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ESSENTIALS Traditional (often synonymous with complementary) medicine can be defined as the knowledge, skill, and practices, based on
the theories, beliefs, and experiences indigenous to different cul- tures, which are used in the maintenance of health and the pre- vention, diagnosis, improvement, or treatment of illness. These practices are found in almost every country, and demand for them is increasing. For individual patients, when of proven quality, safety, and ef- ficacy, traditional medicine contributes to the goal of ensuring that all people have access to care that they feel they need. For medical science, investigators in traditional fields have discovered
new medicines with which to combat important diseases, includ ing the sympathomimetic ephedrine, the antimalarial artemisinin,
and arsenic trioxide used in the treatment of promyelocytic leukaemia. The World Health Organization Traditional Medicine Strategy 2014–2023 has two key goals: to support Member States in harness ing the potential contribution to health, wellness, and people-centred healthcare, and to promote the safe and effective use of traditional medicine through the proper and organized regulation of products, practices, and practitioners. Much benefit will emerge if the science of the West and the rich experience and traditions of medicine in China can work together in an integrated way. Introduction Traditional and complementary medicine are important and often underestimated aspects of healthcare. Not only are the practices found in almost every country; demand is increasing. The im- portance of the approach resides in two qualities: first, when it is of proven quality, safety, and efficacy, traditional and complemen- tary medicine contributes to the goal of ensuring that all people have access to care that they feel they need. Secondly, several in- vestigators in these traditional fields have over the years discovered new medicines with which to combat important diseases. Here we define traditional medicine and discuss several therapeutic contri- butions exemplified by traditional Chinese medicine—including the strategic issues of

disease prevention, health promotion, and affordability. What is traditional medicine? The World Health Organization (WHO) defines traditional medi- cine as follows: ‘Traditional medicine has a long history. It is the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement, or treatment of physical and mental illness.’ The terms ‘complementary medicine’ or ‘alternative medicine’ are used interchangeably with traditional medicine in some countries. They refer to a broad set of healthcare practices that are not part of that country’s own tradition or conventional medicine and are not fully integrated into the dominant healthcare system. Traditional Chinese medicine, Ayurveda, Unani, naturopathy, osteopathy, homeopathy, and chiropractice are frequently included in traditional medicine. In China, the earliest initiatives originated from Shennong, thousands of years ago: he examined the proper- ties and tasted many hundreds of herbs. Ayurveda, or the ‘science of life’, was developed by the seers of ancient India. Practitioners and dispensers now use Ayurveda for treatment. Unani medicine is the traditional practice of South Asian countries and its use is growing in other parts of Asia, such as Bangladesh and India. Naturopathy emphasizes prevention and the promotion of optimal health through the process of self-healing. Homeopathy originated from the belief that a substance which causes the symptoms of a disease in healthy people would cure similar symptoms in those who are unwell. Commonly used treatments and therapeutic techniques for each of these traditional approaches are listed in Box 2.8.1. Certain popu- lations in Africa, Asia, and Latin America continue to use traditional medicine to meet their primary healthcare needs. Meanwhile, in Australia, Europe, and North America, ‘complementary and 2.8 Traditional medicine exemplified by traditional Chinese medicine Fulong Liao, Tingliang Jiang, and Youyou Tu

 alternative medicine’ is increasingly used in parallel to dominant practices of modern medicine, particularly for managing chronic diseases. In these countries, a desire for more personalized healthcare is likely to explain the increasing take up of these approaches. Since traditional Chinese medicine is long established and pro- vides some notably successful therapies, we provide examples that illustrate how traditional approaches remain so much a feature of medicine in China; in some instances, the treatment has been adopted in the parallel world of modern medicine that is dominant elsewhere. Products in the global pharmacopoeia but which originated from traditional Chinese medicine Ephedrine—the first drug transferred to the Western pharmacopoeia from Chinese medicine Since the Han dynasty (206 BCE-200 CE), the herb Mahuang (Ephedra sinica) in traditional Chinese medicine has been known to have antiasthmatic properties. A decoction of ephedra is recorded in the classical ‘Treatise on Febrile and Miscellaneous Diseases’ by Zhang Zhongjing (150–215 CE). Ephedrine was the first drug that origin- ated from traditional Chinese medicine to appear in the Western pharmacopoeia. The first isolation of ephedrine from Ephedra The renowned Japanese organic chemist and pharmacologist Nagai Nagayoshi who had studied in Europe, first succeeded in extracting the active principle, ephedrine, from Ephedra in 1885. He isolated the alkaloid (ephedrine hydrochloride) from the plant and deter- mined its formula and chemical structure. At that time, the pharma- cological effect of ephedrine was best known in the eye in which it causes pupillary dilatation. The agent was largely forgotten until the early 1920s when it was rediscovered by K.K. Chen and C.F. Schmidt. The discovery of ephedrine as a sympathomimetic Dr Chen’s research at Peking Union Medical College sought to understand the pharmacology of chemical components obtained Box 2.8.1 Commonly used therapies and therapeutic techniques in branches

of traditional medicine globally Traditional medicine includes diverse health practices, approaches, knowledge and beliefs incorporating plant, animal and/or mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness. Commonly used therapies and therapeutic techniques Chinese Medicine Ayurveda Unani Naturopathy Osteopathy Homeopathy Chiropractic Herbal medicines Acupuncture/acupressure Manual therapies Spiritual therapies Exercises = commonly incorporates this therapy/therapeutic technique = sometimes incorporates this therapy/therapeutic technique = incorporates therapeutic touch Reprinted from Traditional Medicine Growing Needs and Potential—WHO Policy Perspectives on Medicines, No. 002, May 2002. 

110 section 2 Background to medicine from Chinese herbs and was supported by the Rockefeller founda- tion; his work on ephedrine became very well known. Since the iso- lation of ephedrine by Nagai was unknown to him, Chen set out to develop a method of extraction to obtain the active compound from Ephedra, which he isolated in only a few weeks. Later, he col- laborated with Schmidt to determine the pharmacological actions of ephedrine. The agent was found to increase myocardial contractility, induce sustained elevation of carotid arterial blood pressure, con- tract the blood vessels in skin, mucosa, and internal organs, as well as stimulate central awareness. These actions resemble those of adren- aline (epinephrine), but with long-lasting effects and relatively low toxicity. Chen and Schmidt published their findings in the Journal of Pharmacology and Experimental Therapeutics in 1924. Soon after- wards, the Eli Lilly Company marketed ephedrine (in 1926) for the indications of nasal congestion and bronchial spasm. With the discovery of ephedrine, traditional Chinese medicine had thus borne its first commercial fruit in Western pharmacology. As a sympathomimetic agent, ephedrine is able to cause release of adrenaline and noradrenaline (epinephrine and norepinephrine) and induce relaxation of bronchial smooth muscle. Among other ef- fects, stimulation of ß-adrenergic receptors by ephedrine appears to be responsible for inducing relaxation of bronchial smooth muscle. Ephedrine became a highly popular and effective treatment for asthma, particularly because, unlike the standard therapy of adren- aline at that time, conveniently it could be administered orally. As a treatment for asthma, ephedrine reached its zenith of popularity in the late 1950s. Artemisinin—a gift from traditional Chinese medicine Compared with the time taken to introduce many of contemporary discoveries through drug development into widespread clinical use, the discovery of artemisinin largely followed a relatively simple and direct logical route. This route was fortuitously directed by findings that had been long-reported in the ancient Chinese literature and in this sense, artemisinin, with its unique sesquiterpene lactone gener- ated by phytochemical evolution, is truly a gift from the old practi- tioners of Chinese medicine. In the event, the modern achievement was accomplished by the nationwide collaboration of ‘project 523’ (a national antimalarial project initiated by Chairman Mao Zedong during the war with the United States in Vietnam). This national cooperative project included institutions in Beijing, Shanghai, as well as Shandong, Yunnan, and Guangdong provinces. Each institution contributed to the successful progress of the project in different ways: these in- cluded the identification of the agricultural area where local strains of Artemisia which are rich sources of artemisinin, grew most pro- lifically; the simplified procedure for extraction of artemisinin suitable for large-scale production; determination of the unique stereo-structure of artemisinin; development of active artemisinin derivatives; and, not least, the facility for experimental and clinical investigation of the actions of artemisinin and its derivatives. Breakthrough in antimalarial research in the 1970s Malaria caused by Plasmodium falciparum has

been a life-threatening human disease for millennia. After a failed international attempt to eradicate malaria in the 1950s, the disease rebounded, largely due to the emergence of malarial parasites which were resistant to the existing antimalarial drugs, such as chloroquine, which had been introduced in 1947. Resistance to quinine, often the drug of last resort, had been noted in Brazil in 1907 and had been reported from the Thai–Cambodian border in the mid-1960s. In 1969, the Institute of Chinese Materia Medica, Academy of Traditional Chinese Medicine was engaged in the national '523' antimalarial project, and the senior author of this chapter (YY Tu) was appointed head of an antimalarial research group. The group collected and selected more than 2000 Chinese herb preparations and identi- fied 640 recipes from ancient literatures that might have some antimalarial activities. More than 380 extracts were evaluated in a living model of malaria in mice infected with Plasmodium berghei, but contradictory to what was recorded in the ancient literature, no promising or reproducible result was obtained. In an effort to explain this, Tu intensively re-examined the literature:  in A Handbook of Prescriptions for Emergencies authored by Ge Hong (Jin dynasty, 284–346 CE), the use of Qinghao (the Chinese name of sweet wormwood, Artemisia annua) for alleviating malaria symptoms is described: 'A handful of Qinghao is immersed in 2 litres of water; wring out the juice and drink it all' (Fig. 2.8.1). Tu was struck by the possibility that the heating involved in a con- ventional extraction step might have destroyed the active compo- nents and that extraction at a low temperature might be necessary. First extracting by ether reflux, YY Tu and colleagues subse- quently resolved the extracts into the acidic and neutral fractions and finally obtained a nontoxic neutral extract (No. 191). On 4 October 1971, extract 191 was found to be completely effective in suppressing parasitaemia in the P. berghei-infected mice and later, in monkeys with malaria due to Plasmodium cynomolgi. To accelerate the clinical evaluation of extract 191, Tu and colleagues voluntarily tested the safety of the extract in themselves. Shortly after this, in October 1972, a trial with 30 patients mainly from southern China infected with P. vivax and P. falciparum showed a rapid disappearance of fever and intraerythrocytic parasites. One month later, these results were formally notified to the national '523 project' office, after which further collaborative research on Artemisia annua was promoted. The clear demonstration of anti- malarial efficacy in extract 191, stimulated by the ancient and ac- curate account many centuries earlier by Ge Hong, symbolizes the breakthrough which led to the later discovery and pharmaceutical development of artemisinin. The discovery of artemisinin YY Tu's research group set out to purify the components with anti- malarial activity that were present in extract 191 of Artemisia annua. In 1972, a colourless crystalline substance was identified with a mo- lecular weight of 282 Da, a molecular formula of $C_{15}H_{22}O_5$ absent ni- trogen, and a melting point of 156–157°C. The name of 'Qinghaosu' (artemisinin, 'su' means basic element in Chinese) was given to this newly identified compound. Afterwards, the team found out that only the species of A. annua in the Artemisia genus and its leaves in the alabastrum stage contain abundant artemisinin. The chem- ical properties and behaviour of the compound were identified as a sesquiterpene lactone; finally in 1975, the stereo-structure of arte- misinin was determined unambiguously in collaboration with col- leagues at the Institute of Biophysics, Chinese Academy of Sciences. The structure was first published in 1977 and the new molecule and the paper were immediately cited by the Chemical Abstracts (C.A. 1977, 87, 98788g).

2.8 Traditional medicine exemplified by traditional Chinese medicine 111 Worldwide attention to artemisinin The successful treatment of several thousand patients with artemi- sinin and its derivatives for malaria in China attracted worldwide attention in the 1980s. In 2002, the WHO announced a switch in the recommendations for malaria treatment to artemisinin combin- ation

therapy. In 2006, to prevent malaria parasites from developing resistance to the drug, WHO requested pharmaceutical com- panies to end the marketing and sale of ‘single-drug’ artemisinin, Artemisinin combination treatment is currently widely used, and has saved many lives globally, and especially in Africa. The remedy impressively reduces the intensity of malaria in Africa due to its activity against the gametocyte stages of P. falciparum in the blood which allow transmission from host to host via the mosquito vector. Murray et al. have examined the global mortality due to malaria over the period 1980–2010 (see Fig. 2.8.2): since the global peak in 2004, there has been a substantial decrease in malaria deaths that is H H H D C B A 6 7 8 9 10 3 4 2 1 1 5 3 2 0 0 5 0 0 0 4 12 13 11 H CH3 H3C 15 CH3 14 Fig. 2.8.1 From ancient literature to artemisinin molecule. Life: A Handbook of Prescriptions for Emergencies by Ge Hong (Ming dynasty version, 1574 ce); Middle: ‘A handful of Qinghao immersed with 2 litres of water, wring out the juice, and drink it all’ is printed in volume 3 in the fifth column from the right. Right: the molecular structure of artemisinin. Image courtesy of Prof Liao FL. 2000000 1800000 1600000 1400000 1200000 1000000 800000 600000 400000 200000 0 1980 1985 Deaths (n) 1990 1995 Year 2000 2005 2010 ≥70 years 50–69 years 15–49 years 5–14 years <5 years Fig. 2.8.2 Malaria deaths by age from 1980 to 2010. Reprinted from The Lancet, 379(9814), Murray CJ, et al., Global malaria mortality between 1980 and 2010: a systematic analysis, 413–31. Copyright © 2012, with permission from Elsevier.

112 section 2 Background to medicine attributable to the rapid scale-up of control activities, including the intensified use of artemisinin combination therapy. Arsenic trioxide and the treatment of acute promyelocytic leukaemia Brief medicinal history of arsenic Arsenic is one of the oldest drugs in Western medicine and trad- itional Chinese medicine, since it was cited by Hippocrates (460– 370 BCE) as a treatment of skin ulcer and by the Yellow Emperor’s Internal Classic (263 BCE) for treatment of periodic fever (likely to be attributable to malaria). Arsenic exists in different forms: As4S4, known as realgar; and As2S3, known as orpiment or yellow arsenic; the common term for As2O3 (arsenic trioxide) is white arsenic. The highly poisonous nature of arsenic has long been known and ac- cording to the traditional principle of ‘combating an evil with a toxic agent’ limited amounts of arsenic have been included in traditional medical recipes; it was also recorded by the 16th century Li Shi-Zhen in the Compendium of Meteria Medica. In the late 18th and early 19th centuries, Fowler’s solution, 1% potassium arsenite (KAsO2) solution, was introduced in clinics in Europe to treat periodic fever, chronic myelogenous leukaemia, Hodgkin’s disease, and many other conditions. Some practitioners in Europe used arsenicals as a ‘tonic’ to improve energy in those who complained of fatigue or reduced libido. However, due to its toxicity, including the development of squamous cancers of the skin, and the advent of modern chemo- therapy, the use of Fowler’s solution and other arsenicals was largely discarded in the early decades of the 20th century. The application of arsenic to acute promyelocytic leukaemia Acute promyelocytic leukaemia is one of the most lethal forms of leukaemia. In the 1970s, the combination of anthracyclines and cytosine arabinoside was adopted as the mainstream treatment for acute promyelocytic leukaemia, but the effects were often not cura- tive and adverse events with bleeding related to disseminated intra- vascular coagulation—often initiated by chemotherapy. Enlightened by the ancient eastern wisdom, Chinese doctors never stopped their attempts to blaze a new trail. In the 1980s, inspired by the Chinese philosophy that ‘the evil can be educated to be the good’ and the concept of cancer cell differentiation from the Western literature, Dr Zhenyi Wang’s team of Shanghai Institute of Haematology first ap- plied all-trans retinoic acid to the treatment of acute promyelocytic leukaemia and achieved a complete remission rate of 90%. More im- portantly, this provides a first example that a human cancer can be treated effectively using

inducers of cell differentiation rather than cytotoxic agents. The application of arsenic to the treatment of leu- kaemia was another breakthrough initiated by Chinese clinical in- vestigators and physicians. In 1971, Dr Tingdong Zhang and colleagues affiliated to the First Hospital at Harbin Medical University, chanced upon the potential anticancer effect of arsenic trioxide from a countryside herbalist. Accordingly, Zhang and colleagues prepared a solution for par- enteral administration termed ‘Ailin’ (broadly translated from the Chinese as a cancer-curing mixture): this contained arsenic trioxide and a trace amount of mercury chloride and was administered to patients with chronic myeloid leukaemia. The first report on the ef- fects of Ailin solution was published in 1973 in a local journal en- titled Medicine and Pharmacy of Heilongjiang. In 1976, the authors reported five patients with acute leukaemia who had had a complete remission after administration of Ailin. Later, in 1979, Zhang pub- lished a summary of 55 cases of acute leukaemia treated by Ailin solution or related remedies in which arsenic trioxide had been combined with other agents. All 55 cases were improved to some ex- tent, with a remission rate of 70%; this included 12 patients in whom complete remission occurred. Of note, few or only slight toxic side effects occurred with the small doses of arsenic used. Zhang and col- leagues clearly pointed out that the key component in the Ailin so- lution was arsenic. From 1984 to 1992, they further observed that acute promyelocytic leukaemia was particularly susceptible to ar- senic treatment. In the mid of 1990s, a research group at the Shanghai Institute of Haematology, led by Dr Zhu Chen, established a cooperation with Dr Tingdong Zhang. They then launched the first systematic study of the cellular and molecular mechanisms of arsenic trioxide and confirmed its antileukaemia effects. Grounded in their laboratory findings, Dr Chen’s team conducted a controlled clinical trial of pure arsenic trioxide in relapsed and newly diagnosed patients with acute promyelocytic leukaemia in which high (80%) rates of complete re- mission were observed in both settings. Based on the convincing re- sults of clinical and basic studies by Dr Chen’s group, in August 1999, arsenic trioxide was approved as a new drug by the China Food and Drug Administration. Mechanism of action of arsenic in acute promyelocytic leukaemia Dr Zhu Chen, Dr Saijuan Chen, and colleagues of Shanghai Institute of Haematology investigated the mode of action of arsenic trioxide. A  combination of apoptosis induction and partial differentiation appears to be the cellular mechanisms associated with induction of remission. In molecular terms, the presence of the transloca- tion, t(15;17), causing fusion of the retinoic acid receptor α gene on chromosome 17 with the promyelocytic leukaemia (PML) gene coding for a nuclear protein on chromosome 15, leads to formation of the PML-RARα fusion protein containing sequences from the PML moiety and retinoic acid receptor α. It is notable most patients with acute promyelocytic leukaemia who harbour PML-RARα re- spond well to the therapeutic effect of arsenic trioxide, while there is evidence that those very rare patients without the t(15;17) trans- location and therefore without expression of the PML-RARα fusion protein, such as those with the t(11;17) translocation and resultant PLZF-RARα, are resistant or relatively resistant to arsenic. It has been shown that arsenic trioxide binds directly to cysteine residues located within the specific RING-B box-coiled coil domain of PML-RARα. The identification of the PML-RARα fusion protein as a direct target of arsenic trioxide and at in situ concentrations that are considerably lower than those required to induce apoptosis in other cancer cells, indicates a remarkable selectivity of the molecular target. It is worth noting that the wild-type PML protein is a tumour suppressor in- volved in growth arrest and regulation of apoptosis and senescence. In healthy cells, PML is located in a specific nuclear subdomain (the PML nuclear body). However, in promyelocytic leukaemia, complex formation of PML-RARα with wild-type PML breaks up the nuclear microspeckle pattern and the functions of the protein. Arsenic tri- oxide at therapeutic dosage corresponding to in situ concentrations as low as 10-7 M induces

degradation of both the wild-type PML

2.8 Traditional medicine exemplified by traditional Chinese medicine 113 and PML-RARα fusion proteins with posttranslational modifica- tion by sumoylation, which appears to restore accumulation of the wild-type protein in the formerly leukaemic cells. The sumoylation of the fusion protein is then followed by its degradation through the proteasome-dependent pathway (Fig. 2.8.3). At the level of cells and the whole organism, arsenic trioxide causes partial differentiation of acute promyelocytic leukaemia cells as well as their apoptosis; not- ably it has little effect on other cancer cells under similar conditions. A striking additional finding is that only the disease-associated PML-RARα, but not the wild-type RARα receptor is degraded upon exposure to the drug. Given the striking effects of arsenic trioxide in a leukaemia that is otherwise very challenging to cure, clinicians worldwide have rapidly adopted the original findings. In the first instance, the agent found favour with clinicians who explored use of parenteral ar- senic in patients who had proved resistant to or had relapsed after receiving recommended first-line drugs including the targeted mo- lecular therapy of all-trans retinoic acid which, by also targeting the PML-RARα oncoprotein, can lead to terminal differentiation of malignant promyelocytes to mature neutrophils. However, it is apparent that this treatment alone does not eradicate the ma- lignant clone. Cytotoxic chemotherapy may lead to remission but through the mechanistic studies of the group of Shanghai Institute of Haematology it is now recognized that achievement of a cure in the great majority of acute promyelocytic leukaemia patients requires the addition of arsenic trioxide. The treatment of acute promyelocytic leukaemia is complex, and involves management and prevention of several potentially life- threatening complications such as the promyelocytic leukaemia cell differentiation syndrome, occurring in a small subset of patients within the first three weeks of treatment with all-trans retinoic acid or arsenic trioxide. However, the past three decades have witnessed a great progress in the treatment of the disease largely as a result of original and modern studies related to the traditional use of medi- cinal arsenic in China. Based on the observations that both arsenic trioxide and all-trans retinoic acid bind and trigger proteasomal degradation of PML/ RARα fusion protein but through distinct mechanisms, a syner- gistic targeting strategy has been developed by Dr Zhu Chen and Dr Saijuan Chen’s group for newly diagnosed patients with acute promyelocytic leukaemia. This involves a combination of all-trans retinoic acid and arsenic trioxide, and incorporates chemotherapy in the postremission treatment. This regimen not only reduces the early deaths caused by bleeding or differentiation syndrome, but more importantly yields up to 90% five-year disease-free survival in acute promyelocytic leukaemia. Recent reports from the same group have confirmed the safety of the all-trans retinoic acid/arsenic tri- oxide combination therapy, since no obvious long-term toxicities NB4 cells 0 hr 0.5 hr 6 hr 24 hr PML (a) (b) (d) (c) PML-RARα RARα 0 0 10 20 30 60 0 10 20 30 60 0 10 20 30 60 As2 O3(hr) As2 O3(min) 121 77 181 121 77 181 121 77 181 121 77 kDa kDa kDa 48 77 48 77 Anti-FLAG Anti-FLAG Anti-FLAG Mock Arsenic (ng/mg) 0 5 10 15 20 25 PML P S PML-RARα > RARα > 1 6 12 24 < < < < < Fig. 2.8.3 The effect of arsenic trioxide (ATO) on the posttranslational modification and degradation of PML-RARα and PML is rapid and specific. (a and b) ATO-induced degradation of PML-RARα in the APL cell line NB4 cells, as assessed by Western blotting with RARα antibody and immunofluorescence staining with PML antibody (green). The cells were treated with 1 mM ATO. Scale bar, 10 mm. (c) A time-course study showing the effects of ATO on PML, PML-RARα, or RARα. (<) points to parental proteins, (▼) to modified proteins, and (▽) to degraded fragments. Transfected HEK 293T cells were treated with 2 mM ATO and then lysed in radioimmunoprecipitation assay (RIPA) buffer and fractionated into supernatants (S) and pellets (P) by centrifugation. (d) The arsenic content of

pellets from HEK 293T cells that had been mock-transfected or transfected with a vector encoding PML. Reproduced from Chen Z, Chen SJ, et al. Arsenic trioxide controls the fate of the PML-RARalpha oncoprotein by directly binding PML. Science, 2010, 328:240–3.

114 section 2 Background to medicine were observed among patients in whom treatment is stopped. Based on the risk factors for prognosis in acute promyelocytic leukaemia, optimization of the treatment emphasizes the role of arsenic in in- duction, consolidation and maintenance therapy as a substitute to chemotherapy in low- and intermediate-risk patients, and in potential reduction of chemotherapy in the patients with a high- risk of complications without adverse impact on the outcome. See Chapter 22.3.3 for further discussion. Evolution of pharmaceutical use and commercial development of medicinal arsenic The all-trans retinoic acid/arsenic trioxide/chemotherapy triad therapy achieves a cure rate of more than 90% and costs less than CNY 100 000 in Mainland, China. Since the new round of health reforms launched in 2009, both all-trans retinoic acid and ar- senic trioxide have been listed in the China's National Essential Drug List; moreover, the costs of treatment are covered univer- sally by the health insurance. An oral mixture called Realgar- Natural Indigo Formula containing realgar, natural indigo, Salvia miltiorrhiza, and Radix pseudostellariae, which was developed by Dr Shilin Huang of the 210 Military Hospital in the 1980s, can achieve a 5-year survival rate of 85% by targeting PML-RARα and orchestrating related signal networks. This formula is also effective and affordable. In the recent years, researchers of Hong Kong University, led by Dr Wing-Yan Au and Dr Yok-Lam Kwong, have promoted use of a convenient oral formulation to replace intravenous arsenic in Hong Kong and to avoid exorbitant charges: 150 patients with acute promyelocytic leukaemia have been treated with this alternative, convenient, and affordable first-line therapy. Introduction to compound formulae and disease prevention in traditional Chinese medicine The role of compound formulae The finding of ephedrine as a sympathomimetic, the discovery of the antimalarial, artemisinin and the exploration of arsenic trioxide for treating acute promyelocytic leukaemia have strictly followed the modern pharmaceutical approach. All the three discoveries were based on a single herbal formula and the application of con- temporary molecular science in translational research to develop modern and effective medicines for important conditions. However, the investigation and use of a single herbal principle for the treatment of a specific disease is the rare case in the use of traditional Chinese medicine today. The reality is that popular treat- ments are characterized by the holistic syndrome differentiation for a patient; this leads to the prescription of a herbal formula composed of a group of well-tailored herbs that are related by the practitioner to the syndrome for which treatment is requested. The relationship between individual syndromes and the herbal formulae used, while largely symptom-based and antithetic to the teaching of Western medicine, are established as part of the rich experience in the ad- vancement of traditional Chinese medicine that has evolved over thousands of years. Currently, marketed products of traditional Chinese medicines are mostly patented compound formulae; these account for more than 20% of the whole pharmaceutical market in China. In the 2015 edition of the Chinese pharmacopoeia, 1493 for- mulae and single herb preparations are recorded (of which formulae constitute the majority); 618 medicinal materials and processed herbal slices are the exception. Herbal formulae for treatment of cardiovascular diseases Cardiovascular diseases are common life-threatening conditions and naturally come to the frequent attention of practitioners and doctors. The term of 'blood' in Chinese medicine has a meaning that corresponds closely with that in Western medicine (i.e. the flowing or circulating blood). The syndromes associated with stasis of blood also occur frequently as part of syndrome differentiation, and are

linked closely with vascular diseases. The principle of activating or improving the circulation of blood is a therapeutic concern in many aspects of medicine and is an important aspect of traditional Chinese medicine. Since the 1970s, Keji Chen and colleagues have conducted numerous clinical trials by applying herbal medicine in efforts to stimu- late the circulation of blood as part of the treatment of coronary heart disease, including anginal attacks and restenosis after percutaneous coronary intervention. In collaboration with physicians in working in 16 hospitals in Beijing, Chen and this clinical research team in- vestigated the use of a herbal compound formula simply termed 'coronary heart II' to treat chronic stable anginal pectoris. The for- mula consists of five herbs with properties considered to stimulate or improve the circulation of blood, including Salvia miltiorrhiza and Ligusticum wallichii. The randomized double–blind controlled clinical trial showed that the compound formula could reduce the frequency of anginal attacks; at the same time laboratory studies indicated that the effect might in part be attributed to antiplatelet activity with increased fibrinolysis. The trial supported clinical use of the formula preparation in the treatment of chronic stable an- gina pectoris compared with the placebo. Tetramethylpyrazine, an antiplatelet drug used in China, was detected in extracts from Ligusticum wallichii contained in the aforementioned formula preparation. In the past 30 years, active treatment for acute myocardial in- farction and coronary syndromes has saved many lives. However, coronary artery restenosis after percutaneous coronary interven- tion continues to present a dilemma. To investigate frequently encountered complications such as plaque rupture and the con- tribution of inflammatory factors to obstructive complications of atheromatous coronary heart disease, Chen and colleagues took a holistic view of the ischaemic complications of blood stasis in the coronary circulation and selected XueFu ZhuYu Tang, a well- known Chinese compound formula developed by Wang Qingren (1768–1831 CE) for various syndromes attributed to blood stasis. Pursuing evidence from pharmacological studies, they used Ligusticum phenols and Paeonia glycosides extracted from the for- mula in a preparation for a multicentre clinical trial carried out in 335 patients with potential coronary arterial restenosis after per- cutaneous coronary intervention. Based on a routine treatment of aspirin and ticlopidine, XS0601 capsule (extracted Ligusticum phenols and Paeonia glycosides) showed significant benefit for preventing restenosis compared with placebo. The restenosis rate

2.8 Traditional medicine exemplified by traditional Chinese medicine 115 was significantly reduced in the XS0601 group as compared with that of the placebo (26.0% compared with 47.2%, $p < 0.05$; see Fig. 2.8.4). At up to 1 year of follow-up, the Kaplan–Meier survival curve for freedom from clinical end-point events showed a sig- nificant difference between XS0601 and the placebo; in addition, follow-up angiographic findings support the salutary findings in relation to survival outcome. To request approval for compound formulae from American Food and Drug Administration (FDA) is a new effort of narrowing the gap between traditional Chinese medicine and mainstream Western medical practice. The patent medicine, Compound Danshen Dripping Pill in the Chinese pharmacopoeia, is a typ- ical example. The pill, containing extracts from Salvia miltiorrhiza and Panax notoginseng, is mainly used to treat angina and cor- onary heart diseases. So far it is the first Chinese patent traditional medicine to have completed the FDA's clinical phase II trials and it is encouraging that this medication remains under evaluation in rigorous clinical phase III trials. Also, the drug in tablet form has been approved by drug watchdogs in Canada, Russia, and some Asian/African countries. The manufacturer's data shows that more than millions of people worldwide take this medication annually. Disease prevention, health promotion, and traditional Chinese medicine Disease prevention and health promotion are strategic issues in

medicine. ‘Preventing disease is far superior to treating a dis- order’ is also one of the sacred principles underlying traditional Chinese medicine. A drawing of physical and breathing exer- cises on silk was unearthed from a Han Tomb at Mawangdui, central China in the 1970s. The finding provided early archaeo- logical evidence of exercise employed in healthcare in China some 2000 years ago (Fig. 2.8.5). For disease intervention and healthcare, biomechano-pharmacology, a new borderline dis- cipline, pursues the combinatorial effects of traditional medicine with biomechanical factors that are designed to improve blood flow. Many studies have revealed that endothelial release of ni- tric oxide, endothelin-1, prostacyclin (PGI2), von Willebrand factor, tissue plasminogen activator, intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1, endothelial cell growth factor, and inflammatory factors are all regulated by blood shear stress. Therefore, vessel tension, thrombosis, thrombolysis, cell adhesion, angiogenesis, atherosclerosis can be argued on first principles to be influenced by blood shear stress and hence circulatory flow. The argument in Chinese trad- itional medicine is made that cardiovascular and cerebrovas- cular diseases may benefit from interventions that influence the biological responses of endothelium regulated by biomechanical factors. In most cases, sedentary life style reduces blood flow and cardiac output and with this the level of blood shear stress. As a modern interpretation of blood stasis syndrome, decreased blood shear stress is a common pattern of the syndrome. The an- cestors of modern Chinese utilized exercise to prevent this syn- drome and promote health. The great surgeon, Hua Tuo, before 205 CE, not only created five animal-mimic boxing as a phys- ical fitness exercise, but also realized ‘Diseases are prevented as blood flow is promoted’. This appears today to be a really wise and prescient foresight of the biological effects of blood flow. Pharmacological experiments have recently shown that the joint application of exercise combined with administration of ex- tracts from Chinese medicine may prevent atherosclerosis. For example, the experimental combination of a Yindan Xinnaotong capsule and swimming in experimental rats may prevent athero- sclerosis through a synergistic effect between the capsule and 50 40 26.1 Per patient restenosis Per lesion restenosis New lesion Post-stenting Pre-stenting Follow-up Stent-dilating Restenosis rate (%) 47.2 23.6 39.2 12.3 13.9 Control XS0601 30 20 10 0 Fig. 2.8.4 Restenosis comparison between XS0601 and the controls. Left: Restenosis rates per patient and per lesion and percent of new lesion. XS0601 significantly lowered both per patient and per lesion restenosis as compared with the placebo group ($p < 0.05$). As for new lesions, there was no significant difference between the two groups. Right: Angiographic evidences for a patient in the XS0601 group in the stages of prestenting, stent-dilating, poststenting, and follow-up. Image courtesy of Prof Chen KJ.

 swimming in improving blood circulation, rheological param- eters in the blood, concentration of proatherogenic lipopro- teins, and the vascular endothelium. Vascular remodelling may contribute to the prevention of atherosclerosis by upregulating smooth muscle protein responses—certainly, this whole field continues to be an active field of contemporary research in Chinese medicine. Making traditional medicine available and affordable Large swathes of the populations in the world’s poorest coun- tries are those most in need of inexpensive, effective treatments. The WHO estimates that one-third of the global population still lacks regular access to essential drugs, and that in the poorest parts of Africa and Asia, this figure rises. In these regions, some form of traditional medicine is often a more widely available and more affordable source of healthcare. Clearly to provide a sound basis for efforts to promote traditional medicine and to prevent illness and wasted resources, safe and effective therapies must be identified, The focus should be on safe and effective treatments for diseases which represent the

greatest burden for poor popu- lations, in this context for malaria and HIV/AIDS are of great importance but the value of a safe supply of potable water and simple hygiene also must go hand in hand with treatment for all infectious diseases. Many Member States of WHO have made great efforts to advance traditional medicine, some of which can be attributed to the imple- mentation of the WHO Traditional Medicine Strategy 2002–2005. In recent years, WHO has collaborated with many countries and areas to develop these programmes and to bring traditional medi- cine into the mainstream healthcare system. WHO has developed technical guidelines and standards and organized trainings/work- shops in support of Member States. Fig. 2.8.6 shows the progress of Member States regarding established national policies on traditional medicine and national regulations on herbal medicines. The newly established WHO Traditional Medicine Strategy 2014–2023 has two key goals:  to support Member States in harnessing the potential contribution to health, wellness, and people-centred healthcare and to promote the safe and effective use of traditional medicine through the proper and organized regulation of products, practices, and practitioners. We very much hope that the implementation of this strategy will accelerate the availability and affordability of traditional medicine in the near future. As stated by Mao Zedong, Chinese medicine and pharma- cology are a great treasure-house and we should explore them and raise them to a higher level. Fig. 2.8.5 Drawing of physical and breathing exercise on silk unearthed from a Han Tomb at Mawangdui, central China. It is an early archaeological evidence of exercise employed in healthcare in China some two thousand years ago.

 So much of benefit for humankind will emerge if the science of the West and the rich experience and traditions of medicine in China can work together in an integrated way. Acknowledgements The authors wish to record their gratitude to Professors Chen (Saijuan) and Chen (Zhu) for kindly reviewing this chapter. FURTHER READING Au WY, et al. (2011). Oral arsenic trioxide-based maintenance regi- mens for first complete remission of acute promyelocytic leukemia: a 10-year follow-up study. Blood, 118(25), 6535–43. Chen GQ, et al. (1997). Use of arsenic trioxide (As2O3) in the treat- ment of acute promyelocytic leukemia (APL): I. As2O3 exerts dose- dependent dual effects on APL cells. Blood, 89(9), 3345–53. Chen KJ, et al. (2006). XS0601 reduces the incidence of restenosis: a prospective study of 335 patients undergoing percutaneous cor- onary intervention in China. Chin Med J, 119(1), 6–13. Chen KK, Schmidt CF (1924). The action of ephedrine, the active principle of the Chinese drug Ma Huang. J Pharmacol Exp Ther, 24, 339–57. Hu J, et al. (2009). Long-term efficacy and safety of all-trans ret- inoic acid/arsenic trioxide-based therapy in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci U S A, 106(9), 3342–7. Huang ME, et al. (1988). Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood, 72(2), 567–72. Klayman DL (1985). Qinghaosu (artemisinin): an antimalarial drug from China. Science, 228, 1049–55. Li GQ, et al. (1984). Randomised comparative study of mefloquine, qinghaosu, and pyrimethamine-sulfadoxine in patients with falcip- arum malaria. Lancet, 2(8416), 1360–1. Liao FL, et al. (2006). Biomechanopharmacology: a new borderline discipline. Trends Pharmacol Sci, 27, 287–9. Lo-Coco F, et al. (2013). Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med, 369(2), 111–21. Luo J, et al. (2015). Compound danshen (salvia miltiorrhiza) dripping pill for coronary heart disease: an overview of systematic reviews. Am J Chin Med, 43(1), 25–43. Murray CJ, et al. (2012). Global malaria mortality between 1980 and 2010: a systematic analysis, Lancet, 379(9814), 413–31. Shen ZX, et al. (1997). Use of arsenic trioxide (As2O3) in the treat- ment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood, 89(9), 3354–60. Sun HD, et al. (1992). Ai-Lin I treated 32 cases of acute promyelocytic leu- kemia. Chin J Integrat of Chinese and Western Medicine, 12,

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