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The Evolutional Development of Traditional Chinese Medicine (TCM) Outside the Chinese mainland: Challenges, Training, Practice, Research, and Future Development

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ABSTRACT

This overview has provided an account of evolutional changes of an experience-based traditional medical practice of traditional Chinese medicine (TCM) towards modernisation to keep up with recent advances in analytical and biomedical sciences, and information technology, which may help readers to understand why applying biomedical research methodology to TCM modernisation, while maintaining the experience-based concepts, principles and heritage of TCM's personalised health and medical approaches in balancing body's functions with physical and mental harmony when facing environmental changes, can contribute to gain global appreciation and acceptance of TCM in healthcare. It is envisaged that such future development and integration with biomedicine-based main-stream medicine (MSM) in practice will provide valuable medical care in the development of future personalised health and medicine as well as TCM product development.

Key words: Evolution of MSM & TCM, Challenges, Training, Practice, Research, Integrative development

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INTRODUCTION

This paper describes the author's research paths from pharmaceutical to integrative approaches in basic and clinical research of main-stream medicine (MSM) initially, then Traditional Chinese Medicine (TCM). Through these long and winding paths of working in academic institutes, government bodies and hospitals, in both the northern and southern hemispheres over the past years, the author has collectively summarised his experience of the evolution to the present-day medicine through literature publications and own research outcomes. With this knowledge and experience collated over the decades, some recommendations are provided in this overview the best way forward to steer the global role of TCM in healthcare in the 21st century.

The initial part of the overview deals with short accounts on the development of both MSM and TCM in order to understand their contributions in treating human diseases from evolution of ethnic culture and philosophy. The different views of TCM in the West during the mid-1990s that stimulated a debate on 'For and Against' of its role in health amongst the public, academia and legal bodies is a mile-stone for a closer look of TCM in terms of quality, safety and efficacy at large since that period.

The recent advances of technology in biomedical sciences are consequential to the human genome project, and analytical/instrumental sciences that allow imminent measurement of events occurring in cell/organ programming, and computational sciences that provide databases of both biomedical and analytical parameters for further elucidation and determination of research outcomes, have collectively and indirectly brought the two vastly dissimilar medical concepts to another debate of 'For and Against' in personalised integrative healthcare.

A large number of currently used pharmaceutical medicines are obtained from medicinal plants or natural sources[1]. The development of current practice and pharmaceutical medicines in MSM has a comparatively short history: medieval medicine initiated in Europe into a science-based discipline dates back less than 200 years[2]. This rapid rate of success depended mainly on the advancement of physical sciences and technology[3]. Many pharmaceutical medicines were introduced initially via activity-screening from extracts of medicinal plants and phytochemical isolation and subsequently followed by chemical synthesis of the isolated active compounds. With the help of chemical synthesis and fitting novel chemical entities into quantitative structure-action analysis (QSAR)-models or protein-enzyme models a series of chemical analogues can be screened for new drug development. The successful discovery and development of penicillin (1928–1945)[4], which has been coined as a milestone in 20th century pharmaceutical chemistry, has stimulated introduction of many pharmaceutical drugs during the 1960s, therapeutic armament to develop and improve MSM in the developed countries worldwide, while the developing and under-developed countries/regions have relied on their own ethnic/traditional medicines mainly from medicinal plants even nowadays[5].

In recent years the pharmaceutical industry has produced fewer new agents for treatment of chronic diseases related to metabolic syndromes (cardiovascular complications, diabetes, obesity), rheumatoid arthritis, aging-related degenerative disorders such as Alzheimer diseases, dementia, Parkinson's

diseases and other high burden diseases such as various cancers, infectious diseases caused by drug-resistant microbial infections and others through sexual contacts or contaminated blood such as hepatitis and related carcinomas and HIV. Among many factors the root causes of few new drugs are: relentless health economics pressure; increasing regulatory hurdles; immature state of knowledge and molecular reductionism and management reductionism & diseconomies of scales[6]. Such approach to identify small molecules for drug development becomes more and more expensive. Most national health systems worldwide have suffered from the burden of high cost of pharmaceutical medicines in both primary care and secondary care since the 1990s. Table 1 briefly summarises the key events of evolution and progress of pharmaceutical medicines in OM from ancient time to the future.

The Keeping of the 5000 Years Old TCM in Line with Advances in Science and Technology

TCM as one of the oldest medical traditions since 2800 BC has been practised to maintain health and treat diseases in the Chinese communities and recently adopted by others worldwide. Table 2 concisely summarises the historical development of TCM since ancient times. Nowadays, Chinese materia medica (CMM) and proprietary products of TCM composite formulae (PCM), acupuncture and related medical manipulation (Tuina and related physical therapies), together with life styles (consuming CMM functional foods, practising Taichi, or Qigong meditation) are often used in TCM practice, co-existing with MSM in China and some regions in the Far East. Though used by the public on their own accord, TCM has not been recognised officially in some regions such the European Union and North America as part of the healthcare system run by main stream MSM practice. Such circumstance has delayed the development of traditional medicine in these regions in comparison with that in Australia, Japan (as kampo medicine), Korea (as oriental medicine) and some European countries. The non-recognition can be considered as obstacles for delay in the development and modernisation of TCM in general worldwide[7].

Meanwhile, two unrelated phenomena in medical progresses were observed: Firstly, the population in the well-developed countries have turned to complementary and alternative medicines (CAM) and TCM has been one of the key CAM disciplines attracting most attention as evidenced by a recent overview on a 2010-2015-2025 survey and prediction[8]. Secondly, the human genome programme completed in 2003 has introduced significant advancement of biomedical and analytical technology to further the understanding of the nature of ill-health and offered new hopes to the big pharmaceutical organisations to develop new medicines based on functional genomics, proteomics and systems biology/medicine for treatments of diseases[9]. Indirectly such advances of biomedical and analytical technology may have also influenced the development of TCM and offered opportunity for modernisation to keep up with such advances, which help to convert an experience-based practice towards evidence-based medical practice in order to play a role to integrate into main stream medicine while maintaining its traditional holistic principles for maintaining good health[10].

This overview addresses these key issues and attempts to propose ways for future research and development for TCM into the 21st century. The impact will certainly be modernisation in every aspect of the disciplines to cope with the fast growing demand in quality medicines while maintaining the traditional principles of TCM health holism. Several major areas, which are essential for global development of TCM, are listed for discussion.

Challenges Towards Diverging Opinion on TCM in the 1990s

1. Lack of understanding of TCM principles in health and disease

The holistic approaches of TCM in diagnosis and treatment of diseases and maintaining good health is in contrast to that of MSM. Practice of MSM is based on modern anatomy, molecular cell biology and is characterised by a reductionist approach in analysis and diagnosis of health and diseases. As TCM was established long before the advent of modern science, involving validation and experiences gained over thousands of years, it represents an area of medicine that is more experienced-based with the environmental and philosophical approaches than based on conventionally scientific aspects. Although TCM has played an indispensable role in maintaining the health of people in China and several Asian regions, its value remains largely unproven according to biomedical sciences and many existing systematic reviews or meta-analyses are often inconclusive due to the less stringent clinical design not related to MSM criteria for randomised clinical trials (RCT). This deficiency has led to criticism domestically and internationally. Reasons for underdeveloped TCM research during this period are manifold, including subjective and personalised TCM diagnosis, which is often incompatible with the conventional RCT methodology for clinical research; the complexity and wide diversity of herbal medicines and diseases; as well as the difficulty of choosing correct controls for complex herbal remedies prepared from CMM and acupuncture, etc. Furthermore, lack of research funding and a worldwide shortage of qualified researchers outside the Chinese mainland who understand both TCM and modern biomedical technologies should never be underestimated. These situations have been improved recently as more scientists and practitioners have taken interest to find out how TCM works in their quests for evidence endeavours.

2. Observations on the increasing appreciation and scepticism of TCM

In the west increasing uses of Chinese medicines have created both acceptance and scepticism of TCM practice that have initiated a major debate in medical cycles since the successful randomized clinical trial on the use of ten prescription CMMs on atopic eczema was published in 1992[11]. Quite separately

Table 1. The Evolution of Main Stream Medicines in Europe and Other Developed Countries (Modified from ref.[2]).

ORIGIN:	**Ancient traditional medical practices of various ethic groups**
3000 BC	• Influence of Babylonian and Egyptian cultural and medical records provided initial contributions.
500 BC	• In Europe and surrounding regions, the Greek inheritance of Babylonian and Egyptian medicine, with influence from the East (Ayurvedic and Chinese medicine) led progress.
510 BC to 476 AD	• The Roman Empire brought prosperity, law, the Latin language and Christianity to Europe and the Mediterranean region, but adapted medical practice from the Greek physicians.
476 AD to 14th Century	• Arabic influence on translation and compilation of Greek medical works into Arabic, forming a source of knowledge for Main Stream medicine from the Dark Age, and surviving through the Middle Age (4 to 8th century) to modern times.
14th to 17th Century	• Influence of the Renaissance, started in Italy to France, increasing/accumulating knowledge of anatomy and physiology of human body. • Translation of Arabic medical literature to Latin. • Influence of the evolution of physical sciences, mainly due to Galileo Galilee (1564–1642), Isaac Newton (1642–1727).
Late 18th Century to 19th Century	• Influence of the Industrial Revolution in Britain (1830), then in France & Belgium (after 1870) and in Russia (after 1900). • Modernisation of industry, social and economic issues. • Development of natural sciences, such as chemistry, mathematics and physics, laid the groundwork for nowadays medical developments. • This had a profound influence on the progress of modern medicine from medieval practices (which was based mostly on mainly religious and superstitious beliefs) into a 20th century science-based discipline, in only 100 years. • Isolation and identification of active ingredients from medicinal plants that were used over centuries and discovery of endogenous compounds with medicinal uses from animal sources. Leading to the first therapeutic revolution of the 20th century.
GROWTH:	**Period of Rapid Medical Advances. Some key points are listed**
Late 19th to 20th century	• Development of public health legislation and education. • Development of standardized and vaccination for preventative measures. • Development of anaesthetics and anaesthesia (William Morton, 1846) helping surgical progress. • Development of microscope helping bacteriology and sterile techniques that helped indirectly the progress of medical surgery (Robert Koch, Louis Pasteur, and Joseph Lister). • Discoveries of chemotherapeutic agents stimulated development of rational therapeutics – emerging pharmaceutical industry.
1905	• Salvarsan's selective toxicity against syphilis (1905) led the introduction of sulphonamides.
Early 1900s	• Prontosil's control of streptococcal infections led to the launch of most effective less toxic sulphapyridine in 1938, other antimicrobials included penicillin (1928), streptomycin (1943) chloramphenicol (1949). • Development of rational therapeutics continued under the influence of bioassays and receptor assays using isolated tissues for endogenous neurotransmitters, hormones etc. • Discovery of autonomic functions (due to discovery of pharmacological actions of acetylcholine by Henry Dale in 1940) let to introduction of muscle relaxants, cardiovascular drugs. • Discovery of insulin (action in 1921 by Banting and Best; structure clarified in 1955) standardised by blood sugar concentrations in mice and isolated rat diaphragm. • Discovery of neuroleptics for treatment of schizophrenia (chlorpromazine in 1950). • Discovery of tricyclic antidepressants for treatment of depression (Imipramine 1952). • Introduction of benzodiazepine as tranquillisers and hypnotics (1960's), many other modern synthetic analogues for almost all diagnosed diseases.
1961	• The incidence of thalidomide induced malformation of new-born nearly halted all new drug development due to teratogenic effects. Better quality assurance was demanded for testing toxicity, mutagenicity, carcinogenicity and teratogenicity.
1970s	• Various government interventions on standards and quality assurances in laboratory testing and practice had a great influence on all industries. Good laboratory practice (GLP) guidelines were set to promote and co-ordinate experiments for the purpose of bringing about safety and quality control.
1970 to 1990's	• Setting up legislation by various governments of developed countries to implement Good Manufacturing Practice (GMP) and Good Clinical Trial Practice (GCTP); **launch of ICH for new drugs development in 1990**.
20th to 21st Century & The Future	• Further development of biotechnology in gene therapy, diagnosis and biotechnological pharmaceuticals. • Development of vaccines against parasites of medical concern. • Preventive medicine, reducing cost of primary healthcare. • Improvement of quality of life. • **New medicine for healthcare: Inclusion of quality–assured traditional medicines in integrative medical practice?** • **Towards personalized medicine/precision medicine**

Table 2. The Evolution of Traditional Chinese Medicine (TCM) towards Integrative Healthcare (Modified from ref[2])

PERIOD	The Three Noticeable Legendary and Dynastic Periods
Since 2800 BC	• The Shen Nong Period: development of agriculture and use of medicinal plants by Shen Nong (A Plowman folklore hero) for treatment of illnesses; • The use of 'Bian-Shi' as sharp stones and moxa for relief of minor complaints/pains marked the origin of acupuncture and moxibustion.
2697 to 1 BC	• Development of techniques for diagnosis and treatment by the first Huang Di (Emperor) and his cabinet members in about 2697 BC; • Compilation by many physicians and pharmacists (under the name of Huang Di, in about 100 BC) of **Huang Di Nei Jing** (The Inner Canon of the Yellow Emperor) that consists of 2 main parts (Sù wèn and Líng shū) recording the *Yin Yang Theory, Wu Xing* (Five Elements) *Theory,* and related information, in questions and answers form, on pathology, signs and symptoms (collectively as syndromes), causes of diseases, whole body and the environment, and other holistic principles of traditional Chinese medicine. • Compilation of **Shen Nong Ben Cao Jing** (The Herb Classic of the Divine Plowman is the earliest Materia Medica in China) by various scholars in about 1BC listing of 365 herbal materials (252, 67, and 46 plant, animal and mineral sources respectively) and recording procedures and principles of processing, mixing and formulating them.
221 BC to 1911 AD	Non-stop development and evolution of Chinese medicine and pharmacy throughout; can be summarised by the publication of valuable pharmacopoeia and other medical texts. Each dynasty headed by some enlightening emperors would update and compile these texts with the consequence of including more natural products for use as materia medica; only well known ones (including those translated to other languages) are listed here: • **Shang Han Lun** (Treatise of Cold, Diseases and Miscellaneous Disorders written by Zhang Zhong-Jing during 25 to 220 AD), a classical dispensary handbook describing syndrome differentiation, treatment, and use of material medica, is the foundation of composite prescription (Known as Formulary). Together with Huang Di Nei Jing and Shen Nong Ben Cao Jing, the Shang Han Kun text plays a vital role in the development of Chinese medicine for later generations. • **Tang Ben Cao** (Tang Xin Xiu Ben Cao; Tang Dynasty Materia Medica commissioned by the Emperor and written by Su Jing with 23 other medical and pharmacy scholars who rectified the information and knowledge) is considered to be the earliest pharmacopoeia in the world. It consists of 54 chapters, 850 herbal descriptions with 20 imported herbs (probably via the Silk Road); influencing development of medicine in Korea and Japan; being 800 and 1100 years earlier than the pharmacopoeia from Italy (1499AD) and Denmark (1772 AD) in Europe. • **Ben Cao Gang Mu** (Compendium of Materia Medica, authored by Li ShihZhen, a medical and pharmaceutical practitioner, around 1518 to 1593 AD), consists of 52 volumes, 1892 natural products (350 from minerals, 1099 from plants, 443 from animals), 11096 Fu Fang (composite prescription formulae). This Compendium was published in 1596 AD and was brought to Europe and Japan, translated initially to Latin then in English, French, German and Russian. • **Chinese medicine in other countries** influenced neighbouring countries such as Korea and Japan as early as the period in Qin dynasty (221 to 207 BC) and 57 AD respectively • **Acupuncture** was introduced into Europe in the 16th century when some orthodox physicians picked up the techniques in Japan when trading in the Far East was started via the Dutch East India Company.
POST-DYNASTIC PERIOD 1911 to 1950s	**The Influence of Main Stream Medicine and Decline of Traditional Chinese Medicine** • The collapse of Qing Dynasty introduced chaos to the country leading to western influence/invasion of nearly all aspects of life including political, social and healthcare matters. • Formation of the Republic in 1911 and introduction of orthodox medicine practically eliminated the practice of Chinese medicine. • Knowledge of acupuncture was made more known to other parts of the world when trade was started with European countries.
PERIOD OF RE-INTRODUCTION 1950 to 1980s	**The Influence of Poor Economic after 2nd World War and the Civil War** • The PRC government re-emphasised the importance of TCM from 1956 onwards due to economic and technical limitation for pharmaceutical drugs. • Gradual modernisation and regulation of both western orthodox medicine (OM) and traditional Chinese medicine (TCM) interfered in between by the cultural revolution from the 1970s to 1980s in conjunction with the nation-wide economic development. • Setting up of specialist universities of TCM in major cities in key parts of China: Beijing (north) Chengdu (west), Nanjing (middle), Shanghai (East) and Guangzhou (south) while maintaining provincial colleges of TCM throughout the country.

Table 2. (Continued)

PERIOD OF MODERNISATION 1980s to 1990s 1990s to 21st Century and beyond	**Modernisation of Chinese Medicine was initiated by the State Administration of Traditional Chinese Medicine and various other key government organisations.** Vigorous development of all aspects of traditional Chinese medicine (TCM) led by various government bodies. • International Modernisation of Chinese medicine in all aspects: education and training; basic medical scientific investigation on the biochemical and physiological aspects of acupuncture, herbal treatment and physical therapy (Medical massage, Qigong meditation, Taichi exercise); • Quality control and assurance of Chinese materia medica (CMM) and proprietary Chinese medicines (PCM) from composite formulae (FuFang) via key good practices (GACP, GLP, GMP, GCTP); Development of experimental models to relate TCM principles and MSM pharmacological actions of PCM products; development of modern dosage forms; efficacy and safety of CMM and PCM products; • Improve and promote integration approach for OM and TCM in particular on prevention of diseases. • Systems biology was introduced as a bridge for TCM and molecular pharmacology to elucidate mechanisms of acupuncture and composite formulae. • Application of functional genomics, proteomics, network-pharmacology towards investigations of mechanisms of action for CMM and PCM. • Integration of TCM's diagnostic and treatment procedures from syndrome differentiation of diseases to clinical efficacy investigations. • Incorporate TCM Quality of Life instruments as measures of patients' reported outcomes linked with biomedical parameters as additional measurement of efficacy of TCM treatments and prevention of diseases. • Other key specific projects such as informatics for CMM and TCM practices; proper promotion of functional food in TCM practice, life style for preventative medicine, etc. • Integration of TCM into mainstream of healthcare and medical treatment; establishment of integrative clinics and hospitals. • Improvement of international networking (globalization), collaboration and information sharing in the training, R&D and modernization of TCM.

during this similar period a chronic renal disease was observed in a group of otherwise healthy Belgian women who had ingested a slimming regimen that included a wrong species of CMM, Guang Fangji (Aristolochia Fangchi Radix) containing aristolochic acid instead of Han Fangzi (Stephania Tetrandra Radix). Over time, approximately 100 of these women developed chronic renal insufficiency due to the toxic effects of aristolochic acid[12]. Furthermore available in the market, often found are CMM products adulterated with pharmaceutical drugs and wrongly supplied crude CMM causing liver and kidney toxicity[13]. These unprofessional practices from commercial organizations do not give TCM the right reputation and recognition[14]. It is emphasized that legal regulatory agencies should set up harmonized monographic standards for CMM and regulatory control over the import and export of natural or herbal products to ensure safety of the public who consume these products[15]. Further information will be considered in subsequent texts on this issue.

3. The requirement of expertise and leadership to implement improvement

The advancement of internet access message on CAM is freely available to the public. As such there is the growing demand for and promotion of traditional and herbal medicines including TCM products in countries within Europe and in North America. Adverse effects and health risks exist with the use of TCM in a western environment by persons often unfamiliar with the underlying medical traditions. A recent review[13] indicates several key points concerning usage status of TCM in a survey conducted by experts in the European Union (See Box 1). Therefore, such requirements and resources on professional experts and leadership which determine the quality of practice and standardised TCM medications and non-pharmacological interventions are the pre-requisites before one can assess the safety and efficacy of TCM treatment and prevention of diseases in regions outside China. Global collaboration[16] is one of the ways to look at evidence-based practice of TCM and for integration into healthcare systems worldwide.

Box 1. A summary of key points of the EU survey on TCM status in EU community

- Unlicensed medicines manufactured outside Europe often do not comply with international or European quality standards;
- herbal products used in TCM ranging from medicines, foodstuffs, food supplements, cosmetics to borderline products;
- major differences on legal status of Traditional Chinese Medicine exists in Australia, China, Europe, North America and regions with different regulatory approaches;
- a lack of harmonised requirements for the qualification, training and professional regulation of persons practising TCM;

(To be continued)

(Box 1. Continued)

- a lack of or insufficient knowledge about the impact of TCM in medical and pharmaceutical practices and public health;
- a need for harmonised policies on the products and practices for consumers and patients and from surveillance of the safety on practices and products;
- a need for specific training for TCM-prescribers, dispensers, practitioners and therapists.

Medical Training & Research of TCM Outside China in the 2000s

1. The inclusion of complementary & alternative medicine in MSM

The reductionist and specialisation approach in diagnosis and treatment of diseases in conventional MSM has been questioned as inappropriate for holistic care for patients by experts who are involved in medical curriculum. Since the early 2000s the medical schools in the USA reviewed that although evidence-based medicine remains an important part of medical education, 123 of the 125 Association of American Medical Colleges required students to take at least one complementary/alternative medicine (CAM) course in the academic year[17]. Such changes have been brought about by the patients' desire for alternative therapies, as nearly 40% of American adults had used some forms of CAM, from nutrition and mental relaxation to acupuncture, magnet therapy, and foreign healing systems like traditional Chinese medicine and Indian ayurveda. Medical schools in other regions have also encouraged similar approaches, indicating there is an increasing interest of CAM. Future practice of MSM may embrace and encourage a holistic approach to practice that incorporates patient involvement in self health-care, prevention and lifestyle interventions. In most international CAM conferences we have observed that TCM participation in key themes mainly focuses on acupuncture, qigong/taichi for the benefit of well-being and pain relief with few clinical studies of TCM formulae while research outcomes in assessing quality, safety and clinical efficacy of TCM herbal products in CAM conferences are not plentiful. In general, TCM as a CAM discipline is considered the most widely used CAM worldwide[18,19]. On the other hand, most international conferences of TCM have included a good mix of all 5 disciplines mentioned earlier.

2. The reason for inclusion of biomedical science in TCM curricula

Patients may be at risk from a delay in seeking medical advice for a serious medical condition that is not appropriately treated by complementary therapies. Therefore the practitioner should be competent to recognise the need of knowledge in both TCM and MSM practice. Professionalism and regulations are needed to protect the public.

A consultant paediatrician, who led the clinical trial of a 10 CMM-decoction mixture in treatment of atopical eczema in children[11] and published positive outcomes in 1992, commented:

> *"Those unfamiliar with Chinese medicine should be aware that, in present-day China, it is regarded as perfectly normal for TCM practitioners to prescribe Western-type licensed pharmaceutical products alongside acupuncture and herbal therapies. There is no rigid separation of Western-type medicine and TCM as outsiders might imagine, and the training of TCM practitioners has for several decades included substantial amounts of basic Western medical science including anatomy, physiology and pathology. Likewise, those training in China in Western-type medicine are taught the theories of TCM. The result is considerable cross-fertilisation between these 2 disciplines, despite their superficially exclusive natures. This has been very much to the benefit of patients, who are not infrequently treated simultaneously by both types of practitioner. During my own visits to China I saw this collaboration occurring in many areas of medicine, but perhaps most effectively in the treatment of auto-immune diseases such as systemic lupus erythematosus and dermatomyositis, which are common in China, and in the symptomatic care of patients dying of liver failure, also common in China, and of terminal malignant disease."*[20].

During the 1990s, such medical experts and professionals equipped with both medical disciplines were not plentiful in the west including UK and other regions. If there is the desire of using TCM in the healthcare system in any developed countries there should be training courses that produce practitioners of TCM with good quality and professionalism to safeguard the public interests and their health. This is to check on those who are not qualified and to eliminate unprofessional practice. In most European countries the interest groups of acupuncture and TCM herbalism started more formal training of CM on the initial running of and updating seminars. The earliest group seminars were run during the late 1950s and early 1960s. In recent years, many of the established acupuncture colleges in the UK (also in Australia and the USA) have introduced courses in TCM herbalism. Most of these institutes run part-time courses, mainly in the evenings and weekends, of varying years of duration with certificates and diplomas on graduation. An independent survey on overall situation of TCM practice in UK indicated that available training courses, offered by private schools/institutes, were mainly on part-time basis. Table 3 provides a summary indicating most of the private schools/institutes offered part-time programmes for TCM or acupuncture training, as surveyed by Jin and co-workers[21].

3. Training of professionals in TCM outside the Chinese mainland

3.1 The United Kingdom (UK) experience:

In 1995 the author was conferred Churchill Fellow, which provided funding for him to take on the project "Critical Assessment of Traditional Chinese Medicine in the East". This project enabled him to visits key TCM universities/institutes in

Table 3. TCM full time (FT) and part-time (PT) courses run by institutes in UK during the 1990s (Updated from Jin et al., 1995)[21].

No.	Institution	Courses	Duration	Contact Address
1.	British College of Acupuncture	Undergraduate courses in Acupuncture & TCM	3 & 4 Year (PT)	The Registrar, 8 Hunter Street London WC1N 1BN
2.	Chung San Acupuncture School	Undergraduate course in Acupuncture & TCM	3 & 4 Year (PT)	15 Porchester Gardens London W2 4EY
3.	The Chinese Medical Institute & Register	Foundation and postgraduate courses	FT/PT	101, Camden High Street London NW1 7JN
4.	College of Integrated Chinese Medicine	Training in Acupuncture	6 Months (PT)	The Registrar, 19 Castle Street Reading, London RG1 7SB
5.	Institute for Traditional Medicine	Research & Education on Herbs	PT	Veronica Howard, 5 Waverley Place Adolphus Rd, Finsbnury Park, London N4
6.	Japanese Herbal Medicine, Kohoha School	Japanese Herbal Medicine	45 Week – 1 day per week (360hrs.)	Ms. G D Soriano, C/o 36 Bankhurst Road, London SE6 4XN
7.	London Academy of Oriental Medicine	Acupuncture & Chinese Herbal Medicine	4 Year PT	The Registrar, Newcourt, Street, London NW8 7NA
8.	London School of Acupuncture & Traditional Chinese Medicine	B.Sc. (Hon.) TCM: Acupuncture	3 Year – Full time course	The Registrar, 4th Floor, 60 Bunhill Row, London, EC1Y 8QD
9.	London School of Acupuncture & Traditional Chinese Medicine	Post Graduate Diploma in Chinese Herbal Medicine	2 Year – Part time	The Registrar, 4th Floor, 60 Bunhill Row, London, EC1Y 8QD
10.	Northern College of Acupuncture	Diploma in Acupuncture	3 Year	The Registrar, 124 Acomb Road, York YO2 4EY
11.	Northern College of Herbs	Part time Training course in Chinese Herbs	2 Year	The Registrar, 124 Acomb Road, York YO2 4EY
12.	Middlesex University* (Degree courses since 1997)	Undergraduate course of TCM, jointly run with Beijing University of TCM	FT – 4 Years	The Burroughs, London, NW4 4BT

http://www.mdx.ac.uk/courses/postgraduate/chinese-medicine.

Beijing, Shanghai, Nanjing, Chengdu and Guangzhou in China, Tokyo and Toyama in Japan, Hong Kong, and Taichung and Taipei in Taiwan to investigate the then development of TCM academic programmes and research and build up networking with key institutes[22].

The reported outcomes of the Churchill Fellowship were announced national-wide and had indirectly initiated the establishment of the very first university degree course in Europe: The author, while working at the Ministry of Health in Abu Dhabi as Director of the Zayed Complex for Herbal Research & Traditional Medicine, was appointed Visiting Professorship at Middlesex University (MU) in London and was involved in engineering partnership between MU with Beijing University of TCM to launch the full-time degree course. Box 2 summarises key ethos of the programme.

Box 2. A summary of ethos provided by the London-Beijing degree course

- Provide education and training to produce graduates who will be competent, safe and caring practitioners in all disciplines in TCM: Chinese materia medica and herbal formulary, acupuncture and related medical manipulation (Tuina and related physical therapies), together with life styles (consuming CMM functional foods, practising Taichi, or Qigong meditation);
- Provide students with a thorough preparation in the principles and applications of TCM underpinned by sufficient knowledge and understanding of current orthodox medical anatomy, physiology, pharmacology and pathology,

(To be continued)

(Box 2. Continued)

with diagnostic processes and procedures to become a safe and competent practitioner.

- Develop students as autonomous lifelong learners with the professional curiosity to want to develop knowledge, understanding and skills and to conduct research that will underpin evidence-based practice.
- Provide practice-experience training in Beijing TCM hospital/clinic setting in final years of the course.

The London-Beijing course was eventually started in 1997[23], and since then several other institutes and universities in the UK have also offered accredited degree courses in TCM linked with TCM universities in China. It has survived the test of time and now developed post graduate training for OM qualified professionals. Table 4 summarises the currently available foundation and post-graduate courses of TCM available in the UK. There is improvement in providing academically sound human resources of TCM in UK.

However, at present the UK government via the Department of Health published the Report on the Regulation of Herbal Medicines and Practitioners, which has not agreed to grant Statutory Regulation (SR) for herbal medicines and practitioners as registered health professional alliance to medicine.[24] It recommends continuing the voluntary Professional Statutory Authority (PSA) to accredit herbal practitioners since 2000 recommended for the House of Lords' Science and Technology Select Committee, some 15 years ago. Such decision indicates the herbal profession is not recognised as part of the health profession and has created a

Table 4. Current Full-time (FT) and (part-time) accredited TCM courses offered in UK under the UK Association of TCM.

1	Glyndwr University	BSc Acupuncture & BSc Compl. Therapies	FT	Plas Coch Campus Mold Road Wrexham LL11 2AW
2	Irish Institute of Chinese Medicine	BSc Chinese Medicine	FT/PT	105 Richmond Road Dublin 3 Ireland
3	Middlesex University	BSc Acupuncture, BSc and MSc Chinese Medicine	FT	The Burroughs London NW4 4BT
4	University of Lincoln	Diploma in TCM	FT/PT	Monks Road Lincoln LN2 5HQ
5	College of Integrated Chinese Medicine	Graduate Diploma in Chinese Herbal Medicine	PT	19 Castle Street Reading RG1 7SB
6	College of Naturopathy Medicine	Diploma Acupuncture	PT	39-41 Riding House Street London W1W 7BE
7	Shulan College of Chinese Medicine	Diploma of Chinese Herbal Medicine	PT	Parrs Wood Road, Didsbury Manchester M20 5QA
8	The Chinese Medical Institute & Register	Foundation and postgraduate courses	FT/PT	101, Camden High Street London NW1 7JN
9	University of Westminster	Chinese Medicine Acupuncture BSc Honours	FT	309 Regent Street London W1B 2HW

http://www.atcm.co.uk/education/accreditation.

collective rebuttal action from the education, practitioners and industry sectors[25]. Currently some of the full-time courses for TCM degree courses are not on offer, most probably due to the lack of demand from the public. This may reflect the unfavourable decision of the UK government on not granting Statutory Registration Authority to Herbal Medicine. (See details depicted in Box 3 below):

Box 3. A summary of the collective points made against UK government's decision for not granting Professional Statutory Authority to herbal medicines and practitioners[25].

- The most important issue facing the UK TCM practitioners and their patients is access to good quality and safe manufactured herbal medicines including those used in TCM practice.
- Practitioners on a statutory register would be required to purchase their herbs from suppliers demonstrating quality assurance of their herbal medicines. Under statutory regulation potent herbal medicines could be restricted to use by those on the statutory register. This option is not available under PSA voluntary accreditation.
- In the last two decades, practically every herbal misadventure has occurred at the hands of those practising outside the main UK voluntary registers without adequate training or unethically. With the growing interest in and use of herbal medicine, only statutory regulation can ensure that the sector as a whole works to the highest standards and can integrate herbal medicine into the healthcare systems of the 21st century.
- Herbal medicine, when used as internal medicine, like other types of internal medicine practised in the UK, requires statutory regulation for those who practise it. Professional herbalists provide an important public service and the profession should be integrated into the UK healthcare scheme via statutory regulation at the earliest opportunity.

3.2 The Australia experience:

TCM has an established history in Australia and has expanded rapidly in recent years. The practice was introduced into Australia at the time of gold rush period as early as 1850's. At the Ballarat town of Victoria, a tourist spot where the history of gold mining is maintained, the old clinic of TCM called Bao Kan Tang is one of the major attractions. This reflects the significance of TCM in health care in the early history of Australia[26].

However, the practice of TCM struggles to find its place as a complementary medicine in Australia, despite the fact that around 30% of all complementary medicine consumers use TCM. Over the last decade: Two in three people use complementary medicine each year, with the complementary medicine industry being worth $1.5–2.5 billion per annum[27]. Of those who took complementary medicine, around 27% used TCM[28]. Although there has been many research groups formed across the nation and umbrella institutions such as the National Institute for Complementary Medicine, there has not been any major changes to encourage an 'integrative' approach to healthcare for the benefit of the Australian public. In 2012, Australia is the first country outside China who initiated registration of all qualified TCM practitioners, supported by standards, codes and guidelines. With this recognition of the profession, it would be an enormous advantage to provide an R&D direction for integrating the available well-tried experience-based TCM paradigm with the increasingly advanced MSM paradigm. Yet, only anecdotal records of success using TCM treatment for diseases that have not been cured successfully by MSM have been reported. In the public there had been sceptics advocating against the use of complementary medicine due to limited scientific evidence.

1) The first country outside China formalised the registration of TCM. From 1 July 2012 onwards, TCM practitioners must be registered under the Australia national registration and accreditation scheme with the Chinese Medicine Board of Australia, which is one of the 14 Boards answerable to the Australia Health Practitioner Regulatory Agency (AHPRA; http://www.ahpra.gov.au/National-Boards.aspx), and meet the Board's Registration Standards, in order to practise in Australia. The AHPRA has the legal power to approve or disapprove these courses in TCM including acupuncture,

Chinese herbal medicine, and a combination of both disciplines. (http://www.ahpra.gov.au/Education/Approved-Programs-of-Study/Inactive-Programs-of-Study.aspx). At present there are nine different institutes (universities as well as colleges) throughout the country provide accredited/approved basic bachelor degree courses. Some of these institutes also provide opportunities for graduates and qualified TCM practitioners to study higher/post-graduate level degrees. Most of these degree courses also provide placement training with TCM universities in China.

2) The Joint Chair in TCM Program in New South Wales State (NSW): (http://sydney.edu.au/china_studies_centre/china_express/issue_4/features/The-JCTCM-Programme-in-NSW.shtml; accessed on 15th June 2016). To address some of the above issues, an agreement between The University of Sydney (USyd), Western Sydney University (WSU) and the NSW former Department of State and Regional Development (DSRD), now the Office of Science Research (OSR), was initiated in 2008. The Chair had been a strategic appointment whereby the holder of the Chair should provide national leadership in TCM research and develop synergistic TCM research programs at USyd and WSU. The program is jointly funded, for a period of five years, by DSRD, USyd and the WSU, and the projects are supported through the Faculty of Pharmacy at USyd and the National Institute of complementary Medicine at WSU. A high level Project Plan was developed by the Joint Chair in early 2010 and identified strategic research priorities in TCM development under the Joint Chair programme (See Box 4):

Box 4. Key strategic research priorities under the JCTCM programme

- Assisting with Chinese herb cultivation to address quality supply issues and increase the agricultural potential of Chinese medicinal materials in Australia;
- Initiating, developing and continuing national and international collaborations with other institutes and industry partners;
- Investigating the background of manufacturing and analysis methods to provide herbal product consistency and predictable bioactivity;
- Contributing to R&D product development (pharmacological and clinical investigations, linking biomarkers and patient reported outcomes);
- Contributing to the development of TCM bioinformatics and data management to capture traditional knowledge;
- Developing the national and international profile of NSW and Australia in TCM
- Training future human resources with TCM expertise in research and practice

The JCTCM programme, though challenging, complex and diverse in collaboration, has successfully achieved to provide research and training direction for future human resources, particularly with partners in China. The programme has hosted a variety of TCM related public lectures, seminars, workshops and delegations during the course of the program, and participated in national TCM forums, all contributing to the development of the science and evidence-based aspects of TCM education, future and practice as well as establishing potential collaborations between national and international partners. During the period of the JCTCM programme, notably the following key projects had been carried out (See Box 5).

Box 5. Some key outcomes of the JCTCM Programme 2009–2014

- PhD students (two at USyd and one at WSU), Masters students (one at each university) and several Final Year & Summer project students in the two universities were trained in R&D of TCM: including mechanistic and pharmacological methodology, method development in quality control of Chinese materia medica; bioinformatics related to TCM formulary; development of Quality of life instrument based on TCM principles for patients' reported outcomes research. Over 50 SCI publications were consequential to these training projects.
- The JCTCM received funding support from the Australia-China Science and Research Fund under Group Missions category to work on "The sustainable cultivation in Australia of high quality medicinal plants for use in traditional Chinese medicine" with The Institute of medicinal Plant Development (IMPLAD) as the China partner.
- The JCTCM was appointed by the TGA to be Australia Observer to serve as expert at the TCM Working Group at the European Directorate for Quality Medicines and Healthcare in drafting CMM monographs for the European Pharmacopoeia.

3.3 The Hong Kong experience:

This has been an example of gradual development TCM practitioners into an accredited and registrable profession over the years. The Hong Kong Special Administrative Region (HKSARg) in China was a British colony from 1842 to July 1997 under the Treaty of Nanjing signed by the then Qing Dynasty. Most of Hong Kong residents (Over 90%) are of Chinese origin and have close economic and cultural relations with the the Chinese mainland throughout the period. TCM as an integral part of the Chinese culture has been widely used within the Hong Kong Chinese community for a long time despite western MSM being the main stream in medical care. HKSARg is also an important trade centre port/centre of TCM related products including CMM due to her close economic relationship with the Chinese mainland and Chinese communities overseas. The open policy of the Chinese mainland since the 1980s has created many key trading channels. While China is the main producer and exporter of CMM, Hong Kong is the most important first destination of this import and re-export trade. Over the past decade, after returning to the motherland, HKSARg has been one of the most influential regional communities in terms of economic and technological development and growth and has been ranked as the world's freest economy many years running, and it remains

presently the first of the world's top 5 leading financial centres[29]. This does help to promote global appreciation of the culture, practice and service of TCM outside China.

1) CM in Hong Kong during colonial period. During this period, TCM was not recognised as part of the healthcare system in Hong Kong though R&D towards quality control, toxicology and pharmacology had been set up by the Chinese Materia Medica Research Centre (CMMRC) at the Chinese University of Hong Kong since the early 1980s, which has now been re-developed to the highly recognised Institute of Chinese Medicine. The then HK Government appointed a Working Party on Chinese Medicine (August 1989 to October 1994) to review the practice and use of Chinese medicine in Hong Kong and advised measures that should be taken to promote the proper use and good practice of Chinese medicine. Consequently, a Preparatory Committee on Chinese Medicine (April 1995-March 1999) was established to make recommendations to the government on the promotion, development and regulation of Chinese medicine in Hong Kong. The Committee recommended a statutory body be set up to regulate the practice, use and trading of Chinese medicine; a system of accreditation and regulation which includes registration, examination and discipline of Chinese medicine practitioners be established with transitional arrangements for existing practitioners; and a control mechanism, through systems of registration, licensing and labelling be set up to regulate the manufacture, distribution, retail and import and export of Chinese medicines. Regarding the future development of Chinese medicine, the Preparatory Committee recommended full-time undergraduate courses in Chinese medicine be developed and made available in Hong Kong; scientific researches and developments in Chinese medicine be encouraged and supported; and Chinese medicine be included into Hong Kong's medical and healthcare system on a gradual basis.

2) TCM in Hong Kong after return to China. After 1st July 1997, the policy for the future development of Chinese medicine was enshrined in the Basic Law of the Hong Kong Special Administrative Region. Article 138 of the Basic Law provides that "… the Government of the HKSARg shall, on its own, formulate policies to develop western and traditional Chinese medicine and to improve medical and health services". The then Secretary for Health, Welfare and Food (Now reorganised as Food and Health Bureau) conducted a public consultation on the development of Chinese medicine in the HKSARg in November 1997 to solicit public opinions. Based on the Preparatory Committee's recommendations and public views collected in the consultation, the Chinese Medicine Bill was introduced into the Legislative Council in February 1999 and was passed in July the same year (http://www.cmchk.org.hk/eng/main_deve.htm; accessed on 30th June, 2016).

From 1998 onwards full-time degree courses in Chinese Medicine were set up in three different local public universities recognised by the Government University Grant Council (HKUGC), though there were private colleges of TCM providing part-time courses in the past. There are presently three Schools of Chinese medicine offering fulltime (5-years foundation plus clinical internship) undergraduate degrees courses and par-time masters/post-graduate course at the Chinese University of Hong Kong (http://www.scm.cuhk.edu.hk/), Hong Kong Baptist University (http://scm.hkbu.edu.hk/en/home/index.php) and the University of Hong Kong (http://www.scm.hku.hk/). All undergraduate courses follow similar academic structure to those specified by the State Administration of Traditional Chinese Medicine in Beijing and placement/internship training in their respective teaching out-patient clinics and key TCM university hospitals in Beijing, Chengdu, Guangzhou, Nanjing, Shanghai, and Shenzhen. All courses are taught in three spoken languages when necessary (Cantonese, English and Putonghua) with biomedical curricula taught in English. The graduates have now fully integrated in services either in private practice or at the outpatient-clinics of public hospitals in the 18 districts and hospitals run by non-government organisations. The Hong Kong government University Grant Council has also provided research funding to help research and development of TCM since the mid-1990s.

In the early 2000s Hong Kong Department of Health launched the quality assurance programme on the Hong Kong Chinese Materia Medica Standards "HKCMMS" to develop standards for commonly used CMM in phases to ensure the safe use and the quality of CMM. The then Chief Executive highlighted in his 2009 Policy Address the importance of expediting the setting of standards for CMM commonly used in Hong Kong. It is in this context that the Department of Health embarked on the extension of CMM coverage to about 200 by 2012. The 2011/12 Policy Address of the Chief Executive had reaffirmed the government's commitment to the establishment of standards for CMM. Recently the "Hong Kong Chinese Materia Medica Standards (HKCMMS) Volume 7" was launched in June 2015; seven editions of the HKCMMS covering standards for a total of 236 CMM have been published. The research and development works of HKCMMS are done by institutes from local and overseas universities and the Chinese mainland regulatory/testing institutes, and research outcomes are deliberated and overseen by the International Advisory Board (IAB) consisting of 23 local and international renowned experts. The IAB gives advice on the principles, methodologies, parameters and analytical methods for the development of HKCMM standards. It also decides the contents of the HKCMMS, selects the research institutions to take up the research and laboratory work, and determines the target medicinal plants. The IAB usually meets once per 12 to 18 months to evaluate and endorse the research results. The overall guided principles are summarized in Box 6. (http://cmd.gov.hk/html/eng/index.html, accessed 30th June, 2016)

Box 6. Principles observed when drafting the HKCMMS

- to provide applicable and adoptable reference for the CMM trade;
- to ensure the safety and quality of CMM in protection of public health;
- to harmonize with the international standards; and
- to facilitate the trade in Chinese medicines.

3) The future development of TCM in Hong Kong. In the 2016 HKSARg government policy address, in response to the requests from the academia, industry sector, and TCM community together with the encouragement of the Nobel Prize in Medicine received by Tu You-You's research outcome on QingHaoSu[30], the HKSAR Government has been implementing the recommendations from Chinese Medicine Development Committee in phases: a) the launch of the Integrated Chinese-Western Medicine Pilot Project as new initiative Chinese medicine services by the Hospital Authority; b) the planning and establishment of a testing centre for Chinese medicines to be administered by the Department of Health on top of the completing the compilation of Hong Kong Chinese Materia Medica Standards for CMM commonly used in Hong Kong, and will launch a pilot study on the standard setting for Chinese medicines decoction pieces; c) personnel training and professional development, research and development for the Chinese medicines industry; and d) reserving a site to develop a Chinese medicine hospital. This has been a change for the good of TCM in Hong Kong after the 1997 return to motherland. (http://www.policyaddress.gov.hk/2016/eng/p232.html; access 30th June 2016)

Advance of Analytical, Biomedical and Computational Technology

The holistic integrity of CMM combination contained in the proprietary Chinese herbal medicines (PCM), which creates a challenge in establishing quality assessment and control of standards of the starting materials (crude materials and decoction pieces) and the standardization of finished herbal drugs because no single chemical marker component is contributing to the total efficacy of the herbal prescription[31,32].

Analysis of complex mixtures of TCM products depends heavily on instrumental and chemical analysis technology, which has been the key driving force for nearly all practical measurements in modern physical and medical sciences. Separation technology is an essential component in phytochemical analysis of ingredients in medicinal plants The introduction of unique hyphenated-chromatographic instruments coupled with sophisticated computer technology has allowed analysts to measure the chemical contents of extracts from herbal mixtures[33,34]. These analytical armaments have indeed provided analytical scientists to investigate complex mixtures in the phytochemical elucidation of ingredients in CMM as characteristics in a single CMM or mixtures in the finished products.

1. Application of chemometric analysis on chromatographic finger printing

This analytical approach has enabled the generation of chromatographic fingerprints, which represent a rational approach for the quality assessment of TCM products. Thus, chromatographic fingerprinting analysis of herbal medicines has contributed a comprehensive qualitative approach for the purpose of species authentication, evaluation of quality, and ensuring the consistency and stability of herbal drugs and their related products. The pragmatic comprehensive chromatographic fingerprinting analysis can disclose the detectable ingredients composition and concentration distribution under quantifiable operational conditions and therefore provide real-time quality information. However, this cannot entirely solve the holistic actions of the composite formulae or decoction pieces prescribed for treatment. It may leave a "grey" entity at the primary stage[31] Nevertheless, consecutive studies will be required to develop feasible technology to measure activity and improve the reliability of quality assessment and transparency of TCM products. Chemical fingerprinting pattern alone cannot reflect entirely the quality assurance of the composite/complex mixture products, bioactivity index to confirm the safety and mechanisms of action is needed before large scale of clinical studies for efficacy[35], is conducted as shown by the following example of Phytomic QC.

2. Linking chemical and biological fingerprints of CMM as quality assurance

Recently, Tilton and co-workers using finger-printing technology and gene-expression monitory, worked on the quality assessment of a TCM composite formula (Huang Qin Tang) which was developed as an product with intellectual property protection known as PHY906[36], consisting of four distinct CMMs: the roots of *Scutellaria baicalensis* Georgi. (Huangqin), *Glycyrrhiza uralensis* Fisch. (Gancao) and *Paeonia lactiflora* Pall. (Baishao), and the fruit of *Ziziphus jujuba* Mill (Dajao), which has been documented for nearly 1800 years for treating common gastrointestinal distress, including diarrhoea, abdominal spasms, fever, headache, vomiting, nausea, extreme thirst, and subcardiac distention. In addition to traditional pharmacopoeia analyses, such as heavy metal tests, microbial tests, pesticide residues, a multi-faceted approach, Phytomics QC, integrates (1) high resolution chemical fingerprint focusing on liquid chromatography/mass spectrometry (LC/MS); (2) bioresponse fingerprint with genomics technology on differential cellular gene expression; (3) animal pharmacology for in vivo validation and (4) a sensitive, quantitatively comparison method.

Phytomics Similarity Index (PSI) has been developed by the joint efforts of Yale University and PhytoCeutica, Inc. team to assure the quality consistency of different manufactured batches of PHY906. This kind of multi-faceted technology, trade-marked as "PhytomicsQC" is not only

Figure 1. Distribution of GP-TCM members within and beyond the EU. (A) Fifteen EU member states were involved in GP-TCM. They were Austria, Belgium, Denmark, Estonia, Finland, Germany, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Romania, Spain, Sweden and the UK, as highlighted by red dots. (B) Nine non-EU countries were involved in GP-TCM, including Australia, Burkina Faso, Canada, China, D.R. Congo, Norway, Russia, Thailand and the USA, also highlighted by red dots. [Ref: 38].

good for the quality control of such medicines, but also useful for the discovery of new indications or the development of new formulations. In addition to GMP conditions applied during production, good quality control analyses should include both chemical fingerprints and biological fingerprints of botanicals.

Over a ten-year period of development, the multiplex technology "Phytomics QC" has been used to show batch-to-batch consistency of PHY906 production. Advanced clinical trials are ongoing to demonstrate the effectiveness of PHY906 as an adjuvant therapy for cancer patients undergoing chemotherapy. PHY906 has eventually been approved by the Food and Drug Administration (FDA) to carry out Stage II-clinical trials[37].

The Challenge on Future Development of TCM Outside the Chinese mainland

1. Good Practices of TCM Research in the Post-genomic Era (GP-TCM)

The European Commission under its 7th Framework Programme (FP7) funded the project coined as 'Good Practice' in TCM Research in the Post-genomic Era (GP-TCM)[38], which assembled over 200 scientists and clinicians from 112 institutes in 24 countries (including nine non-European countries, see Figure 1) in collaboration and discussion, who had been actively involved in various disciplines in TCM research and TCM practice and active in clinical research, who took part during the period from May 2009 to October 2012. This consortium coordinated, met and deliberated how best to collect and review the published research data available from reliable journals, texts and reports over the good practice of TCM researches in 10 Work-packages covering quality, safety & toxicology, in vitro, in vivo laboratory methods, clinical research in TCM including acupuncture, and regulatory aspects of TCM and herbal products.

1.1 The formation of the FP-GP-TCM and GP-TCM Research Association

The consortium of GPTCM had provided a comprehensive review report submitted to the European Commission and published 20 peered review papers in the 2012 issue of Journal of Ethnopharmacology, volume 140, which are fully accessible to the public as an information dissimilation process[39-57]. Readers will find these 20 papers useful as they summarise reliable aspects of TCM research and practice since the post-genomic era and offer advice for future research and practice directions. Subsequently this consortium has been evolved in April 2012 to become the Good Practice in TCM Research Association (GP-TCMRA), which has continued the coordinating function of networking and collaboration with the aim of meeting annually, alternating in Europe and Asia, to exchange progress of TCM research work with global scientists and practitioners. (http://www.gp-tcm.org/). The comprehensive reports of the FP7-funded project can be accessed using the following website below: http://cordis.europa.eu/result/rcn/57511_en.html, accessed 30th June, 2016)

1.2 The outcomes of the GP-TCM project

The outcomes of this European funded project have been to achieve the objectives stated in the 10 work-packages described above, to approach and connect the multiplicity of expertise in working on TCM research and practice. It reflects the crucial continuing action is needed to expand networking, cross-cultural research collaboration and open-mindedness for scientific innovation and investigations that link the practice of TCM to the maintenance of good health and treatment of diseases. The key outcome of the EU

coordination project has been the formation of the Good Practice in TCM Research Association (GP-TCMRA), which was established on 16th April, 2012 in Leiden, the Netherlands. Box 7 summarises other key future actions for TCM development. (http://www.gp-tcm.org/2012/04/about-association/, accessed on 30th June 2016).

Box 7. Other key issues for future TCM development

- Disease-oriented studies using the approach of multi-indexed high-throughput technologies and systems biology analyses will be a preferred strategy for future R&D of TCM.
- International collaboration and harmonization is essential for regulation of good quality TCM products.
- Development, dissemination, implementation and refining of good practice guidelines in reviewing and publishing research findings on traditional medicine are matters of vital importance.
- Combining the systems biological investigations of mechanisms of actions of Chinese medicines, ensuing identification of potential biomarkers to be associated with both Western disease concepts and TCM pattern classifications and QOL instruments to monitor patient-reported outcomes, which are in the heart of personalized medicine, would offer common ground for integration.
- Effective pharmacovigilance is essential for the development of appropriate guidelines for safe, effective use of herbal medicines including those derived from Chinese materia medica.
- Structural alerts and *in silico*, *in vitro* and *in vivo* methods could be applied to predict the genotoxicity, teratogenicity and nephrotoxicity of Chinese medicinal products.
- Research in TCM syndrome differentiation will provide the basis of the molecular network of TCM syndrome differentiation for some disease types, in defining the potential mechanism of Chinese medicines

2. The demand of good quality herbal materials for prescribing and manufacturing

Materia medica and herbal products, referred as botanicals in North America, are essential phytomedicines for nearly 80% of the world population particularly in developing countries, where traditional medicine often depends upon[58]. Problems and difficulties arise in the quality assurance of herbal products due to unidentified chemical entities with unknown bioactive components. The uncertainty of how Chinese herbal medicine works, the safety and the incidents of adverse effects of substituted herbs[12] have urged the authorities in some countries to ban use of certain Chinese herbal medicinal (CHM) products containing potent CMM. For examples the use of Ephedra Herba and Aconitii radix and related species are banned from even very experienced TCM practitioners to prescribe in Australia, Northern America, UK and other countries in Europe[59]. Ephedra herba is a commonly prescribed CMM often in combination with other CMM in composite formulae (Fufang) while Aconitii radix, a very potent but useful CMM (when properly used) can only be prescribed by very experience TCM practitioners. In the 2000s, the Food and Drug Administration (FDA) in the USA, after reports of several deaths of misuse as weight-reduction or unsupervised use of over the counter supplements containing Ephedra herba, implemented a complete ban on the CMM (http://umm.edu/health/medical/altmed/herb/ephedra). Such an action does affect the practice of TCM as practitioners do not have access of this CMM for prescribing purposes.

3. Regulatory monographic standards of CMM in various pharmacopoeias

3.1 The Chinese Pharmacopoeia (CP, The Pharmacopoeia of the PRC)

The CMM monographs play a key role in the quality assurance of CMM for TCM practitioners prescribing herbal formulae (Fufang) to patients and TCM manufacturing industry as raw materials for their production of TCM products. One way of giving guidelines to ensure the supply of quality-ensured CMMs is to spell out monographic requirement assurance of herbs and herbal products. The monographic standard of a CMM as laid down in the Pharmacopoeia People's Republic of China (Chinese Pharmacopoeia, CP) is the minimum requirements for all assays and analytical limit tests for each of the CMM included in the CP. These include the characteristics as described in Box 8.

Box 8. Key characteristics described in a monograph of the Chinese Pharmacopoeia[60].

For crude CMM

Name: Official name of the CMM, Pinyin name, Chinese characters of the CMM.

Sources: Origin of medicinal plants with Latin name, collection conditions of dried plant part.

Description: Morphological appearance mentioning shape, size, texture, odour and taste.

Identification: Microscopic appearance of powdered CMM with range of size/shape measurements of distinguishable characteristics of the powdered CMM.

Analytical characteristics: HPTLC pattern; HPLC fingerprint;

Total ash value: Not more than an assigned limits determined from ethanol extraction guided by standard procedure.

Water content: Not more than an assigned limits, determined from ethanol extraction guided by standard procedure.

Extractives: Not less than an assigned limits determined from ethanol extraction guided by standard procedure.

Assay limits: Not less than an assigned limits, determined by an instrumental method (Measurable usually using HPLC, or GLC).

For processed CMM decoction pieces under the same monograph of the crude CMM

(Limit tests are similar to those the crude CMM but including the following descriptions)

Processing method: Assigned method or preparing the decoction pieces.

Property and Flavour: According to TCM characteristics, e.g. Warm; pungent etc.

Meridian tropism: e.g. acting on heart and stomach meridian.

Actions: e.g. to open the orifices and eliminate phlegm.

Indications: tinnitus and deafness, epigastric stuffiness and torpid intake etc.

Administration and dose: ranging from 3–10 grammes.

Storage: Preserve in a dry pace; protect from mould.

3.2 The European situation for non-TCM herbal drugs

In the EU there are monographs issued for all of them in common use. The Commission E in Germany has produced standard monographs for controlling herbal medicines. The European Scientific Cooperative on Phytotherapy (ESCOP) was founded in 1989, consisting of 14 European countries, as an umbrella organisation representing national herbal medicine or phytotherapy associations across Europe, especially in their discussions with European medicines regulators. ESCOP has commissioned the writing of standards provides state-of-the-art reviews (monographs) of the therapeutic use of leading herbal medicinal products, based on the latest evidence and on leading expertise across Europe. Recently an App for Apple and Android devices summarising over 100 ESCOP monograph is available to provide the uses, safety and quality standards of many European phytomedicines. With quality of herbal medicinal products assured the efficacy of them can be assessed by RCT before licenses can be issued. (http://escop.com/, accessed 30th June, 2016). ESCOP has the advisory role but the monographs are not legally binding with regulatory agency in Europe; they serve as reference purposes in that if the herbal products manufactured according to the quality standards laid down in the ESCOP the agency can grant clinical trial certificates for clinical studies before registration for as legal herbal medicines in the country concerned.

3.3 The European consideration on TCM drugs for inclusion in the EP

The increasing availability of imported CMM and related products from China in European countries recorded approximately US$ 12 million over the last few years. They do not fall in the same category of European herbal medicines. As such quality control is considered an important aspects to guarantee the safety use of TCM products by the European Directorate for Quality Medicines & Healthcare (EDQM). The EDQM is an organisation that protects public health by enabling the development, supporting the implementation and monitoring the application of quality standards for medicines and their safe use. These standards are recognised as a scientific benchmark world-wide. The European Pharmacopoeia provides a legal and scientific reference for the quality control of medicines. It is legally binding in 37 member states that have signed the Convention on the elaboration of a European Pharmacopoeia. In addition, the observers of the European Pharmacopeia Commission (including 7 European and 17 non-European countries) benefit from the European experience in work-sharing and harmonisation and have access to the scientific work in the quality control of medicines. For such guarantee on quality of medicines dedicated to human use the European Medicines Agency (EMA) collaborates closely with EDQM. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000574.jsp&mid=WC0b01ac0580789733; accessed on 30th June, 2016).

The Working Party of TCM (WPTCM)[61] was created in 2008 by the Pharmacopeia Europa (Ph Eur) Commission at the EDQM to oversee the elaboration of new Ph Eur TCM herbal drug monographs based on pre-existing monographs published in the Pharmacopoeia of the People's Republic of China (Also so known as Chinese Pharmacopoeia, CP). Recently, it was announced by the Chairman of the WPTCM at the International Summit of Future TCM held in Zhijiang on 29th May 2016 that 66 monographs of CMM, out of a total of 186 herbal drugs, have been included in the European Pharmacopoeia; targeting up to 300 monographs in the future. (http://www.chinanews.com/jk/2016/05-29/7887169.shtml; accessed on 30th June, 2016).

Evidently, there exist different aspects of the details in the deliberation of monographs between the EP and CP as indicated by the authors[61]. This is a good indication of the progressive cooperation in drafting pharmacopoeia monographs for Chinese materia medica between China and EU to focus on good quality of starting materials for TCM products in the future market of the European sector. There remains further harmonization can be achieved on the standardisation of CMM, the starting herbal materials for TCM prescription use and possibly for future manufacturing of TCM products.

3.4 The North America sector and other regional progress in drafting herbal monographs

Quite separately other institutes in the North America sector such as the American Herbal Council, which provides critical information for the American Herbal Pharmacopoeia, have also included herbal monographs on TCM materials with the help of colleagues in China and other countries focusing on TCM and other traditional medicines giving critical reviews on TCM herbal materials as quality assured monographs. These monographs represent the most comprehensive and critically reviewed body of information on herbal medicines in the English language, and serve as a primary reference for academicians, health care providers, manufacturers, and regulators. It is a non-government run organisation, hence the PDF of the monographs can be purchased online. (http://www.herbal-ahp.org/, accessed on 30th June, 2016). On the other hand the Herbal Medicines Compendium (HMC), published by the U.S. Pharmacopeial Convention (USP), is a freely available, online resource that provides standards for herbal ingredients used in herbal medicines. Standards are expressed primarily in monographs, containing general information; these include: the definition of the herbal ingredient relative to the monograph title and then follows with a specification. The specification contains tests for critical quality attributes of the herbal ingredient and includes analytical test procedures and acceptance criteria for specified tests. USP's HMC employs validated analytical procedures for the tests specified in its monographs, using state-of-the-art analytical techniques and allied reference materials. Additional analytical methods and approaches may be referenced in general chapters, which also are available online. Some of the key experts on TCM monographs from the CP in China also serve as USP Council Experts, which is the body that makes the organization's

scientific and standards-setting decisions. When coupled with sound registration processes and manufactured according to suitable Good Manufacturing Practices, standards in HMC can become an important part of the safety net that helps ensure access to good quality herbal medicines. http://hmc.usp.org/about/about-the-herbal-medicines-compendium, accessed 30th June, 2016

3.5. Herbal monographs related to TCM from other countries and regions

Countries and other regions have their own pharmacopoeia focusing on required standards for herbal medicines and products available in their communities. Some of these regulations also cover TCM products. An overview the regulations of Chinese materia medica in various countries and regions indicated there are wide variation of requirements for the quality control on herbal products[15,51]. Box 9 summarises some of the key agencies, which provide standards in their national pharmacopoeia on herbal materials. The overview also suggests that the fast growing demand worldwide for traditional medicines calls for harmonised monographic standards to safeguard quality and safety of herbal products to the public.

Box 9. Agencies provide on standards for herbal medicines (Modified and updated from Reference 15)

(**WHO**: World Health Organisation; **CFDA**: State Food and Drugs Administration, China; **EDQM**: European Directorate for Quality Medicines and Healthcare, European Union; **DH**: Department of Health, Hong Kong Special Administrative Region, China; **MHLW**: The Ministry of Health, Labour and Welfare, Japan; **TFDA**: Thai Food and Drug Administration, Thailand; **BPC**: British Pharmacopoeia Commission, Medicines and Healthcare products Regulatory Agency, UK; **TGA**: Therapeutic Goods Administration, Australia; **ABC**: American Botanical Council, USA; **NNHPD**: Natural and Non-prescription Health Products Directorate, Canada)

• *WHO Monographs on Selected Medicinal Plants*	**WHO**	Unofficial
• *Chinese Pharmacopoeia*,	**CFDA**, China (CN)	Official
• *European Pharmacopoeia*	**EDQM**, EU	Official
• *Hong Kong Chinese Materia Medica Standards*	**DH**, HKSARG, CN	Official
• *Japanese Pharmacopoeia*	**MHLW**, Japan	Official
• *Thai Herbal Pharmacopoeia*	**TFDA**, Thailand,	Official
• *British Pharmacopoeia*	**BPC**, MHRA, UK	Official
• *Australian Regulatory Guidelines for Complementary Medicines*	**TGA**, Australia	Official
• *American Herbal Pharmacopoeia (AHP)*	**ABC**, USA	Unofficial
• *Regulation of Natural & Non-prescription Health Products*	**NNHPD**, Canada	Official

4. Global view on adverse reactions and interactions of TCM with pharmaceutical drugs

Traditional medical systems such as TCM have been used with accumulated experience, and refined over a long period of recorded clinical use, and include well-defined formulary of processing and combination of CMM according to the individual patients' constitutions to maximise efficacy and minimise toxicity. In general, such selection of CMM perceived as harmless, some do exhibit low level or non-symptomatic toxicity and indeed many toxic herbs showing adverse drug reactions (ADRs) have been identified only via painful experience or serendipity; some incidents of wrong supply of intended material exist as in the case of aristolochia species[12]. Because of the vast amount of herbal medicines and related products on the worldwide market and the variability of regulatory control of herbal products in different regions together with poor budgets or support available for herbal research; relatively few reports on the basic scientific assessment of herbal products appear in the literature or official reports from regulatory agencies. Serious ADR events regarding TCM mainly concern those CMM such as *Aconitum* species, which are used very rarely in countries outside China because they are banned from the market and for prescribing[59]. But these potent CMMs are restricted to experienced-based prescribing by registered TCM practitioners.

4.1 An overview on adverse drug reactions to TCM

In a recent overview on adverse drug reactions (ADRs) to traditional Chinese medicines[13], it was pointed out that the safe use of CMM and products in traditional Chinese medicine (TCM) practice conventionally relies on correct pharmacognostic identification, good agricultural and manufacturing practices based on pharmacopoeia standards and rational/correct CMM combinations with TCM-guided clinical prescribing. The experience-based principles on using prescribed formulae of several CMM may not absolutely ensure safety without assurance of proper supply of the herbal materials for detailed toxicological investigations when compared with development of new pharmaceutical drugs. Clinically observed toxicity reports remain as guidance for gathering toxicological evidence, though essential as pharmacovigilance, but are recognised as late events for ensuring safety and can be considered for future awareness and prevention. (See Box 10).

Box 10. High-lighted key points on ADRs in the overview

- Global development of TCM that has affected conventional healthcare as the lay public can easily access unsupervised treatment or health/medicinal products
- Examples of key toxic substances in some CMMs, which are not for general availability but only for restricted TCM-experience-based prescribing;
- Presence of wrong CMM species or contaminants such as pesticides residues, heavy metals and other toxins in CMMs, which fail monographic standardised limit tests, should be rejected, are sources of ADRs in herbal medicines
- Lack of pre-clinical tests before TCM products are used vs well-tried and experience-based TCM prescribed use.
- Regulations of ADR reporting and monitoring was formally set up in 2004 overseen by the China National Centre for

(To be continued)

(Box 10. Continued)

Adverse Drug Reaction Monitoring under the guidance of CFDA, on pharmacovigilance of ADRs related to pharmaceuticals and TCM products[62].

- Reported adverse drug reactions (ADRs) consequential to taking CMM and TCM products by academic circles as literature report/overviews may provide useful pharmacovigilance reference to the occurrence of ADRs[63].
- Proposals on rational approaches to integrate biomedical science and the principles of TCM practice for detecting early ADRs if TCM products and orthodox drugs are involved.
- Emphasis on good control of the quality and standards of CMM and proprietary Chinese medicines can certainly reduce the incidence of ADRs in TCM practice when these medications are under prescribed or guided usage.

A separate expert opinion paper on issues of ADRs methodology focused on the toxicity of herbal medicines appears in the *Science magazine,* which provides guidance on researching ADRs: "Recent advances in functional-omics and bioinformatics now allow the investigation of efficacy and toxicity at systems levels. The modulation of multiple pathways and end-points induced by numerous components can be determined, to enable the elucidation of mechanisms of action and potential threshold behavior for the mixtures. When developed and validated for use on herbals, these methods will enhance the detection of insidious toxicities, providing the necessary background information for effective extended pharmacovigilance of specific herbal medicines. *In vivo* classical tools are still a cornerstone for toxicological evaluation, but appear ill-suited to study multi-component and variable herbal mixtures"[64].

4.2 Dealing with combined use of TCM and pharmaceutical drugs in healthcare

Due to the advances of multimedia to provide information on health and disease matters, the public are more aware or informed, mainly via the Internet, about health and medical products. People become more knowledgeable about matters relating to their health conditions and well-being in curing and preventing illnesses. The author has taken on the task of publishing a comprehensive review, based on previously published text book[65] and current literature, on the topic of interactions between conventional pharmaceutical drugs (PD) and TCM products while focusing on the harmful or beneficial effects of such combined intake with examples from reported clinical studies and interpretation of possible mechanisms of actions[66]. It is feasible to set up laboratory protocol to screen commonly prescribed CMM products against those groups of PD with potential adverse effects when combined with other substances. Many in vivo animal models can be used to screen drug interactions between herbs and drugs. Pharmacokinetic and pharmacodynamic correlation may be achieved using these in vivo models. Pharmacokinetic clearance of PD in presence of CMM products can be studied using in vivo models. The data obtained are useful qualitative guidelines and reference alerts for clinical practice in integrative medicine involved TCM and MSM, but they are not considered as clinically relevant in actual patient care unless the patient's response involved life-threatening danger or irreversible damage. In most literature reports, when ADRs arisen due to TCM-PD interactions or other complementary medicines alone, supportive measures are carried out while the suspected interacting TCM or PD are withdrawn and close observations on patient's clinical conditions are monitored[63]. Accumulation of individual cases of TCM-PD interactions from clinical observations will provide information for further laboratory confirmation. In general PD-PD or TCM-PD interactions may produce enhanced drug effect that is synergistic; the outcomes of interactions may be beneficial or harmful can be classified as:

1) Major: if life-threatening or permanent damage occurs;
2) Moderate: if additional treatment is required; or
3) Minor: if the therapeutic outcome is unnoticeable or not affecting desired therapy goals.

4.3 Harmful effects of TCM-PD interactions

Patients often self-medicate themselves with various health products and over-the-counter medicines apart from prescribed pharmaceutical drugs (PD). Some of those non-prescribed products may have doubtful quality control and contain harmful additives or unchecked ingredients such as pharmaceutical drugs; thus their usefulness is in doubt. The increasing popularity world-wide of using traditional Chinese medicines (TCM) and related over-the-counter (OTC) functional products has raised concerns over their concomitant use with PD and the consequential adverse effects. In most cases the alleged causes of ADRs are linked with herbal sources, although the authorised information on the interactions between TCM-PD is not plentiful in the literature. Most pharmaceutical drug-drug-interactions are related to interference of the pharmacokinetics and pharmcodynamics of the drugs taken simultaneously; thus prescribers should be aware of multiple drug treatment regimes and unintentional co-administration or self-administration. Some of the interactions can be predicted to avoid or changed to other treatment regime, from the properties (pharmacological and physic-chemical as well as pharmacokinetic characteristics). Those that cannot be predicted can be considered as the dynamic interactions at receptors or enzymes systems not clear or idiosyncratic outcomes related to the patient's constitution or disease status (Both MSM and TCM aspects). Key guiding principles on dealing with available information during treatment period are listed in Box 11.

Box 11. Key alert pointers in PD-PD and PD-TCM: Criteria, drug groups, mechanisms

- Drug properties include: Drugs used in multi-drug regimes drugs with narrow therapeutic window during treatment; drugs exhibit accumulation; enzyme induction and metabolic polymorphism.
- Drug groups include: Antacids, Anti-arrhythmics, Anti-asthmatics, Anti-coagulants, Anti-convulsants, Anti-diabetics, Anti-hypertensives, Cardiac glycosides, Cytotoxics, Psychotropics

(To be continued)

(Box 11. Continued)

- Suggested mechanisms: PD-TCM forms complex leading to treatment failure; Transport impairment causing reduced effects TCM affecting PD diuretics & body electrolyte imbalance; TCM glycosides or other ingredients destroyed by acidic PD; TCM ingredients interfere with PD liver metabolism resulting in enzyme inhibition/induction and alteration of PD efficacy

4.4 Beneficial effects of TCM-PD interactions

Experience of integrated MSM and TCM medical practice in China has provided experience of, since the 1950s through experience of practice and recorded case studies, beneficial treatment observations and outcomes with probable explanation or possible mechanisms of interactions between TCM and PD, although more experimental research and clinical evidences are needed to confirm such observations with significant evidence accepted by the MSM circle. This is partly because the MSM gold standard of randomised clinical trials (RCT) is not entirely applicable in the individualised approaches for treatment in CM practice in personal medicine. These case studies were abstracted from medical journals published in China and have been translated into English and edited by the author and co-worker for presentation in the text[65]. The tentative categories of case studies, which illustrate synergy effects of treatment consequential to co-administration of PD and CM medications are summarised in Box 12.

Box 12. Examples of clinical studies indicate beneficial interactions between TCM-PD

- Antibiotics with TCM products producing added beneficial effects
- Treating infection with antibiotics and immune-strengthening TCM products
- Augmenting cardiovascular PD treatment with TCM products
- Augmenting anti-inflammatory action of PD with TCM Products
- Reducing adverse effects due to PD chemotherapy of cancers by TCM products

Many other examples of clinical cases and larger clinical trials have been published in Chinese languages and a review published in 2005 summarises systematically in English language the CMM's role to function as key TCM drugs augmenting the beneficial contribution to the mechanisms as beneficial agents in the treatments indicated[67].

Under these circumstances, there is an urgent need to compile such database. The future professionals in health and medical care should be knowledgeable or aware of what their patients have been taking or given. In actual practice the patients may receive both treatments intentionally or unintentionally, with or without the awareness of the practitioner. In these situations a reliable database for interactions between TCM-PD will be extremely useful for consultation when integrative TCM-PD treatment problems appear or during emergency situations. Their combining of medications may be involved with possible outcomes of adverse reactions or beneficial effects. Such a database will be welcomed by both practitioners of TCM/herbal medicines and MSM practitioners in the emerging trend of integrative medicine[66].

5. Integrative science and medicine in future global clinical development of TCM

To promote TCM to be accepted globally into mainstream medicine and healthcare systems, it is important that up-to-date science and technology can be implemented to interpret the basis of TCM diagnosis and treatment and the assurance of the quality, safety and efficacy of TCM products and treatment modalities. Previous sections on the advances of analytical, biomedical and computational aspects of technology are equipped for the purposes of modernisation in assurance and control of the quality and safety of CMM. Innovative development of methodology to provide evidence of mechanisms of actions in pre-clinical studies of TCM composite formulae (Fufang, consisting of multiple CMMs) and their efficacy in clinical trials as well as TCM treatment approaches require further consideration.

5.1 Linking systems approaches in MSM and TCM principles

The systems biology approach to MSM, recently adopted into biomedical fields, offers the potential to investigate if the principles can be applied to integrate with TCM[68]. The systems biology approach of patient profiling using modern genomics, proteomics and metabolomics technologies[69-70] is a perfect match for the systems diagnosis in TCM[71]. Integration of these approaches may reveal different groupings or sub-phenotypes of patients, which require individualised treatments. Moreover, knowledge about the biological mechanisms behind the personalized herbal formulas used in TCM is expanding through modern herbal chemical and genomic profiling techniques[72-73].

Both TCM and MSM science describe life as a complex, dynamic, non-linear system. As OM scientists discovered the non-linear behaviour of cytokine networks, TCM practitioners and scientists have recognized non-linear patterns in how symptoms change in patients[74]. The fractal properties of the arteries, lungs and heart rate resemble the fractal thinking in TCM[74]. In both sciences, life is considered a self-balancing system for organisation of body functions that is far from equilibrium. Systems thinking can build the cultural, philosophical and scientific bridges that are necessary to share understanding between the two sciences. By studying tools and techniques developed in both the TCM and MSM medical systems, new insights will emerge that are necessary to heal the patient, under his environment and the world he lives in[75-76].

5.2 Progress of biomedical and clinical studies in TCM

In a 2010 review on the situation of clinical trials of TCM in the past decade, including systematic reviews and meta-analyses on TCM clinical trials either focusing on the

treatment of diseases with TCM principles approaches or focusing on one TCM herbal product, on TCM studies either with randomization controlled trial (RCT) methodology or general observation, the authors observed, from the first systematic review of TCM clinical research published in 2002[76], to more clinical trials have also been published internationally[77], and, which has consequently increased the number of systematic reviews (SRs) and meta-analysis of TCM clinical trials[78].

The authors of the 2010 studies summaries the following key points of their observations[76] (Box 13):

Box 13. Observation of TCM clinical studies over a 10 years period

- Most RCT studies of TCM have more methodological limitations than conventional medicine according to some reports[78], although increasing attention have been paid to quality control of the studies;
- More RCTs with higher quality in the future to meet the needs of modern research and development, and that the quality of RCTs will be improved with the generalized RCT registration, standardization of clinical research, and the promotion of evidence-based medicine;
- The innovative design of a RCT with integrating pattern information and disease diagnosis for group classification according to TCM syndrome differentiation will certainly explore more valuable contribution of TCM treatment;
- Meta-analysis as a high-level evidence would increase as there will be increasing amount of high-level, high-quality data to support the systematic review;
- RCT panel studies of TCM formulated products demonstrated that monitoring biomarkers and patients reported outcomes (PROs) before and after intervention with these products can assess efficacy of the TCM products.

5.3 The Health-Related Quality of Life (HRQOL) Instrument for TCM research: ChQOL

It is acceptable that Quality of Life (QOL) indicators are often used as secondary outcome indicators in many clinical studies in conventional MSM. However, the efficacies of TCM treatment using conventional QOL have not been particularly evident in TCM studies. There is a general impression among TCM practitioners that the currently available QOL instruments may not be sensitive enough to detect the health changes that are regarded as important in treatment using TCM. For examples, in TCM diagnosis and treatment regimens, appetite and digestion, routine of urination and bowel, facial and lips colour, spirit in the eyes and adaptation to climates and seasons are very important indicators of health status under the TCM's diagnosis. However, these indicators are usually not included in common health related QOL (HRQOL) measure. Through the development of Chinese medicine based QOL (ChQOL)[79] it is feasible to assess patient-reported outcomes (PROs), generated from ChQOL instrument administered to patients before and after treatment intervention, as a measure of treatment efficacy. PROs include not only health status and quality of life but also reports on the satisfaction with the treatment and care, the adherence to prescribed regimens when directly related to end-result outcomes. Further treatment-related decisions are based on a combination of objective and PROs subjective parameters. The PROs concept is actually similar to one of the four diagnostic methods in TCM: "Interrogation", which has been used since the beginning of TCM, and is a very effective diagnostic and evaluation method in TCM.

The development of the Chinese quality of life (ChQOL) instrument based on the diagnosis and treatment of TCM[79], has allowed us to investigate its application to record patients' feedback as patients' reported outcomes (PROs) after the intervention of TCM treatment or receiving TCM prescription containing mixtures of Chinese materia medica (CMM) or proprietary Chinese medicines (PCM). The opportunity of recording objective and subjective outcome indicators such as biomarker, PROs & HRQOL, and TCM practitioners' treatment records, respectively can also be applied to the evidence-base approaches for assessing TCM treatment efficacy on individual patient cases[79]. This instrument can be a bridge that integrates TCM with conventional MSM and healthcare to assess the efficacy of TCM treatment. The ChQOL instrument has been applied to study patients with congestive heart failure[80] and RCT panel studies of PCM of products containing multiple CMM as a health product[81], in patient suffering from hepatitis[82], in metabolic syndrome[83] and asthma[84]. The evidence level of case report and panel study will be improved and ascertained by applying innovative analysis with modern informatics processing technologies. These new approaches will be more suitable for case reports and panel studies and may pave the way for ascertaining TCM principles of holistic approaches to diagnosis and treatment of diseases and individualized treatment for patients.

Through such integrative approaches utilizing the superiorities of both medical disciplines the future clinical research and practice will be able to provide evidence-based outcomes for TCM practice and products development.

Of particular emphasis to apply such integrative approach, it is feasible that future development of TCM products can be applied towards high burden diseases (See Box 14), which are under the top healthcare agenda in most developed regions worldwide.

Box 14. Examples of key high burden diseases
(Modified and updated from reference 66)

- Cardiovascular system (CVS): hypertensive complications; metabolic syndrome related diseases including cardiovascular complications after stroke attacks; diabetes related CVS complications; vascular dementia
- Central nervous system (CNS): ageing related diseases such as Alzheimer diseases nonvascular dementia; Parkinsonism diseases or related central nervous complications induced by inflammation
- Endocrine system: hormone related cancers (breast, cervical, prostatic cancers)
- Immunological system: inflammatory processes induced complications including rheumatoid arthritis areas of

(To be continued)

(Box 14. Continued)

immune-suppressant medications after surgery centrally affected inflammation-induced CNS diseases

- Transmitted diseases/infections: sexually transmitted/contacted incidents, contaminated blood containing AIDS virus, and Hepatitis B & C; Malaria infections; MRSA; specific viral flu.

6. The integrative approaches for R&D of TCM products for markets outside China

Manufacturers of TCM products are now required in China and other countries worldwide to comply with good practice in manufacturing (GMP). They need to ensure and ascertain the quality of the starting CMMs are in line with the regulatory requirement of minimum pharmacopoeia standards, with good agricultural and collection practice (GACP). Quality assurance of the starting CMMs including decoction pieces and aqueous granules for TCM practitioners' prescribing needs is now the responsibility of manufacturers. They should be aware of and apply the advance technology indicated under the Section for Advance of Analytical Biomedical and Computational Technology for the quality and safety assurance of their products according to pharmacopoeia standards, which are the basic requirements for the initial stage for the herbal markets to satisfy the TCM practice need of prescribing.

6.1 Develop niche TCM drugs focusing on high burden diseases as future targets

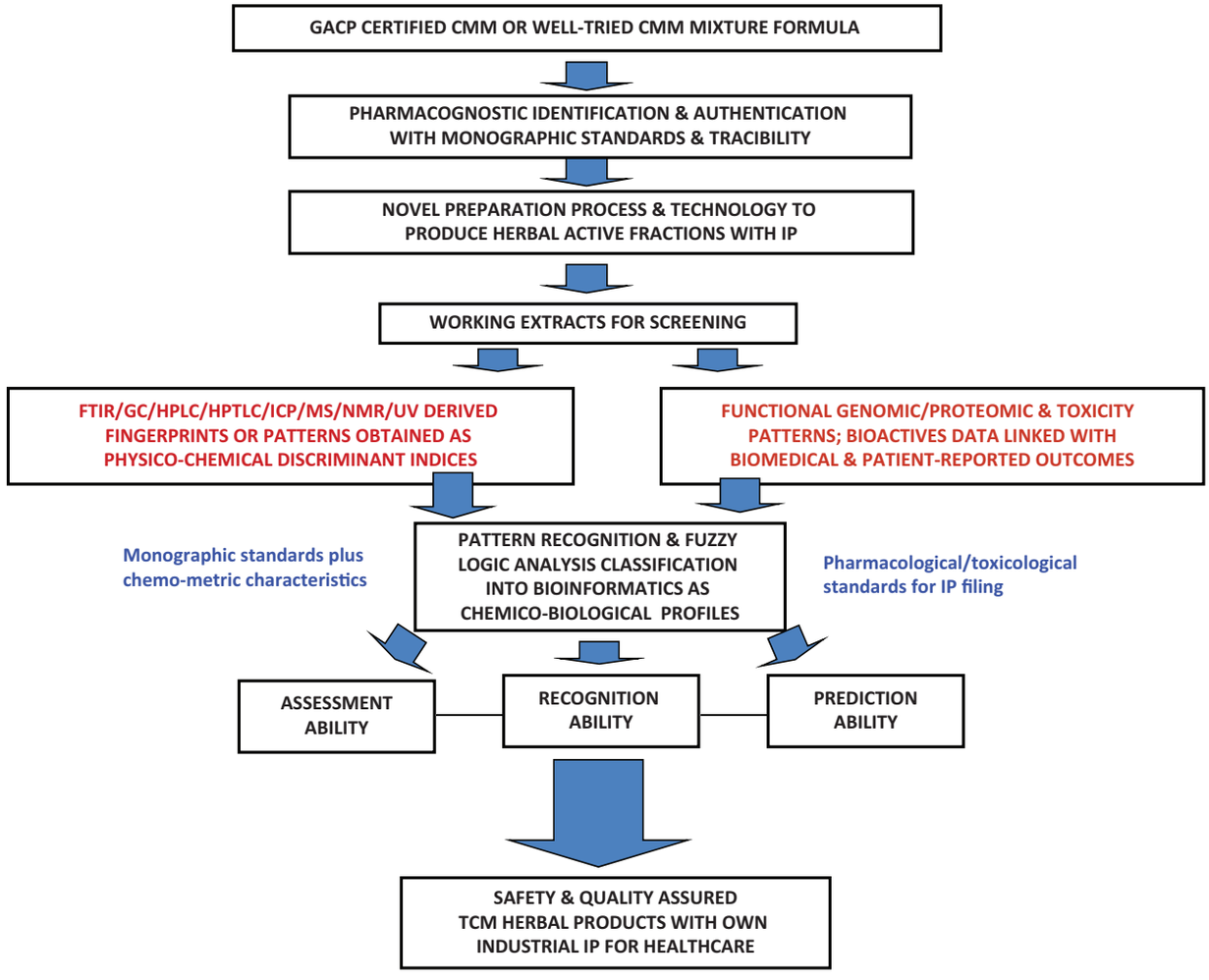
Current worldwide research in drug discovery from medicinal plants involves a multifaceted approach combining botanical, phytochemical, biological, and molecular techniques. Medicinal plant drug discovery continues to provide new and important leads against various pharmacological targets including cancer, HIV/AIDS, Alzheimer's, malaria. Even with all the challenges facing drug discovery from medicinal plants, natural products isolated from medicinal plants can be predicted to remain an essential component in the search for new medicines[1].

However, for TCM manufacturers to compete with conventional pharmaceutical drugs counter-parts they should focus on niche and innovative products via specific R&D programmes with patterned products line based on TCM medicinal plants sources whether as products from single-herbal or multiple TCM formulae. They should also be knowledgeable about the patent policy[85] and regulatory requirements for registration of herbal products in the countries or regions they aim to enter[51], which should be unique for survival of a very drug industry worldwide. In the recently published overview on understanding interactions of TCM-PD[66], it was pointed out that the areas of importance and interest in integrative approaches can focus on the high burden chronic diseases where most national health systems in developed regions experience high and escalating cost in the high burden diseases. It is feasible to include those sexually transmitted and acquired diseases consequential to contacts with contaminated blood sources or infected environments as indicated in Box 14 where both TCM and MSM practices can contribute with great successes if proper collaborations can be arranged.

6.2. Improved RCT design with TCM syndrome differentiation to stratify patient group and PROs

Disease-oriented studies using the approach of multi-indexed high-throughput technologies and systems biology analyses will be the preferred strategy for screening bio-active ingredients in the future R&D of TCM. Combining the systems biological investigations and functional "omics" to elucidate the pre-clinical mechanisms of actions of Chinese medicines/acupuncture will ensure the identification of potential biomarkers to be associated with both Western disease concepts and TCM pattern classifications[37,47]. When these data are available they will provide information for design of future clinical studies where TCM pattern differentiation will facilitate the stratification of patient groupings before clinical trial investigations[57]. Guidelines for RCT trials investigating TCM products should now be available to gear integrative approaches in applying stratified patient groups to increase the probability of useful outcomes[49]. Over the past decades, increasing numbers of clinical trials on TCM treatment efficacy have emerged and we predict that there will be more RCTs with higher quality in the future to meet the needs of modern research and development, and that the quality of RCTs will be improved with the generalized RCT registration, standardization of clinical research, and the promotion of evidence-based medicine (EBM). The worldwide focus on clinical trials in TCM will continue to increase. However we are in need of modified modalities that can focus on the assessment of TCM diagnosis and treatment outcomes of the holistic and individual approach[76]. Based on accepted and recognised models such as Interaction Rules Mining, informatics analysis of data from TCM diagnosis and treatment principles can contribute to the understanding of how the complex mixture of CMM are related to the principles of TCM formulary in treatment of diseases[57].

More importantly, communications between the two different medical modalities needs to be dynamic to facilitate optimal healthcare for the individual measures of treatment outcomes. Including quality of life instruments such as ChQOL[57] or disease-specific instrument with TCM characteristics as a tool for monitoring patient-reported outcomes linked to biomedical markers is another evidence-based measurement for R&D of PCM part from measuring TCM practice treatment indicated before[57]. The use of TCM-specific QOL instrument coincides with the fundamental initial diagnostic measurement in TCM of 'asking questions' which gathers information on the overall health conditions of the patient. This is the heart of personalized medicine and would offer common ground for integration[79]. All these factors can be further linked with mathematical and computational approaches (such as chemometrics) as mentioned earlier[31,32]. The uniqueness of TCM product development at the R&D stages where novel extraction technology and quality assurance with unique pattern characteristics can provide patent rights[85]. Figure 2 illustrates the whole flow steps in development of patentable TCM products.



Modified from: **Chan K (2005) *Journal of Ethnopharmacology*, 96: 1-18**

Figure 2. A scheme proposed for future development of TCM products for high burden diseases.

CONCLUDING REMARKS

Applying bioinformatics technology in collecting and deciphering TCM data depends on the collective combination of knowledge from the fields of information technology, biomedical sciences, statistics, and TCM practice. Combining the strengths of each is essential to improving the quantitative analysis of TCM and broadening our knowledge of the principles that underlie its effectiveness. Continuing feedback between the scientists and practitioners in each field will help us to refine the analytical techniques used for evaluation. Good practice in bioinformatics focusing on TCM will integrate the data from various disciplines of TCM practices, R&D investigations of quality control and standardisation, mechanistic studies, ADRs reports, and regulatory requirements as well as training skills for practitioners will provide valuable information for future modernisation of TCM. The use of good quality big data for future reference and analysis will give bench-marks for improvement and adjustment in order to keep up with advances in biomedical fields[86].

The way forward to identify evidence-base in TCM practice requires multidisciplinary collaborations among different professionals of both MSM and TCM practices with expertise from biomedical, bioinformatics, pharmaceutical and TCM disciplines. There is still a lack of human resources to take up the integrative medical research and practice worldwide. The new wave of general practitioners should be trained in the practice and science of TCM with integrative medicine knowledge. If mainstream medical practitioners have some understanding of the principles of TCM, which is supported by scientific methodology, there would be less opposition and more acceptance of TCM practice. The creation of collaborative networks is vital to overcome these differences so that international, multi-centre clinical trials are comprehensively planned and executed. These opportunities will help define workable integrative medical models for future clinical practice settings.

Due to the advances in biomedical, chemical and computational technology, multidisciplinary approaches for investigating evidence-based aspects of TCM practice are essential[87]. Research linking the quality control in the manufacturing of TCM products[88], relatively new systems biology and experience-based TCM principles is vital to interpret the holistic approach of TCM towards its

integration into mainstream medicine[47,69,71]. However, to achieve these objectives, an integrative approach is crucial to connect the multiplicity of expertise. Networking, cross-cultural research collaboration and open-mindedness are needed to support the scientific innovation and investigations that link the holistic practice of TCM to the maintenance of good health and treatment of diseases. Continuing effort in combined scientific methodology and TCM practice in R&D is the key to providing new knowledge for training the newer generation of human resources in integrative medicine that involves TCM practice.

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REFERENCES

1. Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. *Life Sciences* 2005;78:431–441.
2. Chan K, Lee H. Chapter 1: The Historical Evolution of Chinese Medicine and Orthodox Medicine in China, In: *The Way Forward for Chinese Medicin*. UK: The Taylor and Francis Group, 1st Edition, 2002:1–21.
3. Williamson EM, Chan K. (2014) Chapter 9: A brief review of the evolution of herbal medicine in European and its relationship with modern medicine. In: *Phytotherapies: Efficacy, Safety and Regulation*, edited by Iqbal Ramzan. American: John Wiley Inc, 2014.
4. American Chemical Society International Historic Chemical Landmarks. *Discovery & Development of Penicillin*. http://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html (accessed 28th December, 2015)
5. WHO. WHO Traditional Medicine Strategy 2014-2023. ISBN 978 92 4 150609 0;2013.
6. Robert Thong's SciTechStrategy Blog. Root causes of the pharmaceutical R&D productivity crisis. http://scitechstrategy.com/2015/03/root-causes-of-the-pharmaceutical-rd-productivity-crisis/ (accessed 17th February, 2016)
7. Chan K. Chinese medicinal materials and their interface with Western medical concepts. *Journal of Ethnopharmacology* 2005;96(1–2):1–18.
8. Helmut Kaiser Consultancy. *Traditional Chinese Medicine with Overview Worldwide: Market, Development, Products and companies*. Homepage: (www.hkc22.com); E-mail: hku-tuebingen@t-online.de.
9. Collins FS, Green ED, Guttmacher AE, Guyer MA. A vision for future genomics research. *Nature* 2003;422:1–13.
10. Chan K, Robinson N. How can we optimise research integrating TCM with conventional healthcare practice? *Forschende Komplementarmedizin* 2013;20(Suppl1):59.
11. Atherton DJ, Sheehan MP, Rustin MH, Whittle B, Guy MB. Treatment of atopic eczema with traditional Chinese medicinal plants. *Pediatric Dermatology* 1992;9(4):373–375.
12. Vanherweghem JL, Depierreux M, Tielemans C, Abramowicz D, Dratwa M, Jadoul M, Richard C, Vandervelde D, Verbeelen D, Vanhaelen- Fastre R, Vanhaelen M. Rapidly progressive interstitial renal fibrosis in young women: Association with slimming regimen including Chinese herbs. *Lancet* 1993;341(8842):387–391.
13. Chan K, Zhang H, Lin Z-X. An overview on Adverse drug reactions to traditional Chinese medicines. *British Journal of Clinical Pharmacology* 2015;80(4):834–843.
14. Chan K. Some aspects of toxic contaminants in herbal medicines. *Chemosphere* 2003;52(9):1361–1371.
15. Chan K, Leung KSY, Zhao SS. Harmonization of monographic standards is needed to ensure the quality of Chinese medicinal materials. *BMC-Chinese medicine* 2009;4:18.
16. Chan K, Hu X, Razmovski-Naumovski V, Robinson N. Challenges and opportunities of integrating traditional Chinese medicine into mainstream medicine: A review of the current situation. *European Journal of integrative medicine* 2015;7(1):67–75.
17. Landau MD. Medical schools embrace alternative medicine. http://www.usnews.com/education/best-graduate-schools/articles/2011/04/12/medical-schools-embrace-alternative-medicine?page=2 (Access 18th February, 2016).
18. Scheid V, MacPherson H. *Integrating East Asian medicine into contemporary healthcare*. United Kingdom: Churchill Livingstone, Elsevier; 2011.
19. Pan SY, Litscher G, Gao SH, Zhou SF, Yu ZL, Chen HQ et al. Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources. *Evidence Based Complementary and Alternative Medicine* 2014;2014(1):525340.
20. Atherton D. Chapter 19. An orthodox practitioner's view of Chinese medicine. In: *The Way Forward for Chinese Medicine*, edited by Chan K & Lee H. Publisher: The Taylor and Francis Group, 1st Ed 2002, ISBN: 0-415-27720-5, p397–411.
21. Jin Y, Berry M, Chan K. Chinese herbal medicine in the UK. *Pharmaceutical Journal* 1995;255(Suppl.):R37.
22. Chan K. Critical assessment of traditional Chinese Medicine in the Far East, *An official report submitted as the fulfillment of Churchill Traveling Fellowship*. London: Sir Winston Church Memorial Trust 1996.
23. Lee H, Chan K. A curriculum model for teaching and training Chinese medicine in English language. In: *The Way Forward for Chinese Medicine*, edited by Chan K & Lee H, 1st Ed Chapter 18. Publisher: The Taylor and Francis Group 2002:379–395. ISBN: 0-415-27720-5.
24. Report of the UK Herbal Medicines and Practitioners Working Group. [https://www.gov.uk/government/publications/advice-on-regulating-herbal-medicines-and-practitioners] (published on 26th March 2015).
25. Public Statement from dissenting members of the Herbal Practitioner and Medicines Working Group to Department of Health (DH). https://www.gov.uk/government/publications/advice-on-regulating-herbal-medicines-and-practitioners.
26. Li GQ, Duke C, Roufogalis BD. The progress of Chinese medicine in Australia. In: *The Way Forward for Chinese Medicine*, edited by Chan K, Lee H; Publisher: The Taylor and Francis Group, 1st Ed Chapter 10, 2002:379–395, ISBN: 0-415-27720-5.
27. The National Institute of Complementary Medicine, Western Sydney University, Australia:www.nicm.edu.au.
28. Zhang AL, Story DF, Lin V, Vitetta L, Xue CC. A population survey on the use of 24 common medicinal herbs in Australia. *Pharmacoepidemiology and Drug Safety* 2008;17(10):1006–1013.
29. Hong Kong SAR ranks first at the index of world economic freedom. https://en.wikipedia.org/wiki/Index_of_Economic_Freedom (access on 11th April 2016)
30. Gallaway E, Cyranoski D. Anti-parasitic drugs sweep Nobel prize in medicine 2015. *Nature News & Comments* 2015;526(7572):174–175.
31. Liang YZ, Xie PS, Chan K. Perspective of Chemical fingerprinting of Chinese herbs. *Planta Medica* 2010;76(17):1997–2003.
32. Liang YZ, Xie PS, Chan K. Chromatographic fingerprinting and metabolomics for quality control of TCM. *Combinatorial Chemistry & HTS* 2010;13(10):943–953.
33. Wilson ID, Brinkman UA. Hyphenation and hypernation: the practice and prospects of multiple hyphenation. *J Chromatography A* 2003;1000(1–2):325–356.

34. Phalke P, Kavade S. Review of hyphenated techniques. *International Journal of Chemical Studies* 2013;1:157–161.
35. Chan K. Generating fingerprinting from analytical techniques alone is not enough in the assurance for quality, efficacy and safety of Chinese medicinal herbs and herbal products. *Analytical Sciences* 2001;17(Suppl.):a409–a412.
36. Tilton R, Paiva AA, Guan JQ et al. A comprehensive platform for quality control of botanical drugs (PhytomicsQC): a case study of Huangqin Tang (HQT) and PHY906. *BMC-Chinese Medicine* 2010; 5(1):1–15.
37. Lam W, Busson S, Guan F, Kiang Z, Zhang W, Gullen EA, Liu S, Cheng Y-C. The four-herb Chinese Medicine PHY906 reduces chemotherapy-induced gastrointestinal toxicity. *Science Translational Medicine* 2010;2(45):2841–2857.
38. Uzuner H, Bauer R, Fan TP, Guo DA, Dias A, El-Nezami H, Efferth T, Williamson EM, Heinrich M, Robinson N, Hylands PJ, Hendry BM, Cheng YC, Xu Q. Traditional Chinese medicine research in the post-genomic era: Good practice, priorities, challenges and opportunities. *Journal of Ethnopharmacology* 2012;140(3):458–468.
39. Verpoorte R. Good Practices: The basis for evidence-based medicines. *Journal of Ethnopharmacology* 2012;140(3):455–457.
40. Chan K, Shaw D, Simmonds MS, Leon CJ, Xu Q, Lu A, Sutherland I, Ignatova S, Zhu YP, Verpoorte R, Williamson EM, Duez P. Good practice in reviewing and publishing studies on herbal medicine, with special emphasis on traditional Chinese medicine and Chinese materia medica. *Journal of Ethnopharmacology* 2012;140(3): 469–475.
41. Zhao Z, Guo P, Brand E. The formation of daodi medicinal materials. *Journal of Ethnopharmacology* 2012;140(3):476–481.
42. Sheridan H, Krenn L, Jiang R, Sutherland I, Ignatova S, Marmann A, Liang X, Sendker J. The potential of metabolic fingerprinting as a tool for the modernisation of TCM preparations. *Journal of Ethnopharmacology* 2012;140(3):482–491.
43. Ouedraogo M, Baudoux T, Stévigny C, Nortier J, Colet JM, Efferth T, Qu F, Zhou J, Chan K, Shaw D, Pelkonen O, Duez P. Review of current and "omics" methods for assessing the toxicity (genotoxicity, teratogenicity and nephrotoxicity) of herbal medicines and mushrooms. *Journal of Ethnopharmacology* 2012;140:492–512.
44. Shaw D, Graeme L, Pierre D, Elizabeth W, Chan K. Pharmacovigilance of herbal medicine. *Journal of Ethnopharmacology* 2012;140(3): 513–518.
45. Zhang L, Yan J, Liu X, Ye Z, Yang X, Meyboom R, Chan K, Shaw D, Duez P. Pharmacovigilance practice and risk control of Traditional Chinese Medicine drugs in China: Current status and future perspective. *Journal of Ethnopharmacology* 2015;83(4):262–266.
46. Barlow DJ, Buriani A, Ehrman T, Bosisio E, Eberini I, Hylands PJ. In-silico studies in Chinese herbal medicines' research: Evaluation of in-silico methodologies and phytochemical data sources, and a review of research to date. *Journal of Ethnopharmacology* 2012;140(3): 526–534.
47. Buriani A, Garcia-Bermejo ML, Bosisio E, Xu Q, Li H, Dong X, Simmonds MS, Carrara M, Tejedor N, Lucio-Cazaña J, Hylands PJ. Omic techniques in systems biology approaches to traditional Chinese medicine research: Present and future. *Journal of Ethnopharmacology* 2012;140(3):535–544.
48. Tejedor Garcia N, Garcia Bermejo L, Fernandez Martinez AB, Olmos Centenera G, Kumari R, Xu Q, Cheng X, Watson S, Lucio Cazaña FJ. MEDLINE-based assessment of animal studies on Chinese herbal medicine. *Journal of Ethnopharmacology* 2012;140(3):545–549.
49. Flower A, Witt C, Liu JP, Ulrich-Merzenich G, Yu H, Lewith G. Guidelines for randomised controlled trials investigating Chinese herbal medicine. *Journal of Ethnopharmacology* 2012;140(3): 550–554.
50. Luo H, Li Q, Flower A, Lewith G, Liu J. Comparison of effectiveness and safety between granules and decoction of Chinese herbal medicine: A systematic review of randomized clinical trials. *Journal of Ethnopharmacology* 2012;140(3):555–567.
51. Fan TP, Deal G, Koo HL, Rees D, Sun H, Chen S, Dou JH, Makarov VG, Pozharitskaya ON, Shikov AN, Kim YS, Huang YT, Chang YS, Jia W, Dias A, Wong VC, Chan K. Future development of global regulations of Chinese herbal products. *Journal of Ethnopharmacology* 2012;140(3):568–586.
52. Pelkonen O, Pasanen M, Lindon JC, Chan K, Zhao L, Deal G, Xu Q, Fan TP. Omics and its potential impact on R&D and regulation of complex herbal products. *Journal of Ethnopharmacology* 2012; 140(3):587–593.
53. Jia J, Yu Y, Deng JH, Robinson N, Bovey M, Cui YH, Liu HR, Ding W, Wu HG, Wang XM. A review of Omics research in acupuncture: The relevance and future prospects for understanding the nature of meridians and acupoints. *Journal of Ethnopharmacology* 2012;140(3): 594–603.
54. Robinson N, Lorenc A, Ding W, Jia J, Bovey M, Wang XM. Exploring practice characteristics and research priorities of practitioners of traditional acupuncture in China and the EU-A survey. *Journal of Ethnopharmacology* 2012;140(3):604–613.
55. Liu SH, Cheng YC. Old formula, new Rx: The journey of PHY906 as cancer adjuvant therapy. *Journal of Ethnopharmacology* 2012; 140(3):614–623.
56. Booker A, Johnston D, Heinrich M. Value chains of herbal medicines-Research needs and key challenges in the context of ethnopharmacology. *Journal of Ethnopharmacology* 2012;140(3):624–633.
57. Jiang M, Lu C, Zhang C, Yang J, Tan Y, Lu A, Chan K. Syndrome differentiation in modern research of traditional Chinese medicine. *Journal of Ethnopharmacology* 2012;140(3):634–642.
58. Bodeker G, Ong CK, Grundy C, Burford G, Shein K. WHO Global Atlas of Traditional, Complementary and Alternative Medicine Kobe, *WHO Publications* 2005;118(11):947.
59. Kim EJ, Chen Y, Huang JQ, Li KM, Razmovski-Naumovski V, Poon J, Chan K, Roufogalis BD, McLachlan AJ, Mo SL, Yang D, Yao M, Liu Z, Liu J, Li GQ. Evidence-based toxicity evaluation and scheduling of Chinese herbal medicines. *Journal of Ethnopharmacology* 2013; 146(1):40–61.
60. Pharmacopoeia of the People's Republic of China 2015 (Set of 4, Chinese edition), published by China Medical Science & Technology Press, 6/2015, ISBN/ISSN: 9787506773379/97850677430/9787506 773362/9787506775397.
61. Wang M, Franz G. The role of the European Pharmacopoeia (Ph EU) in quality Control of traditional Chinese herbal medicine in European member states. *World Journal of Traditional Chinese Medicine* 2015; 1(1):5–15.
62. Zhang L, Wong LY, He Y, Wong IC. Pharmacovigilance in China: current situation, successes and challenges. *Drug Safety* 2014;37(10): 765–770.
63. Chan K, Zhang H, Lin Z. Treatments used in complementary and alternative medicines. *Side Effects of Drugs Annuals* 2014;33(1): 745–756.
64. Williamson EM, Chan K, Xu Q, Nachtergae N, Brunel V, Zhang L, Ouedraogo M, Nortier J, Shaw D, Liu X, Stévigny C, Kahumba J, Pelkonen O, Duez P. Integrated toxicological approaches to evaluate the safety of herbal medicine. In: *The Art & Science of Traditional Medicine Science* 2014;S21–S23.
65. Chan K, Cheung L. *Interactions between Chinese Herbal Medicinal Products and Orthodox Drugs*, Taylor & Francis Group, September 11, 2000 by CRC Press, 176 pages, Authors: Kelvin Chan, Lily Cheung; ISBN 9789057024139 Ca#TF3184.
66. Chan K. Understanding interactions between Chinese medicines and pharmaceutical drugs in integrative healthcare. *Chinese Journal of Integrative Medicine* 2015;21(2):83–89.
67. Jiang WY.Therapeutic wisdom in traditional Chinese medicine: a perspective from modern science. *Trends in Pharmacological Sciences* 2005;26:558–563.
68. Clish CB, Davidov E, Oresic M, et al. Integrative biological analysis of the APOE*3-leiden transgenic mouse. *OMICS* 2004;8(1):3–13
69. Wang J, van der Heijden R, Spruit. Quality and safety of Chinese herbal medicines guided by a systems biology perspective. *Journal Ethnopharmacology* 2009;126(1):31–41.

70. Chang WT, Thissen U, Ehlert KA, et al. Effects of growth conditions 710 and processing on ehmannia glutinosa using fingerprint strategy. *Planta Medica* 2006;72(5):458–467.
71. Verpoorte R, Choi YH, Kim HK. Ethnopharmacology and systems biology: a perfect holistic match. *Journal of Ethnopharmacology* 2005;100(1–2):53–56.
72. Callard R, George AJ, Stark J. Cytokines, chaos, and complexity. *Immunity* 1999;11(5):507–513; Higgins JP. Nonlinear systems in medicine. *Yale Journal of Biological Medicine* 2002;75(5–6): 247–260.
73. Van der Greef J. Systems biology, connectivity and the future of medicine. *Systems Biology (Stevenage*) 2005;152(4):174–178.
74. Van der Greef J, Hankemeier T, McBurney RN. Metabolomics-based systems biology and personalized medicine: moving towards n = 1 clinical trials? *Pharmacogenomics* 2015;7(7):1087–1094.
75. Nestler G. Traditional Chinese medicine. *Med Clin North Am* 2002;86:63–73.
76. Jiang M, Yang J, Zhang C, Liu BY, Chan K, Cao HX, Lu AP. Clinical studies with traditional Chinese medicine in the past decade and future research & development. *Planta Medica* 2010;76:2048–2064.
77. Shen YH, Nahas R. Complementary and alternative medicine for treatment of irritable bowel syndrome. *Canadian family physician Medecin de famille canadien* 2009;55:143–148.
78. Leung KF, Liu FB, Zhao L, Fang JQ, Chan K, Lin LZ. Development and validation of the Chinese Quality of Life Instrument. *BMC-Health & Quality of Life Outcomes* 2005;3(26):1–19.
79. Zhao L, Chan K. Building a bridge for integrating Chinese medicine into conventional healthcare: Observations drawn from the development of the Chinese quality of life instrument. *American Journal of Chinese Medicine* 2005;33(6):897–902.
80. Zhao L, Leung KF, Liu FB, Chen J, Chan K. Responsiveness of the Chinese quality of life instrument in patients with congestive heart failure. *Chinese Journal of Integrative Medicine* 2008;14(3):173–179.
81. Chui SH, Chan K, Wong RS. A panel study on the effects of a Chinese medicinal suppository, Vigconic VI-28, on insulin-like growth factor-1 and homocysteine in healthy men. *Methods and Findings in Experimental and Clinical Pharmacology* 2004;26(5):349–355.
82. Chui SH, Chan K, Chui AKK, Shek SL, Wong RNS. The effects of a Chinese medicinal suppository (Vitalliver) on insulin-like growth factor-1 and homocysteine in patients with hepatitis B infection. *Phytotherapy Research* 2006;19(8):674–678.
83. Chui SH, Chow FS, Chan K, Fu S, Seto YS. Slimpid may boost plasma IGF-1 level and improve the quality of life in patients with risk of developing metabolic syndrome. *Journal of Complementary & Integrative Medicine* 2008;5(1):1987–2002.
84. Chui SH, Chan K, Shek SL, Zhao L, Fong MY, Hui I, Shum S. A panel study to assess the quality of life assessments in patients suffering from allergic rhinitis after treatment with a Chinese herbal nasal drop. *Phytother Res* 2010;24(4):609–613.
85. Silins G, Tan J, Chan K. Intellectual property and patent issues with phytotherapy products. In: *Phytotherapies: Efficacy, Safety and Regulation*, edited by Iqbal Ramzan. Chapter 23: Publisher: John Wiley Inc,2014. ISBN: 978-1-118-26806-3.
86. Chan K, Poon J, Poon S, Jiang M, Lu A. An Overview on Evidence-Based Medicine and Medical Informatics in Traditional Chinese Medicine practice. In: Data Analysis for Traditional Chinese Medicine Research (ed. Poon J, Poon S) 2013: 227–248. (http://www.springer.com/978-3-319-03800-1).
87. Guo DA, Han JY (2015). Integration of Traditional Chinese medicine and modern science is the way forward. *World Journal of traditional Chinese medicine* 2015;1(2):1.
88. Zhang Z, Liang Y, Xie P, Chau F, Chan K. Chromatographic fingerprinting and chemometric techniques for quality control of herbal medicines. In: Data Analysis for Traditional Chinese Medicine Research (ed. Poon J, Poon S) 2014:133–154. (http://www.springer.com/978-3-319-03800-1).