CHM and its conventional trading system came along with the culture of central China. Slowly integrating the local and indigenous knowledge of the island, in these past 400 years TCM has gradually established strong roots in Taiwanese society. The torch of the TCM profession is its conventional form of trading that has been passing on from master to pupil and from generation to generation in a closed commerce group. The traditional HoLo (Fukien) way of life, and its He Ro traditional medicine culture, with special social status relegated to TCM physicians, is considered one reason for the vigorous development of HM industry in Taiwan (5).

Migration and Japanese Colonial Rule

Further migration from Fujian and Guangdong provinces in China to Taiwan during the 18th and 19th centuries supplanted aborigines as the dominant population group. It was during those harsh times when difficult journeys made people seek medicine at whatever price, boosting the trade in HM. During 50 years (1895–1945) of Japanese colonial rule, the 'Japanization' of the island included compulsory Japanese education and the forced adoption of Japanese names by residents of Taiwan. One notable influence was the patronage of Western Medicine (WM), which had by then already been introduced into Taiwan by Christian missionaries. It was continued by the Nationalist Chinese (KMT) administration on Taiwan, which came into power in 1945, after World War II. During the 1950s, the KMT authorities implemented a far-reaching and highly successful land reform program on Taiwan, which resulted in overall development. The encouragement of economic reforms generated many entrepreneurs who went on to become Taiwan's first industrial capitalists. Together with refugee businesspersons from the mainland, they managed Taiwan's transition from an agricultural to a commercial and industrial economy. This transition also benefited the rise of HM industry from the status of mortar and pestle to mechanized and automatic units. Depleted by colonial suppression, a shortage of traditional medical practitioners led the government to regularize the licensing system by evaluation. Though criticized by various medical professionals for

the lack of strict educational requirements, by 2001 this system had rolled out 18 229 candidates who successfully passed the 'Qualification Examinations', and out of them 3047 passed the 'Special Examinations' for practicing TCM in Taiwan (6).

The Transition of Informal Practice into Formal Education

Cheng in his recent work (6) nicely narrates the transition of informal practices to formal education leading to the degree of Doctor of Chinese Medicine (DCM) in the late 1960s (1966). The course duration was 7 years (8 years since 1996) and the candidates had to study both WM and TCM. The program is facing some controversies in licensing and a strong lobbying and anti-lobbying tussle is going on between the practitioners of WM and CM. Finally, the government ruled that the 'Qualification Examinations for Taking the Examination of the DCM' is to be cancelled in 2008 and the 'Chinese Medicine Special Examinations' in 2011 (6).

Mainstream health workers are also encouraged to have liberal views toward TCM (7). This is in view of the growing ageing population of Taiwan above 65 years, which now hovers ~10% of the total population, and is estimated to reach 20% by 2031, outnumbering the young population (8). The policy-makers are also concerned by survey findings that most patients (85.39%) who use CM prescriptions were over 40 years of age (9). There is also a widening gap between social status and health problems in the elderly population (10), rising premiums for state health care and its unequal distribution. Hence, from a student's viewpoint, the transition of HM in particular and TCM in general in Taiwan seems to be fueled by dual intentions. Firstly, to cash in on the competitive edge for economic benefits, and secondly to preserve the cultural heritage aimed at managing a growing aging population.

Governmental Initiatives

Global trends toward the use of TCM have also had an impact on the young generation of Taiwanese, who have accepted the strong yet safe healing power of TCM. Today's CHM holds the cumulative wisdom of the Chinese people over several thousands of years. Close documentation of the long clinical history has given big drug companies an opportunity to exploit the benefits of both WM and CM. The field of herbal medicine is also widely considered one of the brightest areas of Taiwan's emerging biotech industry and the development of traditional CHM is recognized as one of the niche markets for Taiwan. To this end, a '5-year Plan for the Industrial Technology Development of CHM' was approved by the Executive Yuan in 2000 and carried out in January 2001. To integrate the efforts of the various organizations deemed responsible for the development of HM (used synonymously for CHM in this article) industry, the Program Office of HM was established in 2002. It has taken up the responsibility of

coordinating the efforts of governmental research agencies in modernizing the HM industry in Taiwan. The modernization attempt began in the mid-1980s when Taiwan, one of the tiger economies of Asia, pumped in resources to shift from 'can do' to 'shall do' research initiatives (11).

The value of the local herbal medicine market has been estimated at approximately NT\$15–25 billion. Pharmaceutical application shares 20% of that amount, with the rest of the market taken up by food supplements. In 2001, imported herbal raw materials amounted to NT\$1.8 billion, >80% of which is imported from Mainland China. This raised the local production value of Chinese medicine to NT\$4.2 billion. The import market of herbal medicine for that period was valued at NT\$10 million and the export market at NT\$ 130 million, while the domestic demand reached NT\$ 4.08 billion (this information was obtained from the report prepared by the Netherlands Trade and Investment Office in Taipei at <http://www.ntio.org.tw/trade/Biotechnology.htm>).

A Huge Commercial Potential has Gained the Attention of Pharmaceutical Companies

The growing popularity of traditional remedies and its huge commercial potential has gained the attention of the pharmaceutical industry. The global herbal medicine market, estimated at roughly over US\$23 billion in 2002, is slated to grow >13% annually. It is further projected that the value of the global herbal medicine market will break through the US\$40 billion mark by 2006, an opportunity Taiwan-based companies are eager to cash in on. The government supports this trend by boosting strategic plans and their execution, pledging new investment of NT\$3.5 billion toward the industry over the next 5 years.

Government's Role and Support

With promotional plans and government funding for a biotechnology industry, development of scientific herbal medicine topped the priority list. Though it will be unfair and inaccurate to say it that way, prominent steps of integrating the then emerging field of biotechnology to CM research began in the middle of the last decade. The beginning of the new millennium saw concrete steps. In 2000 the Ministry of Economic Affairs (MOEA) was assigned the responsibility to integrate all related governmental organizations to develop HM. Billions of NT dollars in funds were set aside for the task of achieving the goal of scientific development of HM and related technology products.

A major boost to the HM industry came with the establishment of the program office of HM in 2002, and a shot in the arm was achieved with HM being integrated in the National Science and Technology Program for Biotechnology and Pharmaceuticals [information used from Ref. (12)]. The program office of herbal medicine was set up with the task of coordinating the work of various governmental research agencies

and publicize their works with an aim to internationalize Taiwan's herbal medicine industry. The government is currently pursuing the promotion of international cooperation. It is offering incentives and opportunities to foreign companies to encourage them to set up research centers in Taiwan or seek collaborations with local companies. The transfer of technology is also on the agenda to assist the international standard of herbal products production and achieve sellable technology. An information service system has been launched to streamline up-to-date information on current progress in the field globally, and government policies and guidelines are in place for those who will benefit in the herbal medicine industry. The domestic herbal industry and related technology development encourage fair competition and alliances among local industries in research and development.

The Herbal Medicine Industry in Taiwan is Basking in its Competitive Edge

The herbal medicine industry in Taiwan is basking in the competitive edge that is built on cultural, social, economical, geopolitical and technological advantages, to name a few. With thousands of years of accumulated knowledge and experience in herbal medicine, there is a will to preserve it at any cost, although in early communist China it was discouraged (13). A 5 year plan to modernize the existing HM industry in Taiwan is pursued seriously by consigning three major players to jointly develop key platform technologies and create a congenial atmosphere. The three institutes chosen for the task are the Biomedical Engineering Center (BMEC) of ITRI, Development Center for Biotechnology (DCB) and Pharmaceutical Industries Technology Development Center (PITDC). The research focuses on diseases such as hepatitis, asthma, immune modulation and stomach ulcers (14). With the 5 year national master plan complete, the outcome of the integration and its achievements are now under analysis.

R&D, Clinical Trials and Quality Products

Policy- and decision-makers involved in TCM research in Taiwan are aware of the claim that CAM trials are non-equivalent or inferior to those of conventional medicine. Now, with charges of foul play in clinical studies and publications, conventional medicine has its own concerns (15). CAM can be subjected to excellent trials, though certain problems with funding (16) and practicality of conducting trials, as with conventional medicine, need to be addressed (17). The challenges in developing excellent new drugs from Chinese Materia Medica (CMM) in the post-genomic era (18) will not be easy to overcome.

Leading the Asian countries in revealing a new face of TCM (19), Taiwan has Asia's highest concentration of clinical trial centers capable of handling clinical trials of the best standards. The Center for Drug Evaluation (CDE) and the Department of Health Committee on Chinese Medicine and Pharmacy

(CCMP) have developed and now supervise clinical trials at the nine specialized herbal medicine clinical trial centers throughout the island (12). CCMP has established TCM clinical centers in 10 excellent teaching hospitals, with necessary network configuration and standard operation procedures. In addition, encouraging private sector involvement, the committee has received 14 pharmaceutical companies' IND/NDA applications to conduct clinical trials, and after thorough review by the committee six companies were reportedly given a green light (20). The current state of imported new drugs (IND) and new drug application (NDA) in Taiwan has been made swifter, with the review time shortened from 9.9 months (IND) and 2.9 months (NDA) in 1997 to 4.2 and 1.2 months, respectively, in 2001 (21).

Good Clinical Practice and Good Manufacturing Practice Implementation

The Taiwanese government is investing NT\$200 million each year for a period of 5 years to establish a general clinical research center (GCRC) in Taiwan. Good clinical practice (GCP) compliance has been a mandatory step in IND/NDA clinical trials since its implementation in 1997. Strong coordination of related agencies is emphasized in an attempt to globalize efficient, safe and quality HM products and securing Taiwan's position as a strong hub of R&D in the world. To ensure adequate drug safety standards and to help local pharmaceutical companies meet international standards, the Department of Health (DOH) announced that it would enforce the new Good Manufacturing Practice (GMP) regulations on all domestic pharmaceutical companies engaging in the manufacturing of herbal medicine, starting from 1 March 2005. This effort is intended to stop industry-damaging practices such as the selling of spurious Chinese medicinal ingredients, adulteration of herbal medicine with Western pharmaceuticals, the selling of herbal medicine on the streets and the broadcast of commercials containing unsubstantiated claims about a particular herbal product. There are currently 73 Chinese pharmaceutical companies in Taiwan that already implement GMP. The remaining 95 traditional pharmaceutical companies were expected to join the crowd and start implementing GMP from 1 March 2005. After the GMP implementation for both WM and CM 25 years ago, this new GMP implementation project for pharmaceutical companies manufacturing Chinese medicine marks another milestone for the island's medical industry (22). To make available the best quality raw materials for the herbal medicine industry, the government in Taiwan plans to establish a quality assessment center for CM entering Taiwan from China.

Integration of Ancient Tradition with Modern Technology

Taiwan as a whole presents a museum view of this fine blend of ancient culture and modern technology, and any alert eyes

can see it in every part of day-to-day activities including health (23). Experts of TCM belief that while developing CMM as modern medicine it should not be forgotten that the use of CMM is always governed by the conformation dictated by TCM diagnosis and principles. They are firm in their belief and capable of influencing policy-makers in HM industry of Taiwan that blending modern scientific technology to the ancient tradition is the way out for CMM based new medicines. This is bound to help efficiently design, generate, and validate in the mainstream pharmaceutical market of the 21st century (24). Drug discovery and development in this age of rapid strides in the field of genomic and proteomic technologies have benefited from the high throughput screening. Taiwan, with its top IT technology development, is making the best use of every possible integration opportunity. They intend to remain a step ahead to create opportunity, including application of bioinformatics data mining to ancient and rare TCM books. With a government supported gene therapy program project initiated in 1994 (25), genetic diseases and ethnicity based drug development from HM is definitely under consideration. Tissue (26), cDNA (27) and protein array for evaluation of herbs is already an old story here. The integration spreads beyond the field of clinical trial and areas of analysis, benefiting preparation and administration. Integration for human health care (28) even in animals (2) to attain the concept of sustainable medicine based on the utilization of the best of all forms of medication is an emerging school of thought in Taiwan.

Pattern of CHM Utilization in Taiwan

A utilization pattern for herbal medicine is just emerging in Taiwan. Uninformed patients, unscrupulous traders, adulterated preparations, unlicensed practitioners, and illegal sources for herbal medicines have been blamed for creating a bad image of HM use in Taiwan (29,30). A survey by Chen's group (10) reported that males (59.36%) were more likely to use CHM than females (40.64%). The common primary ailments for seeking CHM treatment were insomnia (15.58%), menopause (5.22%), constipation, functional disorders of the stomach and allergic rhinitis in the range of ~5%. Successful treatment by CHM has been reported in pediatric oncology (31), topical medications (32), childhood bronchial asthma (33) and a range of other ailments. Mostly herbal formulas are prescribed (66.09%), with the average number of drugs per CM prescription being 4.87 (10). The decision to cover CHM treatment under National Health Insurance (NHI) in 1992 had a big impact on the pattern of CHM utilization in Taiwan.

Taiwan has an excellent national health care system at a cheaper rate than other industrialized countries, with each individual paying an average of ~\$20 per month for full health care coverage. That \$20 a month includes maternity, dental, vision and all medical visits. It even helps cover prescription drug costs, which are dramatically lower in Taiwan than they are in the United States. Taiwanese citizens receive care that is nearly as good as the care received in the United States,

and yet they are paying only 1/20th of the costs that are paid by an average American (<http://www.newstarget.com/001896.html>). However, the drawbacks of the system in Taiwan include unwise use of excess pills by those who are not very ill. There is a lack of clear information about the overall CHM utilization pattern in Taiwan, except for some survey studies of general hospitals and elderly homes. It is noteworthy that numbers of big general hospitals performing Western medical treatment are beginning to set up Chinese medicine departments. I sense a great danger of herb-medicine interaction in elderly patients of Taiwan, as state covered prescription medicine and cultural inclination for CHM make a deadly cocktail if not used properly.

Chinese Herbal Medicine for Sex Enhancement

Chinese men have always been interested in increasing virility and sexual satisfaction to the extent of using any means possible, an aspect that has been well documented. Ancient Chinese manuscripts are full of recipes for aphrodisiacs and philters (34), while in the modern era anything from rhino horn to mice testes ends up as medicine. One of the major attractions for tourists in Taipei is the snake alley, in a famous night market. Live snakes, tortoises, seafood, animal testes and varieties of insects are offered for their believed sex enhancing potentialities. Recent studies in the androgen status of middle age and elderly Chinese men showed that the total testosterone and sex hormone binding protein were lower in those suffering from erectile dysfunction, which mirrored the findings from other ethnic populations. However, a contrast reporting from the work was the higher free testosterone in erectile dysfunction cases, indicating a possible ethnic difference (35). Without speculation of any possible link between the finding and the seeking of virility boosting agents by middle-aged and elderly Chinese men, it is true that this medical area has a huge market in Taiwan.

Among the most probable underlying medical causes for the problem is the stress of workaholic lifestyle and pollution of industries and emission of over 8 million vehicles in Taiwan. In the early half of the last decade, this market put Taiwan in the limelight for the wrong reason. Stocks of rhinoceros horns in Taiwan created a bad image in Taiwan. Imports of ~2000 kg of tiger bone to produce tiger bone wine each year and restaurants in Taiwan selling tiger penis soup were some of those thousands of news reports making the rounds in international media during the period 1992–94 (36,37). The results of the media highlights had severe effects on Taiwan's TCM trade and international relationships, even leading to the invoking of the Pelly Amendment from the United States and Taiwan losing more than US\$30 000 000 per year (6). Although rhinos and tigers in the jungles of Royal Chitwan National Park, Nepal and other parks in India continue to die, the Convention on International Trade in Endangered Species of Wild Fauna and Flora has greatly changed the shape of

traditional aphrodisiac materials in TCM. Still, deer antlers, horns of domestic animals, farmed bear gall bladder, etc. are still available through an underground trafficking of illegal substances.

Screening of herbs for their possible role in hormone replacement therapy in menopause and andropause management, and possible aphrodisiac roles, is gaining momentum in Taiwan (38,39). In our own investigation of several herbal medicines for potential steroidogenic activity, we have screened over a hundred herbs both *in vivo* and *in vitro* to analyze their effect on steroid hormones (testosterone, progesterone, cortisol). Utilizing advanced techniques, key enzymes and proteins in the various steps of steroidogenesis within the cells are minutely scrutinized to establish the signal transduction pathway for the active component in the potent herb extract. Changes in the intracellular environment in the steroidogenic cells due to aging and stress and experiments with various herbal extracts to rectify the damage in an attempt to create aging-regulating formulas are currently underway in our research (40).

Herbal Medicine for Veterinary Use

In spite of the huge potentiality of business prospect of HM for veterinary use, Taiwanese manufacturers have shied away from investing on it. Reasons for such neglect are quite baffling, but a major one is the lack of research in this field. To promote research and awareness in this field the Chinese Society of Traditional Veterinary Science (CSTVS) based in Taipei is pushing hard. Regular training courses and seminars on the possible incorporation of TCM for veterinary use are conducted and they are starting to bear fruits. Acupuncture is now becoming an integral part of the pet animal care in major city clinics of Taiwan. Equine and bovine practice with TCM is limited to failed cases of WM treatment, mostly related to skeleto-muscular or gynaecological disorders. However, faint voice on the need for sustainable animal farming awareness is beginning to be raised in gathering of veterinarians. This promises that in future use of TCM will be widely employed in animal health care. Regional co-operation to hasten wider acceptance is being mulled to establish safe food production scenario for future. In such an attempt, Asian Society of Traditional Veterinary Science (ASTVS) was formed with representation from Japan, South Korea, China, Taiwan and Nepal. Having said that, HM for veterinary use will only get impetus if more research is allocated in this field, and commercial production starts to tap the potential market.

Conclusion

The trend toward natural health methods has set off tremendous changes in the international and domestic market of Taiwan offering unprecedented opportunities for the development of herbal medicine. Taiwan is taking full advantage of the links to the ancient cumulative wisdom of the Chinese

people, extending over several thousands of years. Considered one of the brightest areas of Taiwan's emerging biotech industry, advancement in CHM is growing with leaps and bounds. With the global herbal medicine market estimated at roughly US\$23 billion in 2002 and slated to grow by >13% annually, Taiwan knows where the cash is. It is further projected that the value of the global herbal medicine market will break through the US\$40 billion mark by 2006, and Taiwan is striving to grab a major share of it. Although the government is pumping in lot of resources toward the development of CHM, its policy to push for biotechnology and integrated big projects overlooks basic research. Taiwanese decision-makers should learn lessons from the recent Korean debacle in advance biotechnical science. With restraints in funding, small researchers cannot sustain rigorous testing of the medicinal properties of herbal extracts. In the same line, there is much that the Taiwanese government can do to introduce TCM therapy in animals kept both for food and companionship purposes, acknowledging that the global use of medicine in animals far exceeds that in humans. Hence, to sustain the development of CHM, Taiwan needs to reflect on all the shortcomings and push for greater reforms in quality research and production. An effort must also be made to ensure that the availability of raw materials for the herbal medicine industry is protected in a sustainable way and that the rush to biotech era medicine does not trample the grass roots researchers who discover the new compounds.

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