Review

Science of Traditional Chinese Medicine

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Theory and scientificity of traditional Chinese medicine

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Abstract

The Nobel Prize for artemisinin and the COVID-19 pandemic have heightened interest in the disease prevention and treatment of traditional Chinese medicine (TCM). However, uncertainty and misinformation remain about some key issues. Herein, we discuss the current literature showing that, despite TCM gaining recognition, the theoretical systems of TCM and Western medicine rooted in different cultural backgrounds have huge differences in their theories and treatments. How to achieve accurate diagnosis in TCM, how to give scientific treatment, what is the mechanism of treatment, and what are the effect and safety of treatment, all need to be more clearly explained and require high-quality modern scientific evidence. An emerging consensus exists that, with the help of modern technology and scientific methods, it is necessary to excavate the essence of TCM that truly conforms to the laws of human life movement and disease development, realize cross-complementation with Western medicine, enhance human understanding of diseases, enrich diagnosis and treatment methods, and promote a new level in the field of life sciences.

Keywords: Basic theory; Scientific connotation; Traditional Chinese medicine

1. Introduction

Formed in the process of the Chinese people's long-term struggle with nature and diseases, traditional Chinese medicine (TCM) is one of the oldest existing treatment systems. TCM encompasses a wide range of practices, including some that are familiar to the West, such as Chinese Materia Media (CMM) and acupuncture, plus others that remain peculiar to most Westerners, such as cupping (heated cup therapy), Tui Na (massage), Qigong (movement and breathing exercises), and moxibustion (burnt mugwort therapy).[1] Traditional medicines are often seen as more accessible, more affordable, and more acceptable to people than contemporary drugs; therefore, the former also represents a tool to help achieve universal health coverage[2] and deal with a series of global health challenges in the 21st century, especially in the field of chronic diseases and population aging. TCM is commonly used in most parts of Asia, Africa, and Latin America. For millions of people living in rural areas of developing countries, herbal medicine, traditional therapies, and traditional practitioners are the main and sometimes only source of health care. In an era of soaring medical costs and general austerity, the affordability of most traditional medicines makes them highly attractive. In developed countries, these methods are usually used as a supplement to modern medicine to meet individual needs.[3] Nearly a quarter of modern medicines come from natural products, many of which were originally used in traditional medicines. Therefore, TCM is a resource for basic medical services and a source of innovation and discovery. However, TCM needs rigorous scientific data to prove its theory and efficacy, and it also needs evidence-based standards for quality and safety assessment to support its proper supervision.[2] Here, we identified references for this review through searches of Medline, Web of Science, Embase, and Google Scholar from the databases' inception to June 1, 2023. Publications in English were identified with various search terms for "traditional medicine" "traditional Chinese medicine" and "meta-analysis" among others. We organized new developments into topical areas, which then formed the basis for additional searches. We aimed to clarify some of the common misconceptions surrounding TCM via existing international evidence and provided suggestions for the modernization of TCM.

2. Fundamental theory and characteristics of traditional Chinese medicine: culture and science

TCM includes many tenets derived from Taoism, Confucianism, and ancient Indian philosophies that describe the natural world, life, and the human body. Concepts include Yin and Yang, which represent opposing yet complementary essences of nature; Five Elements, which covers the five basic elements of the universe (wood, fire, earth, metal, and water); Qi, which is used to represent intangible functions and energy; and Xue (the blood), which is used to represent the tangible material basis.[4] This terminology purports to be concerned with disease and human health but cannot be defined in terms of biochemical or biological facts or indeed measured. As a result, modern medical and scientific communities are commonly skeptical of such mystical concepts. However, with the continuous deepening of the understanding and research of Chinese medicine, an increasing number of scholars realized that the knowledge of Chinese medicine on the human body in BC had reached a certain height.[5,6]

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Yellow Emperor's Inner Classic (*Huang Di Nei Jing*) records fei (respiratory system) chao bai mai,[7] which is consistent with today's view that the lungs govern breathing, and the strength of the lungs affects the circulation and function of the body's blood. TCM believes that the "spleen and stomach (similar to the digestive system of modern medicine) are the foundation of acquired life." In the treatment of many diseases, regulating the spleen and stomach to restore their normal state is usually the key principle in TCM. Recent studies have found that cardiovascular disease, diabetes, obesity, and Alzheimer disease (AD) are all related to intestinal microecological imbalance.[8] TCM can significantly affect the intestinal microbial metabolism in these disease states, and the resulting changes can remain stable for a long time.[9] TCM has its system in theory and methods. The use of TCM is similar to the use of soldiers, focusing on the characteristics of CMM, such as Yaoxing (hot, warm, cool, or cold natures), Peiwu (sovereign, minister, assistant, and envoy), and treatment principles (such as adjusting Yin and Yang, strengthening body resistance, and eliminating evil).[10] This Chinese philosophy is reflected in TCM diagnosis and treatment.

2.1. Holism: "the unity of human and nature"

TCM emphasizes treating "people who are ill" instead of "illnesses in people." The 2 completely different treatment principles reflect the fundamentally different cultural bases of Chinese and Western medicine. The starting point of Western medicine theory is the concept of anatomy, the location of diseases, and the search for pathogens. Along this line of thinking, it gradually forms the core medical system to study human organs and tissue and the physiological and pathological changes of the interaction between pathogens in nature and various internal factors of the human body.[11] TCM attaches great importance to the influence of nature and social environment on health and disease, believes that the mind and body are inseparable, and emphasizes the coordination and mutual influence of physiology and psychology.[12] For instance, irritable bowel syndrome (IBS) is classified as "abdominal pain" "Xiexie" and "Yuzheng" in TCM. The etiology of IBS is summarized as abnormal of emotion, diet, and external evil. Liver depression and spleen deficiency, spleen and kidney Yang deficiency, cold, and heat are regarded as the key factors of IBS. TCM emphasizes that the human body is an extremely complex organic whole. The various parts of the human body are indivisible in structure, functionally interrelated, metabolically interconnected, and pathologically influencing each other.[13] The five Zang (viscera) organs are the essence of Zangfu manifestation (Zang Xiang) theory, which is a system in which each Zang represents a set of functions, and all the organs and tissue in the body can be classified into one of these.[14] The specific relationships are as follows: liver system, including the liver, gallbladder sinews, eyes, and nails; heart system, including the heart, small intestine, vessels, tongue, and face; spleen system, including the spleen, stomach, flesh, mouth, and lips; lung system, including the lung, large intestine, skin, nose, and body hairs; and kidney system, including the kidney, bladder, marrow, ears, and hair.[15] These five systems are not completely independent and separate from one another; they are connected through the channel system that covers all of the body and determines the flow of Qi and blood to every section. The functions of the five Zang (viscera) organs all work together in harmonious unity and are an important part of ensuring physiological balance in the human body. The concept of Western medicine highlights the substance and has a specific structure. It can be observed with the help of sense organs or other technical means and through research with certain quantitative standards. The concepts used in TCM theories are mostly relational concepts, which are generally not substantive, and grasp the essence of things in terms of functions, changes, and external manifestations. This holistic view is regarded as a vague concept by Western medicine. Modern Western medicine genetics has also developed from the study of individuals and a few genes to genomics research, as well as the adverse effects of environmental factors on the body.[16] Regarding the unity of the human body, modern medicine has realized that the human body's nervous system, immune system, and endocrine system are closely connected.[17] They jointly maintain the body's physiological activities and regulate the influence of internal and external environments on the body so that the human body is in a relatively balanced and healthy state. TCM and Western medicine are similar to each other but in different ways. TCM is advanced in that its philosophy is holistic and systematic.

2.2. Health is about balance and harmony

Yin-Yang theory explains how the five Zang (viscera) organ systems form a system of checks and balances and work synergistically to maintain dynamic equilibrium. The Five Elements theory explains the interrelationships between the five Zang (viscera) organs and how they form a whole that supports and controls each structure and function in the body[18] (Fig. 1). TCM emphasizes the importance of harmony in maintaining health, and the internal organs must be in harmony with one another to be healthy. In addition, emotions must be expressed moderately and appropriately, and people should be able to adapt to different environments. The root of good health is "only when the Yin remains calm and harmonious will the Yang Qi be contained and not be overly expansive"[19] or what we would call Yin-Yang dynamic equilibrium in modern terms.[13] Disease causation is divided into 3 categories: external causes including Six Excessive Qi (wind, cold, summer-heat, dampness, dryness, and fire) and pestilence; internal damage, including the Seven Emotions (joy, anger, worry, reflection, sadness, fear, and fright), improper diet, excessive work, and rest; and miscellaneous causes, including external injury, parasites, disease transmission to the fetus, poisoning, and erroneous medical treatment. *Yellow Emperor's Inner Classic* states that "when there is sufficient healthy Qi inside the body, the evil cannot invade the body." These statements concisely describe the principle of TCM, which is that illness occurs as a result of internal and external factors. When there is a cause of a loss of dynamic equilibrium in the functions of the body, then external factors are allowed to invade. We often say that "TCM uses medicinals with strong functional directions to treat strong misdirection in the body." This expression means TCM emphasizes using the qualities of medicinals to correct the imbalances that have been caused by illness factors. This is a fundamental treatment principle that focuses on solving the overall dysfunctional state caused by pathogenic factors. Foreign scholars have proposed the concept of biological response modifiers (BRMs), emphasizing the simultaneous use of BRMs in tumor chemotherapy, radiotherapy, or surgery, which can improve the patient's antitumor immunity and prevent surgery, radiotherapy, and chemotherapy from affecting the immune system and hematopoietic system, thereby improving the effectiveness of tumor treatment.[20] Using BRM and strengthening the body and foundation of TCM can enhance or regulate the immune function of the body, reduce the damage of pathogenic factors to the body, improve the body's disease resistance, and achieve the purpose of disease prevention and treatment.

2.3. Pattern diagnosis and individualized treatment

Both diagnosis and treatment are tailored to the person, time and season, and geographical place. This process is called "treating based on patterns differentiation." "Pattern differentiation" of TCM is based on the 4 examinations, namely, observing, listening/smelling, asking, and palpating, as well as the information that they provide us about

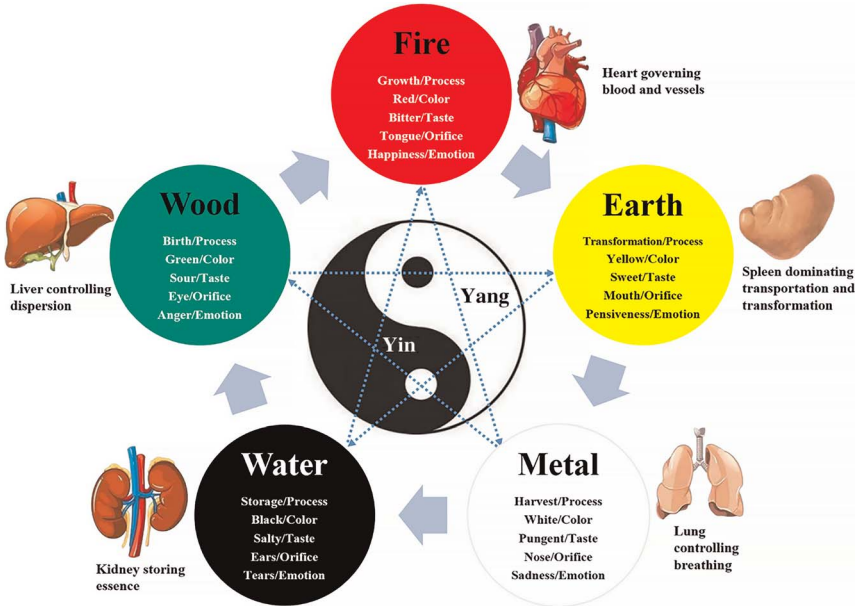

Figure 1. Yin-Yang and Five Elements theory in TCM. Yin and Yang signify essential signs and natures of human health conditions, including both external conditions such as cold, heat, warmth, seasons, and ecosystems as well as internal conditions such as Yin deficiency and Yang deficiency. The Five Elements theory is thus used to understand the properties of things or phenomena according to the functions and properties of the five basic materials and to state and deduce the mutual relationships and rules for interaction among things or phenomena based on the mutual generation and restriction of the five materials. The relationships of mutual generation, restriction, overwhelming, and rebellion among the five elements are mapped to the physiological and pathological relationships among the five viscera (liver, heart, spleen, lungs, and kidneys). TCM = traditional Chinese medicine.

the signs, symptoms, and constitution of an individual. TCM comprehensively analyzes these to ascertain causative factors, the nature of the illness, the location of the disorder, and the relationship between healthy and unhealthy Qi, so as to summarize and determine the specific pattern of symptoms and their nature. "Determining treatment" is based on the results of pattern identification, taking into account the constitution of the patient, the physical and geographical environment, and the season and climate. The treatment methods and principles are determined from these factors. The response of the patient in the course of treatment also determines how to proceed. TCM can be very flexible and tailor treatment to the specific situation; however, physicians must grasp what is the root and what is the branch and how to modify treatments based on presenting conditions to fully manifest the advantages of individualized treatment and flexible thinking. For example, common colds are divided into wind-heat and wind-cold, and the constitution of the person is considered. The choice of treatment principles (such as heat-clearing or cold-dissipating) and respective herbs or formulae (cold-dissipating herbs: cinnamon twig, ephedra, ginger, and perilla leaf; heat-clearing formula: Lonicera and Forsythia powder) is based on the pattern's differentiation. Therefore, the treatment given varies from person to person. If explained by black box theory, syndrome differentiation and treatment are the black box method used by TCM to deal with human diseases. Whether it is a holistic view or syndrome differentiation, various factors such as society and the environment must be considered when a disease is investigated. This is a humanistic medicine model. Modern genomics research has observed that disease-causing genes are polymorphic, leading to different clinical manifestations of the same disease in different individuals because of differences in the amount or function of biologically active substances.[21] Genetic polymorphism research has begun to emphasize the individualization of clinical medication.[22] The idea of individualized medicine is unified in Chinese and Western medicine. Studies have shown that disease or health is directly or indirectly related to genes, but not all diseases can be treated by gene therapy.[23] Future treatment should start with regulating genes rather than changing or correcting the structure of genes. This idea of emphasizing functions and neglecting structure coincides with TCM. Integrated diagnosis and treatment of diseases indicate the future development of medicine.

2.4. Health cultivation and preventing illness

TCM emphasizes the relationship between lifestyle and illness and advocates prevention and cultivation as the primary task of medicine. Regulating our emotions, balancing work and rest, having a regular diet, and practicing proper daily habits and housing are all important. Moreover, these can be used as interventions based on the constitution and the state of the disease. Nourishing the mind and body, supporting healthy Qi, and increasing resistance to evil Qi can all lead to greater health and prevent illness. Under the guidance of TCM thinking on health preservation, physicians have created health and fitness methods such as Tai Chi, Wu Qin Xi, Yi Jin Jing, and Ba Duan Jin.[24] TCM pays attention to the entire course of illness and its formation and strives to "first prevent illness before it occurs, prevent the further development of current diseases, and promote recovery after illness."[25] The idea of "preventive treatment of disease" in TCM is to prevent the occurrence and development of diseases, which is one of the main features of TCM. According to a survey by the World Health Organization (WHO), more than one-third of the population is in a "sub-healthy" state between healthy and sick. The US Centers for Disease Control and Prevention has officially named this chronic fatigue syndrome, which has no confirmatory physical signs or characteristic laboratory abnormalities, and the etiology and pathophysiology remain unknown.[26] TCM emphasizes the use of the body's autonomous survival force. These health concepts and various health-preserving methods of TCM are unique in dealing with "sub-health" conditions.[27]

2.5. Using multiple medicinals in "formulas" and the art of combining medicinals

TCM practitioners formulate their herbal remedies according to a set of principles (Peiwu), which organize ingredients in any Fufang into 4 functional roles: sovereign, minister, assistant, and envoy. The sovereign is the ingredient with major pharmacological activity. The ministers provide additive or synergistic activities. Assistants can augment the pharmacological effect, detoxify, or even counteract an excessively strong action. Envoys harmonize the whole recipe to ensure that all the substances in the Fufang are compatible.[28] There is early evidence supporting the Peiwu principles. A team analyzed the Realgar Indigo naturalis formula, which is a TCM-based leukemia treatment containing realgar, indigo minerals, and the herb red sage root.[29] The formula is composed of multiple components to achieve interaction and pharmacological synergy (multipathway and multitarget). This strategy may improve the therapeutic effect and provide the flexibility of personalized treatment. It is critical to explore the interactions between CMM components and disease targets for the modernization of TCM.[30] In a recent study, an integrative pharmacological strategy was applied to identify the antiviral and anti-inflammatory bioactive compounds from Huashi Baidu decoction (Q-14). A total of 343 chemical compounds were initially characterized, and 60 prototype compounds in Q-14 were subsequently traced. Among the 60 compounds, 6 compounds were identified to show notable anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) effects, including 2 inhibitors of the main protease, as well as 2 inhibitors of the RNA-dependent RNA polymerase. Meanwhile, 3 anti-inflammatory components were identified in a SARS-CoV-2–infected inflammatory cell model. In addition, glycyrrhisoflavone and licoisoflavone A also displayed strong inhibitory activities against cAMP-specific 3′,5′-cyclic phosphodiesterase 4 (PDE4), and both compounds bind in the active site of PDE4 with similar interactions.[31] These results suggested that the synergistic effect of multicomponents and multitargets might be the reason for TCMFs to exert clinical efficacy.

Both Chinese and Western medicines originated from local knowledge with cultural attributes. Different cultural factors may be the biggest obstacle to bridging the gap between the East and the West. Both Chinese and Western medicines have natural science attributes, and they both have the common goal of improving human health. Because of its extensive assimilation of knowledge from natural science and humanities, TCM has not only become a therapeutic approach but also profoundly influenced people's way of life. The remedies used in TCM to combat diseases embody a comprehensive perspective that emphasizes harmony, individuality, simplicity, and preventive treatment. This holistic outlook is a result of integrating principles from various scientific disciplines and humanities, leading to a distinctive and specialized approach to health care.[32]

3. Does it work?

As an important category of complementary and alternative medicine, the use of TCM has grown substantially in Western countries.[33] However, the Western world has very different voices about TCM. For some Westerners, apart from the well-known successful cases of artemisinin in the treatment of malaria and arsenic trioxide in the treatment of leukemia, ancient TCM is mysterious and lacks scientifically proven treatment methods,[34] whereas others believe that TCM is an empirical treatment that has been passed down for thousands of years. Although there is no scientific explanation, they affirm the efficacy and value of TCM. Such people often disagree that military terms are often used in modern medical terms to describe concepts such as immunology and virology and the practice of describing the disease and the body as a war between offensive and defensive parties.[35] More and more studies have confirmed the curative effect of TCM, which not only plays an eye-catching role in the prevention and treatment of common and frequently occurring diseases but also has advantages in the treatment of many chronic and difficult diseases, and it relieves the lack of treatment methods in Western medicine.[36,37] In recent years, social biopsychological medicine, integrated medicine, precision medicine, systems biology, and complex science, among others, have emerged, and they are cross-integrated with the theories and methods of TCM from different perspectives.[38] Technical methods and methods in related hot research fields such as intestinal microbiology, brain science, immunity and inflammation, and tumors also provide reference and support for TCM theory and clinical research.[39,40]

3.1. Cancer

The concept of TCM treatment of cancer is "strengthening the body and removing the evils," which is similar to modern medicine to improve immunity and function. Often, TCM is used to repress the progress of the tumor, reduce concurrent diseases and complications of the surgery, and increase the sensitivity to chemotherapy and radiation therapy. The goal is to increase immune functions in the body and decrease the harmful effects of each stage of surgical treatment, chemotherapy, or radiation, while treating cancer itself.[41] Using some forms of TCM while undergoing cancer treatment is a very widespread practice in China. A review of 2385 randomized and controlled trials and 579 nonrandomized and controlled trials that included 253,434 patients found that 72% used Chinese and Western medicines together, whereas 28% used TCM alone.[42] A randomized, unblinded, and controlled clinical trial conducted in Japan showed that shoosaikoto (TJ-9), an extract of 7 CMM, helps prevent liver cancer in patients with cirrhosis.[43] In addition, Chinese medicine prescriptions are currently used to alleviate the adverse effects of nonhematological toxicity caused by chemotherapy, including diarrhea, nausea, vomiting, and fatigue. Among them, Huangqin decoction (PHY906) composed of 4 CMM can improve the efficacy index of the chemotherapy drug irinotecan in the treatment of metastatic colon cancer and rectal cancer. Phase 1/2 or Phase 2 clinical trials in the United States have shown that PHY906 may have beneficial effects on irinotecan or capecitabine in the treatment of patients with advanced colorectal cancer, liver cancer, and pancreatic cancer.[44] This prescription has been used to treat gastrointestinal diseases for about 1800 years.

3.2. Cardiovascular and cerebrovascular diseases

Several studies on the treatment of cardiovascular and cerebrovascular diseases by Western medicine have embodied the main principle of TCM for the treatment of cardiovascular and cerebrovascular diseases—promoting blood circulation and removing blood stasis. A multicenter, randomized, double-blind, and placebo-controlled trial (n = 335, 6 months) showed that, compared with placebo, the rate of restenosis after coronary intervention treatment with CMM extracts was significantly reduced (26.0% vs. 47.2%).[45] In the treatment of ischemic diseases and the management of myocardial ischemia-reperfusion injury, there is evidence to support the therapeutic value of Chinese medicine–related strategies aimed at promoting blood circulation.[46] Some random and prospective clinical studies have shown that Shexiang Baoxin Pills can reduce the frequency of angina pectoris caused by coronary heart disease and the daily use of nitroglycerin[47] and can even reduce ischemic myocardial changes measured by electrocardiogram and perfusion imaging.[48] The emerging biomechanical pharmacology combines the pharmacological effects of TCM with the biomechanical properties of blood flow.[49]

The combined application of exercise (increasing the shear stress of blood flow) and the Shenlian extract helps prevent atherosclerosis.[50]

3.3. Neurodegenerative disorders

The symptoms of Parkinson disease (PD) were first seen in the tremor paralysis in the *Yellow Emperor's Inner Classic*. A meta-analysis showed that, compared with the Western medicine control group, the adjuvant treatment of TCM improved the severity score of the clinical symptoms of PD patients, with fewer adverse reactions; the adjuvant treatment of TCM was generally safe and well tolerated, and it could significantly reduce the adverse effects caused by conventional drugs.[51] Neurodegeneration is a complex process involving a variety of pathophysiological mechanisms. TCM mixture has long been used to treat AD and PD. For example, Huanglian Jiedu decoction[51] and Fuzisan[52] for AD, Jiawei Liujunzi decoction,[53] or Sanhuang Xiexin decoction[54] for PD can improve the symptoms and communication ability of PD patients. In addition, a double-blind and placebo-controlled clinical trial conducted in the United Kingdom showed that a compound consisting of 10 CMM produced a significant therapeutic effect in the treatment of atopic eczema that was resistant to traditional steroid therapy.[55] These studies have shown that TCM is effective for conventional diseases, and even when traditional Western therapies are not enough to provide relief treatment, its treatments are equally effective.[56]

3.4. Pain-related disorders

Acupuncture is an important part of TCM. As the world's intangible cultural heritage, acupuncture has become the most widely used alternative medicine therapy in the world. The latest research shows that acupuncture and moxibustion have a definite effect on analgesia and body regulation. More than 60% of acupuncture treatments worldwide are related to pain.[57] A single-case meta-analysis of 39 randomized and controlled acupuncture clinical trials (n = 20,827) carried out in Western countries from 2008 to 2015 proved that acupuncture was significantly better than the treatment of head, neck, shoulder, and lower back pain. The analgesic effect of follow-up after 1 year only decreased by 15%. The difference in effect size between the acupuncture group and the nonacupuncture control group was 0.5 standard deviations, and the difference between the effect size and the placebo acupuncture control was only 0.2 standard deviations. It shows that the curative effect of acupuncture in the treatment of chronic pain continues to be stable, denying the view that acupuncture is only equivalent to a placebo effect.[58,59] Acupuncture as an adjuvant therapy can improve the number and degree of angina pectoris in patients with chronic stable angina pectoris, improve the severity of angina pectoris, and reduce the symptoms of anxiety and depression in patients.[60] In 2014, the therapeutic effect of acupuncture on sepsis was discovered for the first time. In the Zusanli point of the mouse, the effect of acupuncture can be simulated, which can effectively alleviate the symptoms of sepsis in the mouse and reduce the mortality rate.[61] In 2016, researchers used electric acupuncture to stimulate the human vagus nerve, which effectively reduced the body's immune response and relieved the symptoms of rheumatoid arthritis.[62] The latest research combines the characteristics of acupuncture and moxibustion with the principles of clinical epidemiology and evidence-based medicine and draws on internationally accepted methods to provide clinical research on acupuncture treatment of migraine,[63] functional dyspepsia,[64] and other diseases to obtain high-quality clinical evidence.

3.5. Pandemics and infectious diseases

The outbreak of pandemics and infectious diseases such as COVID-19 is not the first threat, and it will not be the last. The clinical practice of TCM in fighting the epidemic of infectious diseases has proven to be effective. In 2003, the SARS epidemic in China resulted in 5327 cases of infection, with more than 60% of cases reported worldwide. Globally, the mortality rate for SARS was 9.5%. However, it was only 6.5% within mainland China. The reasons for this success included the fact that TCM was a part of the treatment protocol for many patients (58% received TCM).[65] In Guangzhou Province, TCM physicians participated at the earliest stage and the deepest level, compared with other provinces. Therefore, it is interesting to note that, in Guangzhou, mortality rates were only 4%.[66] In Beijing, the inclusion of TCM physicians and medicinals into SARS treatment led to an 80% drop in mortality rates.[67] Average costs for biomedical treatment were 50,000 RMB per patient, whereas CMM was very significantly less. The Affiliated Hospital of Guangzhou Chinese Medicine University reported that the most expensive case of treatment of SARS with CMM was only 5000 RMB. Because treatment included large doses of antibiotics and other drugs, SARS patients who received biomedical treatment have suffered from complications of pulmonary fibrosis and femur necrosis at rates that exceed 30%, of these 30% also have diabetes. However, patients who chose TCM treatments have not exhibited these complications.[68] Similarly, TCM has gained world attention owing to its effectiveness in treating infectious diseases such as the H1N1 flu virus, human H7N9 avian flu, HIV/AIDS, and hand, foot, and mouth disease.[69] Recently, people in China and around the world were infected by SARS-COV-2, who might exhibit severe lung injury and lymphopenia.[70] TCM has made great contributions to the treatment of COVID-19[71] with greater than 90% involvement all over China[72] and showed a high effective rate in multicenter, prospective, randomized, and controlled clinical trials.[73,74] Several systematic reviews and meta-analyses have shown that integrated Chinese and Western medicine treatment can increase the disappearance rate of fever, cough, sputum, fatigue, chest tightness, and anorexia and reduce the patient's fever and fatigue time without increasing adverse reactions. TCM is used as an adjuvant treatment, and standard nursing care can help improve the symptoms and signs of COVID-19 patients.[75–77] These effects are probably through the mechanism of inhibiting the SARS-COV-2 replication and reducing proinflammatory cytokines.[31,78,79] The 12-month results of the largest longitudinal cohort study of COVID-19 hospitalized adult survivors to date showed that many COVID-19 patients will fully recover after more than 1 year.[80]

Western medicine relies on science to standardize the creation and evaluation of drugs at the molecular level. The complexity and variability of TCM through syndrome differentiation and treatment and personalized prescription drugs are difficult to evaluate, as well as its effectiveness and safety through the current standard methods of randomized and controlled clinical trials. Redesigning clinical trials will accelerate the integration of these 2 treatments. Integrating the principles of personalized medicine into randomized controlled trials (RCTs) leads to personalized explanatory RCTs and personalized pragmatic RCTs.[81] These types of trials select patients according to their genotype rather than the normal methods based on shared clinical diagnostic and biological characteristics. Moreover, this concept of personalized medicine has similarities to the individualized diagnostic and treatment methods of traditional Asian medicines (even though the molecular mechanisms have yet to be elucidated).

4. Biological essence and inspiration

4.1. Acupuncture

In the theory of TCM, meridians are channels that run Qi and blood and penetrate the internal organs of the human body, and acupoints

are important nodes on the meridians. Only when acupuncture is placed at specific acupoints, which affects the movement of specific meridians, can it play the expected role. Scientific research has partially proved that the ancient art of acupuncture and moxibustion does have clinical value, but it is not yet clear what biological process acupuncture works through.

A recent study has confirmed that electrical acupuncture stimulation drives sympathetic nerve pathways in a somatic and intensity-dependent manner. Studies have revealed that low-intensity acupuncture to stimulate acupoints on the hind limbs of mice (such as Zusanli ST36) can activate the vagus nerve–adrenal anti-inflammatory pathway, whereas acupuncture to stimulate abdominal acupoints (such as Tianshu ST25) cannot induce this anti-inflammatory pathway.[82] The team's further research shows that a type of PROKR2-Cre–labeled dorsal root ganglion sensory neurons is essential for low-intensity acupuncture stimulation to activate the vagus nerve–adrenal anti-inflammatory pathway.[83] What is more noteworthy is that, according to the somatic distribution characteristics of such nerves, the anti-inflammatory effects of low-intensity electroacupuncture at different locations can be predicted, thereby providing a modern neuroanatomical basis for the relatively specific existence of acupoints. In addition, acupuncture intensity, depth, and test result indicators are all important factors that affect the specificity of acupuncture points. These findings enrich the modern scientific connotation of surface stimulation therapy such as acupuncture and moxibustion and provide an important scientific basis for the clinical optimization of acupuncture stimulation parameters and inducing different autonomic reflexes to treat specific diseases.

Research on the biological basis of acupuncture has now been extended into several different areas of the life sciences, and the dynamic nature of clinical acupuncture treatment and the individualization of treatment have all led to frontiers in scientific research as science grapples with these issues. Because of the known effects of acupuncture needling on the vagus nerve, the National Institutes of Health in the United States initiated the SPARC (stimulating peripheral activity to relieve conditions) project in 2016. The project aims to look at how peripheral stimulation can alleviate symptoms and conditions. The ultimate purpose is to study how precisely regulation of internal organs can occur by using nerve coding to transmit signals to the internal organs. The SPARC project has already focused on analyzing how peripheral nerve stimulation may affect migraine headaches, type 2 diabetes, heart failure, overactive bladder syndrome, pelvic disorders, and inflammation.[84] These are all conditions for which acupuncture has shown to be effective and often superior to biomedicine. The goal of this project is to elucidate how internal organ regulation is achieved through the pathways of the nervous system, making it overlap with basic research on acupuncture serendipitously. The results from the SPARC project may turn out to stimulate new avenues of acupuncture research. Recent research reports show that using ultrasound-guided and noninvasive stimulation of the spinal segment connected to the hepatic portal vein can regulate blood sugar. Similarly, ultrasound-guided stimulation of the spinal segment connected to the spleen can regulate immune and anti-inflammatory responses.[85] From this, we can see that SPARC researchers have extended their project to include stimulation on the surface of the body. Acupuncture research aims to explain the concepts of "needles, moxibustion, and medicinals,"[86] whereas the SPARC project represents an attempt to explain the pathways that allow "molecular medicine" to become "electrical medicine." This is a development and an improvement in research on therapies that use stimulation of the surface of the body to treat medical conditions. The implications for acupuncture, as the most representative therapy on the surface of the body, are quite significant. In July 2019, the National Institutes of Health's National Center for Complementary and Integrative Health in the United States convened a conference on "problems related to acupuncture points" signifying a growing understanding of the central scientific issues in acupuncture research and basic scientific research on acupuncture. Acupuncture regulates the self-healing mechanisms in the human body, which precisely mirrors the current trend toward emphasizing wellness and not just the absence of disease in medicine.

4.2. Molecular mechanisms

The emerging advanced technologies such as multi-omics, molecular biology, and bioinformatics have made great progress in realizing high-level expression and production of natural active ingredients or transgenic ingredients of medicinal plants (MPs) and revealing the biological properties of genuine medicinal materials (Daodi herbs). MPs serve as primary sources of specialized pharmacologically active natural metabolites, such as artemisinin for antimalarial purposes, tanshinones for anticardiovascular diseases, and taxol and vinblastine for anticancer treatments. Researchers have extensively studied MPs and used omics technologies, bioinformatic tools, and databases to investigate their properties. These technologies include taxonomics, transcriptomics, metabolomics, proteomics, genomics, pangenomics, epigenomics, and mutagenomics. However, because of the intricate biological regulatory networks, single-omics approaches often fail to fully elucidate specific biological phenomena. In recent years, there has been an increase in integrated multi-omics studies of MPs. The outcomes derived from multi-omics data sets not only lay the foundation for identifying MP species with high yield, good quality, and disease resistance through molecular breeding but also provide a theoretical basis for achieving consistent biotransformation of desired secondary metabolites through synthetic biology. Notably, it is now feasible to identify functional genes that control key biological traits and determine the catalytic mechanisms of key enzymes involved in the biosynthetic pathways of active compounds through multi-omics and bioinformatic studies. For example, the presence of anticancer clerodane diterpenoids serves as a chemotaxonomic marker for *Scutellaria barbata*, although the molecular mechanisms underlying clerodane biosynthesis remain unknown. Li et al.[87] have reported a high-quality assembly of the 414.98 Mb genome of *S barbata* into 13 pseudochromosomes. They have also mapped the plastidial metabolism of kaurene (gibberellins), abietane, and clerodane diterpenes in 3 species of the Lamiaceae family (*S barbata*, *Scutellaria baicalensis*, and *Salvia splendens*) using phylogenomic and biochemical data. These findings offer significant insights into the evolution of clerodane biosynthetic pathways in the mint family, Lamiaceae, and will facilitate the production of anticancer clerodanes through future metabolic engineering endeavors. In another review by Zheng et al.,[88] the transcriptional regulation modes of biosynthetic pathways for various high-value active ingredients in *Artemisia annua*, *Salvia miltiorrhiza*, *Catharanthus roseus*, *Taxus wallichiana*, and *Panax ginseng* are examined from the perspectives of environmental factors and hormone signals. The review concludes that the "environmental factors–hormone signals–transcription factors–active ingredient" regulatory network, along with its associated research methods, plays a crucial role. In this network, multiple transcription factors concurrently control numerous synthase genes (Fig. 2). Understanding the molecular mechanisms influencing the transcriptional regulation of active ingredients is essential for developing new breeding possibilities. This research provides a theoretical basis for unraveling the effects of adversity and the formation mechanism of genuine medicinal materials. It also serves as a reference for future gene editing germplasm innovation methods to construct the regulatory network of active ingredients.

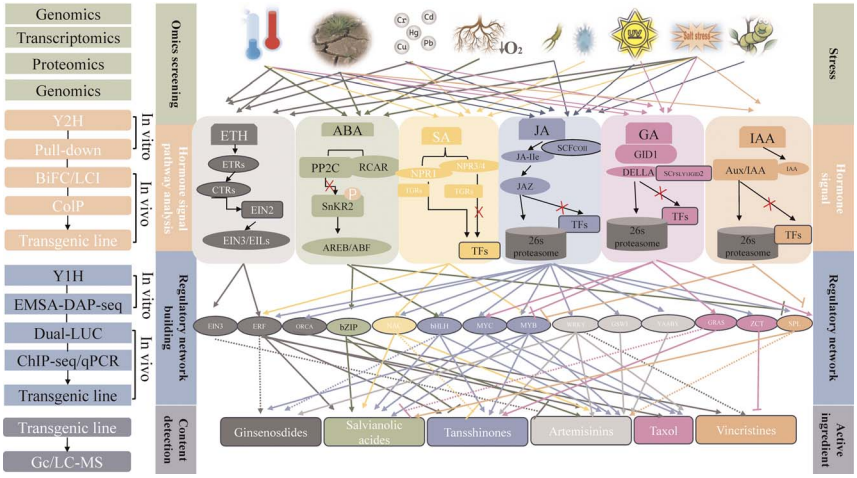

Figure 2. Transcriptional regulatory network of active ingredients and multi-omics integration in medical plants.[88] (A) 'Omics data and molecular biology technology can be used to decipher the molecular mechanism of transcriptional regulation of active ingredients. (B) The transcriptional regulatory network of active ingredients is the most important tie between the production and environment in medical plants. Multi-omics integration can effectively identify TFs involved in multiple families and the various signaling pathways that regulate active ingredient biosynthesis in medical plants. ABA = abscisic acid; BiFC/LCI = bimolecular fluorescence complementation/ firefly luciferase complementation imaging; ChIP-seq = chromatin immunoprecipitation sequencing; CoIP = coimmunoprecipitation; DAP-seq = DNA affinity purification and sequencing; EMSA = electrophoretic mobility shift assay; Eth = ethylene; GA = gibberellic acid; GC/LC-MS = gas chromatography/liquid chromatography-mass spectrometry; IAA = indole acetic acid; JA = jasmonic acid; LUC = luciferase; SA = salicylic acid; TF = transcription factor.

In the foreseeable future, precise gene editing technology can simulate adversity effects by constructing specific regulatory networks. This can reshape the physiological processes of MPs or enhance the accumulation of target active ingredients, providing a theoretical framework for germplasm innovation in the field of MPs.

However, several challenges remain unresolved in genome editing and the manipulation of functional genes in MPs because of the absence of suitable transformation and regeneration techniques. Synthetic biology, which involves strain improvement, microbial system development, and the reconstruction and optimization of metabolic models tailored to specific metabolite types, presents significant challenges. There is promise in using machine learning and artificial intelligence as tools for integrating and analyzing multi-omics data sets. These approaches demonstrate predictive performance, flexibility, and the ability to capture hierarchical and nonlinear features.[89] With an increasing number of studies focusing on MPs, the availability of omics databases and bioinformatics tools is expected to expand. This progress will enable researchers to transition from single-omics to multi-omics approaches. Integrated multi-omics studies on MPs hold the potential to enhance and streamline the development of molecular breeding techniques and synthetic biology approaches in the field.[90]

5. Development and prospects

The world's TCM service market is valued at approximately US $50 billion per year.[91] In 2015, the export value of CMM products was US$3.77 billion, a year-on-year increase of 4.95%. In the WHO Traditional Medicine Strategy 2014–2023, they reported that there are 100,000 Chinese medicine clinics worldwide and 300,000 Chinese medicine physicians and related health care workers. In addition, acupuncture is the most popular modality, with CMM playing a secondary role.[92] The World Health Assembly (WHA) resolutions WHA56.31 and WHA67.18 have played a significant role in enabling countries to promote the safety, quality, and effectiveness of traditional and complementary medicine (T&CM). As a result, many countries have taken the initiative to develop national policies, regulatory frameworks and strategic plans for T&CM products, practices, and providers. By 2018, 98 of the 193 countries had established national policies and regulations on T&CM, whereas 79 countries had implemented T&CM programs. In addition, 75 countries had established dedicated national research institutes focusing specifically on T&CM. These efforts reflect the growing recognition and integration of T&CM within health care systems worldwide.[93] Up to 2019, 45 ISO standards had been issued. On May 26, 2019, the 72nd World Health Congress approved the 11th International Classification of Diseases Revised Version and included traditional medicine from China for the first time in its history. The additional section on TCM represents the international acceptance of TCM by global governmental authorities.[94] Despite the growing acceptance and inclusion of T&CM in national health systems, several challenges persist. These challenges include a perceived lack of strong political support; inadequate infrastructure for research and evaluation of T&CM products' safety, quality, and efficacy; and weak regulatory frameworks for monitoring T&CM practices, products, and providers. Notably, although 34 countries have incorporated herbal medicines into their national essential medicines lists, there is still work to be done to fully integrate T&CM into health care systems. Addressing these challenges is crucial to ensure the effective and safe integration of T&CM into national health systems and to maximize their potential benefits.

At present, the development of TCM has ushered in an unprecedented opportunity. The Chinese government attaches great importance to the development of TCM. Based on the work carried out under the WHO Traditional Medicine Strategy 2002–2005,[95] the 2014–2023 update strategy places more emphasis on health services and systems than the previous strategy, including TCM products, therapies, and practitioners.[92] In addition, complexity science with the core of exploring the essence of life at the intersection of matter and information and system biology with the advantage of understanding the connectivity and dependence of the components in dynamic and nonlinear systems is expected to promote human alignment for the understanding of medicine. On the basis that ICD11 allows Chinese syndrome coding based on Western medicine diagnosis, the development of high-quality evidence-based

medicine will bring new opportunities for the evaluation of the efficacy and safety of TCM. Because an evaluation system that fits the particular characteristics of TCM is gradually established, people will grasp the relative advantages of Chinese and Western medicine. The advantages of Western medicine in the prevention and treatment of infectious diseases, the treatment of acute and emergency conditions, and acute pain relief are indisputable.[96] However, biomedicine has made slow progress in the understanding and treatment of chronic and degenerative diseases. It is precisely these conditions that have led to soaring medical costs and unsustainable treatment in Western countries. In stark contrast, the potential of TCM to treat diseases such as influenza cannot be ignored, whereas the advantages of TCM are particularly evident when we consider the treatment of a wide variety of diseases that do not have an infectious component but are rather due to internal imbalances in the immune system or other biological systems. In brief, the 2 systems cannot replace each other. Instead, they will fill each other out. Looking to the future, TCM will hopefully play a leading role in the treatment of human disease, a supporting role in the treatment of major diseases, and a central role in rehabilitation medicine.

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None.

Statement of ethics

None.

Conflict of interest statement

The authors declare that they have no financial conflict of interest about the content of this report. Luqi Huang is the Editor in Chief, and Lanping Guo is the Editorial Board Member of Science of Traditional Chinese Medicine.

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Data availability statement

All study data are included in the article and/or appendix.

Author contributions

None.

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