



Traditional Knowledge-based Medicine: A Review of History, Principles, and Relevance in the Present Context of P4 Systems Medicine

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ABSTRACT

Wellness and healing are the challenges traditionally addressed by medicine, empirically shaped along with the evolution of civilizations. Western medicine (WM) originates from Middle-Eastern and Mediterranean medicine (during the Egyptian, Greek, and Roman empires) and has established itself as the reference in most countries with undisputable benefits on health and life expectancy. Traditional medicines (TMs) are millennia old and offer empirical practices including medication with natural elements and focus on overall wellness. Although the purpose of relief is similar in WM and TM approaches, the philosophies and methodologies differ. TM emphasizes the consideration of the patient body and mind as a whole for diagnosis, prevention, and treatment; WM focuses on the suppression of symptoms on targeted parts of the body. The acceptance of TM by the scientific community is limited by the lack of ground-breaking scientific evidence of its benefits and efficiency, coupled to the ignorance of its inherent medical basis. We review the origins and concepts of TM from Southern and Eastern Asia, as compared with WM, and believe it can help to create a modern systems biology-based approach to health and healing, in the sense of predictive, preventive, personalized, and participatory (P4) medicine.

Keywords: Traditional knowledge-based medicine, Traditional Chinese medicine, Kampo, Sa-sang, Ayurveda, Western medicine, P4 medicine, Systems medicine, Systems biology

From traditional to general medicine

Origins and development of mainstream medicine

The first traces of medicine in the Middle-Eastern area date back almost 4 millennia to Ancient Egypt, with the *Kahun Gynaecological Papyrus*: 1800 BCE, the *Edwin Smith Papyrus*: 1600 BCE, and the *Ebers Papyrus*: 1550 BCE. Back then, the explanation and treatment of all sorts of diseases was based on sacred and spiritual beliefs. Thus, healing of patients involved a mix of prayers, magic practices, and herbal mixtures. Egyptian physicians, mostly priests, developed early surgery and anatomy knowledge thanks to the dissection of human bodies.^[1,2] Later during Antiquity, in the Greek

civilization, Hippocrates (ca. 470–471 BCE) was the first to reject divine causality in medicine and to develop a new approach to diseases based on scientific observation of the human body. Hippocrates work was in opposition with the mainstream Aesclepi-an beliefs, based on religion. This marked the first split between science-based and religion-based medicine, and Hippocrates is nowadays considered as the Father of Medicine—the Hippocratic Oath being an ethical reference and motto in the medical community worldwide. Galen, a Greek physician, later contributed to the expansion of Greek medical knowledge within the Roman Empire, which became the dominant reference for more than a millennium.^[3] Indeed, after the fall of Rome, medicine did not evolve significantly for centuries, and most of its practice remained based on religious practices. However, the knowledge build by Greek Medicine was transmitted and preserved within Arabic Medicine during the medieval times,^[4] and was brought as far as the Indian subcontinent with the Mughal invasions. Not until the Renaissance did medicine experience a significant revival based upon a better understanding of anatomy and the functions of organisms (neurology, blood circulation). Emergence of new tools during the post-Renaissance period (thermometer: 16th century; micro-

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Abbreviations and Acronyms

BCE = Before current era

CE = Current era

TCM = Traditional Chinese medicine

TKBM = Traditional knowledge-based medicine

TM = Traditional medicine

WM = Western medicine

scope: 17th century; stethoscope: 19th century; anesthesia and X-rays: 20th century) triggered significant progress within several domains: hematology with William Harvey (1578–1657: blood circulation), Athanasius Kircher (1601–1680: blood observation), Richard Lower (1631–1691: transfusion), William Hewson (1739–1774: blood coagulation); histology with Marcello Malpighi (1628–1694: glandula and viscera physiology); bacteriology with Louis Pasteur (1822–1895) and Robert Koch (1843–1910) for pathogenic micro-organisms; and surgery and experimental medicine with John Hunter (1728–1793) and Claude Bernard (1813–1878).

The 19th century industrial revolution led to several advances, playing a role in the rise of modern medicine. Indeed, the improvement of life conditions, hygiene and sterilization helped in better understanding of pathological causes. During the 20th century, laboratory research became an integral component of medical practice at hospitals and universities.

Introducing traditional medicines

Modern medicine was largely disseminated across the world during recent centuries by explorers, missionaries, and merchants, following the path of trans-continental history and human migration events, and more recently through the industrial revolution and the globalization of the pharmaceutical market. It is now widely used as the conventional medicine of reference in a majority of countries and cultures. Even though progresses in medicine are based on scientifically proven evidence contributed by laboratory research or clinical outcomes, it has emerged gradually from the empirical knowledge of traditional medicines in ancient civilizations (Egypt, Mesopotamia, Greece, India, China).

Despite the indisputable benefits of modern medicine, leveraging scientific assays and results to establish diagnosis and fight against diseases, a large part of the world still relies on the contemporary forms of Traditional, Complementary, and Alternative Medicines (TCAM or CAM),^[5] which will be here referred to as traditional knowledge-based medicine (TKBM) to avoid confusion with the traditional Chinese medicine (TCM) acronym. TKBM is notably popular in Asia, where, for instance, TCM, Kampo, Sa-sang, and Ayurveda are respectively linked to the Chinese, Japanese, Korean, and Indian cultures and societies. TKBM is even integrated in the national health-care program in some countries. The approaches in TKBM drastically differ from conventional Western medicine (WM). Basically, using a wide variety of therapies, from administration of natural herbal products to chiropractic therapies, the Asian TKBMs place the patient wellness at the center of care and treatment instead of focusing on the eradication of the pathology symptoms as in WM. Although TKBM developed based on some kind of scientific evidence in terms of diagnosis and treatment, as an ancient medicine it was much limited by the primitive tools available for both medical observation and evaluation; hence, the understanding of human health and disease status was not based on anatomy and physiology in such a precise manner than currently. Nevertheless, many efforts are made nowadays to address

these issues with clinical trials, identification of active ingredients, receptors, and involved pathways.

Clearly, modern medicine evolved in the context of Western and Mediterranean cultures from a background of ancient TKBM. But how did TKBM evolve in other parts of the world like Asia within the context of current contemporary civilizations with the imprints of local cultures? We will now describe the principles and context of 2 Asian TKBMs: TCM, which derived in Japan and Korea into Kampo and Sa-sang respectively, and Ayurveda, a prominent Indian practice of medicine, and highlight the main similarities and differences between TKBM and WM, then discuss how the ongoing transition from reactive to proactive medicine could benefit from their convergence.

TKBM in China and nearby cultures

Traditional Chinese medicine

Origins and history

Sources from ancient China. Although it is not clear when TCM originated, it is believed to be the result of a continuous series of observations and works, with one of the most important domains being the use of herbs toward medicinal purposes, or *Materia Medica*. The Chinese *Materia Medica* (*Compendium of Materia Medica*, or *Ben Cao Gang Mu*) compiled by Li Shi Zhen (1518–1593) includes works dating back as early as 1100 BCE,^[6] and gathers more than 1800 entries with over 11,000 formulae. It is considered as the most complete reference in herbal information for medicinal application in TCM. Archaeological evidence has been dated back to the Shang era during the Bronze Age (16th to 11th century BCE),^[7] although it is not completely clear whether herbal medicine was used at that time.^[8] Previously, several works developed in the framework of the TCM philosophy and application, which were based not only on *Materia Medica*, but also on other practices such as acupuncture, moxibustion, tuna massage, and qigong exercise. The *Inner Canon of the Yellow Emperor* (*Huangdi Neijing*) was compiled during a period including the late Warring States period (475–221 BCE) and the early Han period (206 BCE to 220 CE). It is believed to be the earliest and most important piece of Chinese ancient medicine work. Written under the form of a dialog between the Yellow Emperor and his acupuncturist Qi Bo, one important figure in his government among other ministers, it depicts the philosophy and basics of TCM, without making reference to the magical and shamanistic beliefs. Instead, it is centered on means to develop a natural equilibrium of the body and mind through a balanced lifestyle, and thus to reach wellness and health. Along with the *Huangdi Neijing*, further works developed among the medical communities were integrated in the framework of TCM such as *Huangdi Bashi Yi Nanjing*: the Huang Emperor's Canon of Eighty-One Difficult Issues, 1st century BCE and *Shang Han Za Bing Lun*: the Treatise on Cold Damage Disorders, 2nd century CE.

Toward the adoption of conventional medicine. During the succession of dynasties in the following centuries, the principles and theories of TCM did not evolve very much. Instead, each dynasty attempted to compile its own medical books, retrieving as much of the ancient and increasing knowledge. This was facilitated by the 10th century development of woodblock printing to combine works on particular medical domains. As a result, by the 17th and 18th centuries, TCM had not evolved as much as WM in Europe, and China took the benefits of the first Christian missionaries to reach their land. More efficient and safe practices were thus introduced, for example, Jennerian smallpox vaccination in Canton in 1805,^[9] which produced better results than the TCM-based preventive in-

oculation of small amounts of smallpox dried crusts into subjects nostrils.^[10] WM became thus greatly trusted and spread easily in the next century to become the medicine of choice in developed areas. However, TCM was still valued over the whole country, and the governments in the second half of the 20th century helped in the creation of hospitals and schools based on TCM. To date, WM remains the medicine of choice, but both medicines coexist, TCM being strongly anchored into the Chinese culture.

Principles: The Chinese philosophy

Yin and Yang concept. Chinese Medicine principles rely on the theory that the human body is an open organism operating in a continuous biological and mental exchange process with the outside environment. When exchanges are in a balanced state, then the health of the human organism is optimal. On the contrary, a challenged or compromised balance means illness occurrence. The understanding of this dual conception of 2 parts having influence on each other leads to the Chinese concept of *yin* and *yang*, 2 fundamentals of the Chinese philosophy, of equal forces in a balanced condition, and representing the positive and negative factors, which influence equilibrium.^[11] Starting from this concept, the variations of positive (*Yang*) and negative (*Yin*) influences around equilibrium are applicable to dichotomous factors (Table 1).

Qi, meridians, oxygen and blood vessels. In TCM, the proper functioning and homeostasis of the human body within its surrounding environment is permitted thanks to an efficient absorption, circulation, and distribution of what is widely taught and known as the “energy” through the organism, moving from the absorbing parts to the storage and transformation parts. This “energy” is named *qi*. Due to historical misconceptions and misleading interpretations,^[12] it is known in Western civilization as an invisible “energy” that could be considered as the source of life that allows the flow of nutriment and molecules necessary to maintain the organism in a balanced condition. This “energy” flows within specific pathways, called “meridians,” forming a sort of metaphysical network of lines running through the body. These initial translations of the definitions developed in the absence of better, more faithful and relevant words. Actually, a more proper translation for *qi* would be “air,” and the word “meridian” may have derived from the Chinese word *mai*, which means “vessel.” In that context, *xue mai* would mean the “blood vessel.” It may be easier for the noninitiated persons in Western cultures to understand that the Chinese physicians in ancient times referred to oxygen as the source of life, circulating through the blood vessels, than to make sense of an

“energy” circulating through “meridians.” However, by extension and misconception, *qi* refers in modern terms to the invisible “energy” flowing through bodies, thus also referring to the invisible mind part of an organism. As medical knowledge of body anatomy and physiology was not as exhaustive as in current modern medicine, it is understandable that the TCM definitions were only vaguely approaching the contemporary accurate descriptions of how human body functions.^[13]

Classification of organs. Chinese Medicine divides the organs into 2 categories: the storing organs and the transforming organs. Thus, the function of an organ is of greater importance than its structure. The psychological consequence of an organ function or dysfunction is also depicted in TCM, which emphasizes the importance of psychosomatic disorders.

Classification of organs—The storing organs: The 5 Zang.

There are 5 storing organs, named *Zang*. They are solid organs: *Xin*, *Gan*, *Pi*, *Fei*, and *Shen*. They are symbolically associated with natural elements to point their role; each of them includes an organ, a biological function, and a psychological function. *Xin* is associated with fire: it spans the heart, brain function, and psychological function of the mind. *Gan* is associated with wood: it spans the liver, the liver function, and sensory-motor system, the psychological function of equilibrium and tranquility. *Pi* is associated with earth: it spans the spleen and pancreas, the functions of absorption, digestion, distribution and utilization of nutriment, and the psychological components of temper and intelligence. *Fei* is associated with metal: it spans the lung, the respiratory function and the psychological function of willpower. *Shen* is associated with water: it spans the kidney, the endocrine system, and the psychological function of willingness.

Classification of organs—The transforming organs: The 6 Fu.

Complementary to the 5 solid organs, there are 6 transforming organs, named *Fu*. They are hollow organs: *Dan*, *Xiaochang*, *Wei*, *Dachang*, *Panguang*, and *Sanjiao*. Similar to the 5 *Zang*, each is also associated with elements, organs, a function or system, and a psychological function. *Dan* is associated with wood: it includes the gall bladder, controls the circulation of body fluids, and the psychological function of equilibrium and tranquility. *Xiaochang* is associated with fire: it includes the small intestine, the absorption of nutriment and transportation of waste, and the psychological function of the mind. *Wei* is associated with earth: it includes the stomach, the digestion function and muscular contraction system, and the psychological function of temper and intelligence. *Dachang* is associated with metal: it includes the large intestine, the immunological system and cellular response to pathogen, and the psychological function of willpower. *Panguang* is associated with water: it includes the urinary bladder, the water balance and excretion system, and the psychological function of compliance. Additionally, another entity named *Sanjiao*, which could be considered as the sixth *fu*, is associated with fire, and is the coordinator of the 3 parts of the body: the upper zone with the respiratory and cardiovascular system, the middle zone with digestion, and the lower zone with excretion. It is also known under the “Triple Burner” name. Note that each of these types corresponds more to a system than to any particular anatomical feature or organ. Thus, at its theoretical heart, TCM is a systems-oriented interpretation of medical science.

Eight principles for differentiation of syndromes. The 8 principles were also firstly discussed early in the Yellow Emperor’s Classic of Internal Medicine. TCM differentiates signs and symptoms of a disease by 8 principles that are in 4 pairs of 2, for exam-

TABLE 1.

Examples of Dichotomies in TCM

Concept	Yin	Yang
Gender	Female	Male
Body	Interior	Exterior
	Front	Back
	Solid organs	Hollow organs
	Legs (below waist parts)	Trunk/head (above waist parts)
	Passive, weak, slow body aspects	Active, strong, fast body aspects
Disease	Hypofunction	Hyperfunction
Universe	Earth	Heavens

Variations of positive (*Yang*) and negative (*Yin*) influences around equilibrium are applicable to dichotomous factors, such as, but not limited to, gender, body, disease, or universe.

ple, cold and heat, exterior and interior, deficiency and excess, and *Yin* and *Yang*. Cold and heat are 2 principles differentiating the nature of a disease, in that cold refers to syndromes caused by exogenous pathogenic cold, whereas heat represents syndromes caused by exogenous pathogenic heat. Cold syndromes include aversion to cold and preference for warmth, tastelessness in the mouth, absence of thirst, pallor, cold extremities, clear and profuse urine, loose stool, pale tongue proper with a white slippery coating, slow pulse, etc.; the symptoms of heat include fever, preference for cold, thirst with preference for cold drinks, flushed cheeks and redness of the eyes, yellowish and scanty urine, constipation, red tongue proper with a dry yellowish coating, rapid pulse, etc. Exterior and interior are 2 principles indicating the depth and development of a disease. Exterior refers to syndromes caused by the invasion of exogenous pathogenic factors into the surface of the body and generally located in the superficial portion, whereas interior refers to syndromes caused by the transmission of exogenous pathogenic factors into the interior of body or from the dysfunction of the *Zang-Fu* organs. Deficiency and excess are 2 principles used to analyze the opposing forces between the body's defense and pathogenic factors during the course of a disease. Deficiency refers to symptoms caused by the weakness and insufficiency of body defense, whereas excess refers to symptoms induced by an overabundance of exogenous pathogenic factors. Deficiency syndromes are mainly due to an insufficiency of antipathogenic factors when exogenous pathogenic factors are also in a weakened state. An excess of exogenous pathogenic factors mainly causes excess syndromes, with body defense not yet weakened. *Yin* and *Yang* are 2 general principles used to categorize the other 6 principles, that is, heat, exterior, and excess belong to the category of *Yang*, whereas cold, interior, and deficiency belong to *Yin*.^[14]

Diagnosis and stages of pathology. TCM identifies different patterns of the evolution of disease by classifying factors of pathology according to climatic influences.^[15] Those factors are wind, cold, heat, dampness, dryness, and fire. Such factors impact the organism by triggering modification of the body homeostasis. The understanding is that climatic factors foster the development of pathology because of the transport of pathogens (virus, bacteria), and promote the establishment of such pathogens with proper temperature and humidity conditions. The establishment of a diagnosis in TCM is a crucial step after several actions such as a visual observation, interrogation, body palpation, body sounds, and smell.^[16] Those examinations lead to a diagnosis based on established signs and symptoms about the patient physical and psychological status. A complete diagnosis pattern in TCM will thus include not only the localization of the organism disbalance source, but also its nature.

One of the classification methods of the established patterns dates back to 220 CE and is exposed in the *Shanghan Lun*, or Treatise on Cold Damage Disorders, written by Zhang Zhongjing. This treatise develops 6 stages of disease, supposedly relating the evolution of disease from symptoms of a simple cold to death. The 6 stages are *Tai Yang*, or Greater Yang; *Yang Ming*, or Bright Yang; *Shao Yang*, or Lesser Yang; *Tai Yin*, or Greater Yin; *Shao Yin*, or Lesser Yin; and *Jue Yin*, or Absolute Yin. Even though the theory of the 6 stages was of great importance during centuries in TCM, even leading to subsequent theories such as the Four Levels (in *Wen Bing Lun*, or Discussion of Warm Diseases by Ye Tian Shi, 1746), it is now less used, accounting for as little as 5% of all Chinese herbal formula prescription in Taiwan for instance.^[15]

Therapeutic strategies. TCM prescribes formula to treat diseases. Typically formulae consist of 4 types of medicinal herbs or

minerals, *Jun* (Emperor), *Chen* (Minister), *Zuo* (Assistant), and *Shi* (Delivering Servant). Emperor refers to the principal agents targeting the causative abnormality and coping with the main symptom of the disease; Minister is designed to enhance therapeutic efficacy of Emperor or to treat the secondary disorder; Assistant optimizes the activities and/or eliminates toxicity of Emperor; Delivering servant helps the Emperor to reach its target organ(s). It is believed that combinatory use of these components could hit multiple targets, strengthen "healthy elements" and eradicate "evil" (pathogenic) factors, and modulate and restore inner balance of *Yin/Yang*, hence resulting in synergic efficacies with minimized side effects.^[14,17]

Current forecast

Although the current system in China provides education for WM before learning TCM,^[18] the strong link between TCM and Chinese culture makes it challenging to widely adopt WM in the remote parts of the country. Another aspect is the modernization of TCM, which could benefit from the latest advances of modern medicine technologies to develop more evidence-based and personalized medicine.^[19,20] Current biomolecular technologies could be useful to assess the quality control of the herbal formulations.^[21] This is moreover emphasized because the popularity of TCM herbal treatment is growing worldwide, especially in Western societies.^[22] Understanding the origins and principles of TCM is crucial although it is valuable to understand the difference between ancient TCM and the current practice and knowledge of traditional medicine in China.^[23] To date, the China Food and Drug Administration (CFDA) and the State Administration of Traditional Chinese Medicine (SATCM) regulate the TCM industry and edit laws and policy plans and drug registration.

Kampo: Traditional Japanese medicine

TCM adaptation

TCM as a source. The earlier steps of Japanese medicine are linked to the spread of TCM. The name to design this medicine, Kampo (or Kanpo) is derived from 2 symbols: 漢 means *kan* and represents the Han dynasty, and 方 means *ho* or *po*, which means "method." It literally means "method from the Han period."^[24] TCM was brought to Japan through the Korean peninsula during the Ancient era in the 5th century. As further exchanges increased with China during the Asuka and Nara periods (6th to 8th centuries), TCM was adopted in the Japanese islands, and soon the first medical laws were set during the reforming period of the early 8th century (Ishisuryo in the Taihō Code, 701 CE).^[25] *Ishinpo* is the oldest medical book comprising 30 volumes of works, stating the importance of foreign medical texts, such as TCM, on Japanese medicine development.^[26] Yasuyori Tamba compiled it in 984 CE, during the Heian period (8th to 12th centuries).

The Edo period. Until the 16th century and the Azuchi-Momoyama period, Japanese medicine remained an adapted imitation of TCM. Private schools, or *ryūha*, were then opened and the imported knowledge was adapted to the Japanese culture. With the decision of the Edo period government to cease exchanges with overseas nations during 265 years from the 17th to 19th century (1603–1868), the importance of private schools soared, and the Japanese medicine identity strengthened. Several physicians and doctors travelled to Europe and brought modern methods back to Japan, attempting to integrate and harmonize them with the developing Japanese medicine. Tōdō Yoshimasu (1702–1773), who founded the Koiho School, stated that much suitable support could be dispensed to patients if the chosen medication would

match pre-identified patterns.^[27] Tōyō Yamawaki (1705–1762) rejected the 5 *zang* and 6 *fu* Chinese description of human anatomy after performance of dissection on prisoners,^[28] thus merging Japanese medicine with WM knowledge. Seishū Hanaoka (1760–1835) was a surgeon who performed in 1804 the first surgical treatment of a breast cancer patient under general anesthesia.^[29] Kampo took shape during this auto-sufficiency era by removing the speculative aspects of TCM philosophy, and by simplifying the enormous amount of herbal medications available in TCM, reducing their complexity to about 300 extracts.^[24] This represents up to one-fifth of the total amounts of herbs used in TCM, the main reason being the difficulty to provide Japan with overseas herbs, and the need to replace them with local flora.^[30]

Decline and revival. By the 19th century during the Meiji period, the commercial and cultural exchanges with the foreign countries had started again, mainly through Dutch representatives. This triggered the rise of Western culture in Japan, collaterally forsaking the development of Kampo medicine to fully embrace WM. In the process, Kampo was left behind and no longer taught nor recognized as a medical profession. Despite the decision to abrogate Kampo as a branch of the Japanese medicine, a few physicians, for example, Dōmei (Shirō) Yakazu (1905–2002) and Keisetsu Otsuka (1900–1980), kept practicing and teaching Kampo through associations, such as the Japanese Kampo Medicine Association founded in 1934. A few years later in 1937, lectures on Kampo were given in Takushoku University. By the middle of the 20th century, Kampo was simplified to a modern concept, which allowed understanding and acceptance for WM trained doctors and physicians. As a result of those efforts, the first 4 Kampo formulas were accepted into the national health-care program in 1967. Nine years later, Taro Takemi (1904–1983), as the 11th President of the Japan Medical Association, convinced the government to integrate 148 herbal prescriptions to the national health-care program.^[28,30] The various formulae have been systematized, standardized, and in some cases subjected to clinical trials.

Current status. To date, Kampo medicine courses are offered in all 80 medical schools from the Japanese public and private universities, with mitigated success and heterogeneous teaching,^[31] and with less visibility and importance than WM. Even though the utilization of Kampo drugs is different from one medical domain to another, a vast majority (83.5%) of physicians in Japan use Kampo drugs in their clinical practice,^[32] but most of the patients receiving Kampo treatments are also simultaneously prescribed with Western biomedical drugs (92.2% of them), which reduces the rate of exclusive Kampo prescription to 1.34% of all patients.^[33] Kampo medications are even used for life-threatening pathologies with high expectancies such as cancer. Thus, among physicians working in the cancer field, Kampo drugs were delivered to 73.5% of cancer patients.^[34]

Principles: The elaboration of Sho

Based on the principles of TCM, Kampo medicine could be interpreted as a simplified version of TCM. Still, the purpose to deliver an optimal treatment to a patient is set by defining patterns, from which the most appropriate medication can be administered against various symptoms. Unlike Western conventional medicine, the focus is on the patient condition rather than on the eradication of the pathology. Any disease is explained by a deviation of the patient equilibrium from the normal status, either in deficiency or in excess. The diagnosis in Kampo medicine will require the physician to establish in which terms and which amplitude this deviation occurs. The tools used differ from those in WM and rely on intuitive

examination of the general condition of the patient organism and mind, resulting in qualitative descriptions, rather than the quantitative results. This intuitive examination relies on 4 main points, similar to those encountered in TCM (see Diagnosis and stages of pathology): an overall visual observation; characteristics of the organism sounds; characteristics of the body odor and results of body palpation; and interpretation of the patients' verbal reports.^[35]

The solution considered in Kampo medicine is to assist the organism to adapt and return to homeostasis rather than eradicate the pathology. The level reached by the deviation in either direction, positive or negative, corresponds to a codified definition of the symptoms, leading to predefined patterns. To each pattern corresponds one formulation of herbal extracts; the challenge is then to determine the appropriate matching of pattern and formula.^[30] The art of defining the most exact pattern of one patient is named *Sho*, and it may fall into several categories according to the following dichotomies: opposition between *yin* and *yang* (positive or negative direction of the symptom effect on the body, considering neutral equilibrium), opposition between *netsu* and *kan* (hot or cold status of the organism), opposition between *kyo* and *jitsu* (full or hollow aspect of the symptom). To these categories are added the main substances of the body, named after *ki* ("energy," mind, see Qi, meridians, oxygen and blood vessels), *ketsu* (blood), and *sui* (body fluids). Kampo medicine may also require the use of subtle TCM stages of the pathology derived from the Chinese *Shanghan Lun* (see Diagnosis and stages of pathology). The elaboration of *Sho* leads to the prescription of herbal extracts, or formula, among the 148 covered by the Japanese health insurance program.^[36,37]

Sa-sang: Traditional Korean medicine

Origins

The development of traditional medicine in Korea derives from 2 major philosophical traditions in China: Taoism and Confucianism. The first developed on the basis of the relevant classical texts of Chinese medicine, such as *Huangdi Neijing* (黃帝內經) and *Shanghan lun* (傷寒論), which are Taoist in their inspiration. Taoism in medicine can be seen to emphasize nature, the universe, and therefore the environmental influences on health and disease. The circular flow of "life energy" or *qi* includes the environment within the circuits and so highlights the environment's role in maintaining the equilibria on which healthy life depends. This tradition matches that of Western systems approaches to medicine in regarding organisms as fully open systems.

Confucianism by contrast emphasized the inner person, the strengths and weaknesses of the individual. The influence of its philosophy on social aspects, politics, economics, and ethics was profound. But Confucianism largely left science and medicine to the Taoists.

Korea became very strongly Confucian during the long Jeonson dynasty (1392–1897), when the more Taoist-friendly Buddhism was sidelined.^[38] Confucianism was pursued even more strongly in Korea than in either China or Japan. It is not therefore surprising that Korean traditional medicine grew out of a need to synthesize the Taoist and Confucian systems of thought and practice.

This synthesis was almost entirely achieved through the work of one man, Lee Je-ma (李濟馬), during the second half of the 19th century.^[39] His book *Dongui Suse Bowon* (東醫壽世保元, 동의수세보원) was published in 1894, just 3 years before the fall of Jeonson. It has been translated only recently (1996, 2nd edition 2009) into English with the title *Longevity and life Preservation in Eastern Medicine*.^[40] The translator, Choi Seung-hoon, is himself a leading scholar of Korean traditional medicine and has played a major role in the development of the modern scientific investigation of its basis.

The book consists of 2 parts. The first describes Lee Je-ma's synthesis of the 2 Chinese-derived philosophies. It is difficult reading even for practitioners of traditional Korean medicine, who naturally focus on the second part, which is essentially a formulary based on sources such as the *Shanghanlun*.

Principles

Korean traditional medicine is not therefore very different from TCM in its use of herbal formulas and other treatments. What makes it unique is rather the Confucian approach to the patient and his/her inner characteristics.^[41] It is a typology. Treatment is decided on the basis of that typology.

To be sure, there were also typologies in ancient Chinese medicine, notably *Yin Yang Ershiwu ren* (陰陽二十五人 Yin-yang with 25 types of people) within the *Huangdi Neijing*. Lee Je-ma's system consists of just 4 types, based on the yin-yang balance principle. Each of the 2 can be high or low, giving the 4 types (Table 2): High yang (Tae-yang, TY), low yang (So-yang, SY), high yin (Tae-eum, TE), or low yin (So-eum, SE), so creating Sa-sang (4 types) constitutional medicine (四象醫學). Each type is based on assessments of personality, psychological state, and functions of organs of the body represented as the equilibrium status of 2 seesaws between the intake and discharge processes and between the catabolism and anabolism processes.^[42]

Medication is prescribed on the basis of this classification so that, in principle, each patient receives medication according to his/her type. Sa-sang is therefore an early version of patient-specific medication. Moreover, herbal medicine is strictly regulated and controlled to comply with the Korean Good Manufacturing Practice standards.^[43]

Current forecast

Modern research on Sa-sang is focused on quantifying the diagnostic methods, including analyses of face shape, body shape, voice characteristics, skin properties, pulse properties, temperament, and other ordinary symptoms. This research has transformed these features into various quantified variables and integrated them to develop algorithms for constitutional typing. This work was recently reviewed.^[44]

Medical research in Korea today has attracted many modern scientists to work on Sa-sang, including a major national Institute, the Korean Institute of Oriental Medicine (KIOM), and many Korean Universities and medical schools, including notably Kyung-Hee University. Notably, Sa-sang typology is investigated in current diseases or health conditions, such as obesity,^[45] cardiovascular disease,^[46] diabetes,^[47] cancer incidence,^[48] or allergic rhinitis.^[49] Current technologies also contribute to assess the personalized level of Korean medicine, retrieving genome-wide association of particular loci,^[50] or assessing wellness index to Sa-sang types.^[51]

The 21st century will therefore witness the ideas and methods being put on a firm scientific basis. It will be interesting to see what

happens in consequence to the typology. Will physiological analysis confirm the usefulness of 4 basic types (much easier for a practitioner than 25 types!) or will it develop toward a much larger classification of patients? How will it relate to Western-style research on patient classification using genomics and phenotyping? These are questions for future research.

Ayurveda: Traditional Indian medicine

The term "Ayurveda" basically means the "knowledge (*veda*) of life (*ayur*)."^[52] Ayurveda is an Indian system of life sciences, documented and practiced since 1500 BCE.^[53,54] This ancient Indian system of predictive and personalized medicine still holds contemporary in the current era of P4 (Predictive, Preventive, Personalized, Participatory) systems medicine as it also has a proactive component, which is aimed at optimizing the homeostatic and rejuvenating potential of the system, thus promoting regeneration and health. It is a recognized medical system with all regulatory procedures, related to health care, education, and quality standards of medicines in place. In Ayurveda, etiological factors, pathogenesis, clinical features, and therapeutic modalities of diseases are described based on subtype, stage, and severity of the disease. Delivery of medicines in a personalized manner is possible with a thorough examination of diseased individual, advised to select appropriate medicine in appropriate dosage for the right person. Understanding of human individuality through assessment of each individual constitution type forms the fundamental basis for this 3500-year-old medical system, comparable with current P4 systems medicine, as it also promotes a proactive attitude to disease understanding and treatment.

From the Vedic roots to Western influences

Vedic and medieval eras

The foundations of traditional medical knowledge in the Indian subcontinent are known to date back to the ancient Vedic era (ca. 1500–500 BCE), during the settlements of the first Indo-Aryan tribes in Northwest India and the Ganges plains. This period corresponds to the composition of the 4 Vedas (*Rig-Veda*, *Sama-Veda*, *Yajur-Veda*, *Atharva-Veda*) and the rise of the Vedic practices. There is a close link between traditional medicine in India and Veda, wherein the philosophical and spiritual aspects of Ayurveda are described in *Atharva-Veda*.^[55]

Nevertheless, the matter of healing still opposed heterodox tradition (evidence based and empirical exploration of healing organisms) to orthodox tradition (based on religious rituals and beliefs).^[56] The presence of elaborate documentation dating back to 1500 BCE indicates that this medicinal system might have even earlier origins. Even though Ayurveda knowledge is 3500 years old, there has been a continuous evolution of subjects and texts dating back to 3 major time periods.^[55,57,58] This highlights the nature of

TABLE 2.

Basic Characteristics of the Sa-sang Constitutions in Korean Traditional Medicine

Constitution	SE	SY	TE	TY
Strong function	Food discharge	Food intake	Anabolism	Catabolism
Weak function	Food intake	Food discharge	Catabolism	Anabolism
Body shape	Slender	Muscular	Obese	Slender
Temperament	Calm, careful	Hot-tempered	Slow, steady	Progressive

Sa-sang (4 types) constitutional medicine is composed of 4 types, based on TCM high and low dichotomy of yin and yang: low yin (So-eum, SE), low yang (So-yang, SY), high yin (Tae-eum, TE), and high yang (Tae-yang, TY). Each type includes distinct assessments of personality, psychological state, and functions of organs of the body.

Ayurveda as a living tradition. In the ancient times (*Prachin Kaala*), dating back from ca. 1500 BCE to the 12th century CE, major compendia (*Samhitās*) were created, attributed to different authors like Caraka, Suśruta, and Kashyapa. For instance, the *Caraka Samhitā*, which relates internal medicine teachings of Punarvasu Atreya to his students, was originally written by one of the students, Agniveśa (1500 BCE), revised by Caraka around 200 BCE, and reconstructed 6 centuries later by Dridhabala. Another important piece of work is the *Suśruta Samhitā*, relating surgery knowledge. Again, several authors contributed: Nagarjuna, 8 centuries later related the original works of Suśruta (ca. 400 BCE), later reviewed by Chandrata (ca. 1000 CE). *Samhitās* are the master texts, from which all the current prevailing documents are based, and were periodically edited over the centuries.^[59] The knowledge included in the *Samhitās* relates to the tremendous advances made by physicians (eg, Caraka) and surgeons (eg, Suśruta) to describe and study human being functioning as a whole, that is, mind and body. A second period (6th- to 12th-century CE) was *Sangraha Kaala*, during which compilations such as *Aṣṭāṅga Sangraha*, *Aṣṭāṅga Hrudaya* (ca. 600 CE), and *Hariata Samhitā*, mostly attributed to *Vagbhatta I & II*, were developed, easier to read and recite, and thus could be adopted widely. The Medieval times (*Madhya Kaala*) marked the development of elaborate compendia on individual herbs, their properties, and classification. This era is most commonly referred to as *Nighantu Kaala* (7th CE to 16th CE), during which compilations such as *Madhava Nidana*, *Śārṅgadhar Samhitā* (ca. 1300 CE), *Bhavaprakasha*, *Chakradutta*, and *Yogataringini* were developed. This was followed by *Ras Kaala* (8th CE to 16th CE), during which exhaustive accounts of mineral and metallic preparations, with their purification and processing before internal use, were provided. These descriptions indicate the advancement in knowledge and understanding of chemistry during this period. The most referred text of this time is *Rasa Ratna Samuchaya* by *Vaghbhatta* in the 13th century. During the modern period (*Adhunika Kaala*, 18th to 20th century), many compilations were made available, mainly with commentaries on the original texts, developed in different parts of the country. These rather suggest a demand for the system to continuously evolve in the contemporary era. Currently, more than 2000 herbs, 150 minerals, and over 97,000 formulations are documented for hundreds of diseases. Importantly, the therapeutic mechanisms of action have also been described along with their use in diseases.^[60,61]

Back in the Vedic era, medicine was in such an advanced stage that 8 medical specializations were developed: *Kāyachikitsā* (internal medicine), *Kumārabhṛitya* (pediatrics, gynecology, and obstetrics), *Bhutavidyā* (psychotherapy), *Śālākya tantra* (otorhinolaryngology, including ophthalmology), *Śhalya chikitsā* (surgery), *Agada tantra* (toxicology), *Rasayana tantra* (geriatrics including regenerative and promotive medicine toward positive health), and *Vājīkaraṇa tantra* (science of virility, including reproductive system health). Even the tools used for diagnosis, therapeutic modalities including surgeries were elaborate and advanced with some of them quite novel considering the present knowledge of medicine. Interestingly, it transpires from the textual references that Ayurveda as a medicine was highly regulated as only those who had obtained the required training and approval from a federal structure (*Rajanugya*) could initiate a practice,^[62] and it was stated that lethargy (*Rajapramada*) in enforcement of this regulatory process could lead to thriving of quacks (*Rogabhisara*) in the system.^[53] There was a continuing tradition of training and practice of Ayurveda through old gurukul systems and family tradition wherein the education was imparted through verbal and practical approaches (*Vaidya Paramara*). Some of the present day pharma-

ceutical companies like Aryavaidyashala, Zandu, and Sandu have their origins from these lineages.

From colonial influences to post-Indian independence era

Advances made by medicine in India before the medieval era was truly substantial for surgery, healing knowledge and tools. Although stagnation of conventional medicine occurred during the Middle Ages, when efforts contributed to foster healing and treatment through alternative solutions, mostly leaving out heterodox tradition,^[56] the arrival of European conquerors brought European medicine knowledge to India. Portuguese, French, and Dutch colons settled, respectively, in Goa, Puducherry, and Kochi, and were joined finally by the British during the 19th- and 20th-century British Raj, bringing their own physicians and knowledge. The establishment of a national medical system started once the British took over the other European colonizers during the middle of the 18th century. From then on, the public health system was organized with several Acts, such as, for instance, the Quarantine Act (1825), the Vaccination Act (1880), the Birth and Death Registration Act (1896), the Epidemic Diseases Act (1897), and the Glanders and Farcy Act (1899). Several medical colleges were established to teach WM all over the country (Madras, Calcutta: 1835, Bombay: 1843, Hyderabad: 1846, Lahore: 1860, Nagpur: 1867, Patna: 1874, Pune: 1878, Sindh: 1881). By 1934, the Medical Council of India was created to foster medical education, and in 1946, a total of 38 medical schools were created.^[57,63]

From the 19th-century public-funded Institutes of Ayurveda also started getting built with early formation of a Native Medical institute (Calcutta) in 1822 and an Ayurveda Vidyapeeth in 1908. There has been a gradual process of formalization of Ayurveda education and research with establishment of colleges offering graduate programs, as well as postgraduate programs, for example in Jamnagar (1956) and Banaras Hindu University (1963), including establishment of many mono-faculty universities of Ayurveda. In the first of its kind in 2010, there has been an establishment of an All India Institute of Ayurveda in par with the premier All India Institute of Medical Sciences in Delhi. Many councils were set up also to formulate research and education with appropriate policies, for example, the setting up of a Bharatiya Chikitsa Parishad (1926) to grant recognition to Ayurvedic colleges, followed by Indian Medicine Act (1939), Central Board of Sidha & Ayurveda Education (1964), Central Council for Research in Indian Medicine & Homeopathy (1969), Central Council of Indian Medicine (1971), Pharmacopeia Laboratory of Indian medicine (1970), and a dedicated Central Council of Research in Ayurveda and Sidha (CCRAS, 1978). The formalization of practice and development of regulatory policies also happened concurrently with enforcement of Drug and Cosmetic Act for Ayurveda, Siddha, and Unani Medicine (1940), and formation of testing laboratories (PLIM), all under the umbrella of a separate department on Indian System of Medicine and Homeopathy (ISM&H) in Ministry of Health and Family Welfare, which has recently become an independent Ministry of AYUSH (2014) in the Government of India.^[64]

Presently, Ayurveda is practiced across the country, being for nearly 70–80% of rural India the primary health-care system. Even though WM is the system of choice in the Indian subcontinent, the urban population opts for Ayurveda mainly in the areas of lifestyle where common and complex diseases originated. Ayurveda is practiced by about 250,000 physicians, whereas more than a million physicians are registered for WM.^[64] In the delivery of health care and recommendations, different communities use Ayurveda with some variations to suit biological requirements of those populations, based on geo-climatic conditions and sociocultural

practices. The same principles of understanding the disease, their diagnosis, and treatment are used from the Ancient classical texts, *Caraka* and *Suśruta Samhitā*, and followed by physicians across the country. The gradual shift in attitude from mainstream to alternative and traditional system of medicine has many reasons. The original language, principles, and practice were completely alien to the colonial settlers. Despite this, the practice of Ayurveda over generations was mostly alive in traditional households. A later systematization into mainstream education led to most of the knowledge being retrofitted in a structural framework that was better synchronized with the WM. In the modern period, ayurvedic education and research is quite exhaustive and formalized in an undergraduate degree (BAMS, Bachelor of Ayurveda Medicine and Surgery), which is awarded after a 5.5-year course, including a 1-year compulsory internship similar to modern medicine graduation (MBBS). Almost all subjects, anatomy, physiology, pharmacology, pathology, medicines, etc., which are a part of the undergraduate program of MBBS in India, are part of syllabi of Ayurveda degree course in addition to the study of these subjects from original texts of Ayurveda. The postgraduate course in Ayurveda (MD) is a 3-year training and research program.

There are nearly 2842 hospitals (43,639 beds) and 262,070 institutional qualified registered practitioners. In India, more than 250 educational institutes offer Ayurveda graduation and nearly 100 offer postgraduate courses.^[64] There is a large number of MDs in different branches similar to WM and PhD research programs in Ayurveda that carry out research toward understanding the principles and practice described in Ayurveda.

Unavailability of a reference in modern language has been one of the major reasons for unawareness of the documentation extent encompassing all aspects of Ayurvedic medicine. Traditional Knowledge Digital Library (TKDL) is first of its kind to make the knowledge available in English and other languages.^[60,61] Many research programs from the Department of Science and Technology, the Council of Scientific and Industrial Research (CSIR), and the Indian Council of Medical Research in the last decade have provided a thrust for exploring the scientific principles of Ayurveda. There are a few recent dedicated establishments, such as the Institute of Ayurveda and Integrative Medicine^[65] and CSIR Ayurgenomics Unit (TRISUTRA), which aim to provide an interdisciplinary platform for enabling translational research through cross-talks among Ayurveda, WM, and omics sciences for affordable health-care solutions.^[66]

Principles: From biology of Tridoshas to diagnosis and treatments

Connectivity in the system through a common organizing principle of Tridosha

The reason why Ayurveda has become important today is because it is a system-level medicine, which aims to bring harmony between external and internal environments through a common principle of *Panchmahabhuta*, or the 5 elements (space, air, fire, water, and earth). The relative proportions of these elements determine the characteristic nature of any system—environment, food and drugs with different tastes (bitter, astringent, sour, salty, pungent, and sweet), and plant and animals including their internal structures.^[53] Understanding the relatedness of the 2 environments is the basis of a holistic approach. In addition, investigating the inter-relatedness among physical, mental, and emotional (body, mind, and soul) states, and the harmony between all these systems, is the ultimate goal. The *Panchmahabhuta* manifests in the form of *Tridosha*, comprising of 3 physiological entities: kinetic (*Vata*), metabolic (*Pitta*), and structural (*Kapha*).^[67] The relative proportion of each

Tridosha is further responsible for different forms and structure in the human body, and also governs physiology at all functional hierarchies. Interrelatedness between the external and internal etiological factors through *Panchmahabhuta* also forms the basis for rhythmic nature of oscillations such as circadian, diurnal, or seasonal in the human body. Depending on the time, age, and season, there would be a dynamic aspect (*Vaikarik*) of *Tridosha* in an individual.^[68] Thus, in the healthy state, there is an allowable threshold, which is determined by the static and the dynamic components.

Prakriti: Basis of a human individuality

A unique aspect of Ayurveda is the comprehensive understanding of biological basis of human individuality through *Prakriti* (literally meaning basic nature or the healthy state). This can be assessed through a comprehensive examination of anatomical, physiological, and psychological attributes. According to Ayurveda, an individual is born with a specific *Prakriti* that not only determines his overall phenotype but also predicts the susceptibility to diseases and responsiveness to extrinsic and intrinsic environments. Based on the initial proportion of *Tridosha* at the time of fertilization, the overall features of the human body would vary, thus determining the constitution of an individual.^[69,70] *Tridosha*, *Vata*, *Pitta*, and *Kapha* are pervasive across systems, present in all cells including the gametes. Based on the proportion of *Vata* (V), *Pitta* (P), *Kapha* (K), an individual can be classified into 7 broad constitution types: V, P, K, VP, PK, VK, or VKP. Moreover, each *dosha* includes 5 subcategories detailing precise phenotypes.^[71] Inherent proportions of *Tridoshas* are also described for different tissues (*Sapta Dhatus*) and organ systems (*Avayava* and *Srotas*) of the body. In other words, each organ system is developed with its own characteristic proportions of VPK and body tissues in accordance with their physiological functions. Thus, variability in the proportion of *Tridoshas* (analogous to variability at the molecular and cellular levels) leads to different phenotypic outcomes from each tissue including organ systems. This is somewhat analogous to the modern understanding that even though the overall genetic background is identical throughout the cells of an organism, different tissues exhibit specific expression. Thus, an individual of a V constitution with a higher basal level of V *dosha* would exhibit more differentiating features in tissues that are V predominant, for example, the nervous tissue (Figure 1). For diseases in which V *dosha* is perturbed, due to either extrinsic or intrinsic causes, the phenotypic manifestation would be more evident through examination of these tissues. This forms the fundamental basis of systems medicine in Ayurveda.

Prakriti is established at the time of birth and the proportions of *Tridoshas* are also governed by the relative contribution of parents (*Shukra Shonita*), prenatal environment (*Matur Ahar*, *Vihar*, *Kalagarbhashaya*), ethnicity (*Jatipraskta*), geography (*Deshpraskta*), and familial characteristics (*Kulpraskta*), and individual specific components (*Pratatmaniyata*). Even though the *Prakriti* is invariant, the phenotypes change with age (*Vayanupatini*), time (*Kalanupatini*), and geography (*Deshanupatini*) and the apportionment to each of these components can be dissected during phenotypic assessment. The set points differ between *Prakriti* types and disease states are perturbations from these set points. Homeostasis is achieved through restoration of V, P, K perturbations to their threshold states.

Clinical outcomes

Prakriti-specific variability affects the basic features of health, well-being, and disease outcomes in an individual. This is because the trajectory of the change in response to a modification of the extrinsic environment is predictive, based on the inherent propor-

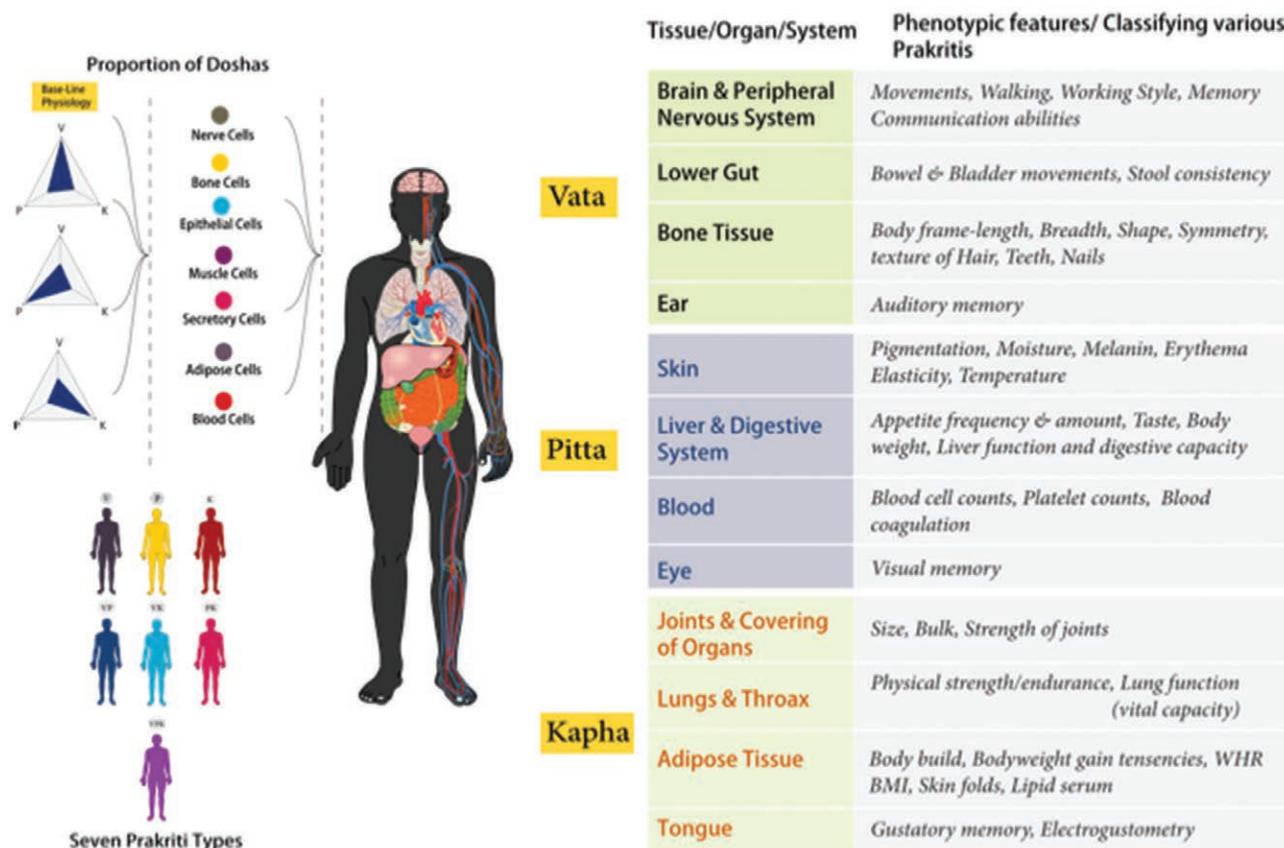


Figure 1. Overview of Phenotypic Features related to Doshas and Prakriti Types.

tions of *Tridoshas* in an individual specific *Prakriti*. This understanding of variability in health forms the basis for understanding the variability of diseases, their occurrence, and progression, and the development of customized solutions for their treatment.^[53,62,68] Diagnosis of a disease begins even before the individual manifests the overt symptoms of the disease. According to Ayurveda, there are 6 stages to differentiation of a disease, and each disease undergoes a specific combination of biological phenomena for its characteristic clinical manifestation (*Samprapti*), and differentiation into specific subtypes, with natural history and progression. Each of these stages implies clinical action points literally expressed in Sanskrit as *Shad Kriya Kal* (6 time points to act). The steps include initiation of *dosha* accumulation (*Sanchaya*), *dosha* aggravation site (*Prakopa*), spread of *dosha* into other tissues/systems (*Prasara*), their local interaction and effect on target systems (*Sthana samshraya*), leading to disease manifestation (*Vyakti*), and further differentiation (*Bheda*). Manifestation and progression of pathogenesis process is, to a large extent, dependent on baseline variability leading to individual specific differential prognosis. All diseases are classified into subtypes based on their curative or palliative nature, which is further decided on the basis of strength and severity of disease, as well as that of an individual strength. As is evident, Ayurvedic system of medicine was quite advanced and draws several parallels to the prevailing ideas of P4 systems medicine. For instance, in the modern times, the need for classification of diseases based on intermediate patho-phenotypes is increasingly being appreciated.

Health and disease management through knowledge of Trisutra

The interconnectedness among the 3 axes of causes (*Hetu*), features (*Linga*), and therapeutics (*Aushadha*), for both a healthy and

diseased individual, is described as *TRISUTRA*, which forms the basis for translation of this science into management of health and disease.^[53,70] *Hetu*, causes of diseases, are ascribed to lifestyle, dietary regimen, and thought processes that affect the behavior of various metabolic pathways. These are described with signs and symptoms, and the correction of the disturbed metabolic pathways is done through both natural and therapeutic interventions. The management of health and disease has both a preventive and personalized component.^[53,62,68] Thus, disturbance, restoration, or suitability in a human system is assessed, modulated, or predicted, respectively, through the management of *Tridosha* by appropriate drug, dietary, and lifestyle recommendations in a personalized manner. This includes detoxification with *panchakarma* therapeutics both in health and disease states. The nature and state of disease, the strength of the diseased individual compared with his/her baseline health state, and the geo-climatic environment are all considered for deciding the line of treatment. Such a framework, which integrates so many diverse aspects of variability, suggests that this field has evolved after intensive observations in large number of individuals, spanning long periods of time as it led to establishment of tenets, which are still contemporary and would fall in the realm of modern “Big Data Analysis.”

Current prospects Documentation of traditional knowledge of Ayurveda.

Knowledge of the usage of herbs, their method of preparation, formulation, and routes of administration for different diseases is extensively documented in Ayurveda. Indian traditional medicine is rich of thousands of plants.^[53,62,72,73] They are used in various forms: decoction (*kwatha*), hot (*phanta*) or cold (*hima*) infusions, liquid extracts (*arka*), powders (*churna*), resins (*guggul*), or medi-

cated oils (*taila*). The effects of plants on the patient are codified under several categories, from the taste to the thermal, post-digestive or therapeutic effects.^[74] With the tools of modern research and the claim of potential benefits of various plants, the impact of such plants on particular common diseases is investigated. Thus, the effects of various plants on asthma offer fewer side effects and a wide range of options.^[75] The composition of the herbal mixtures and their molecular targets are described in the literature in the context of diseases, such as cancer^[76] or asthma.^[77,78] Such exhaustive information retaining all the details is available as a TKDL^[61] developed and maintained by Council of Scientific and Industrial Research (CSIR) India in collaboration with AYUSH, Government of India.^[69,79,80] Out of 150 published books, nearly 75 have been digitized by TKDL, and total number of formulations available is over 97,000. An update of this knowledge base including a larger number of books is ongoing. This library is made available to patent offices for prior art search (EPO, IPO, USPTO, CIPO, UKPTO, JPO, AIPO), and has led to withdrawal of more than 200 patent applications due to availability of prior art in Ayurveda texts. This, beside of working as a protection of Indian intellectual property, also indicates the scientific validity of the system. Noteworthy, many drugs such as levodopa, reserpine, chloroquin, aspirin, codeine, vincristin, vinblastin, bromohexine, and many others have their origins in medicinal plants described in Ayurveda where they are also used to treat the same diseases.^[81–84]

Translation of knowledge in drug discovery. One of the most prominent discoveries that have been inspired from Ayurveda is that of Reserpine, a molecule from the herb *Sarpagandha*, which led to the dissection of entire dopaminergic pathways and facilitated the merger of neurochemistry and psychopharmacology. This also fetched 2 Nobel prizes in 1965 and 2001.^[85] Efficacy and potential of Ayurvedic medicines is also evident from many recent scientific publications, for example, investigation on *Aswhagandha* (*Withania somnifera*) that led to discovery of novel therapeutic strategy for Alzheimer disease reversal.^[86]

Metabolic and genetic fingerprinting of more than 140 varieties of *Aswhagandha* has led to the identification of an elite variety for cultivation that is most potent, containing a higher amount of active ingredients.^[87,88] Recently, it has been shown that combination of piperine with the anti-mycobacterial drug rifampicin increased the bioavailability of rifampicin through inhibition of a multidrug efflux protein of *Mycobacterium tuberculosis*, resulting in the lowering of dosage and side effect of the drug.^[89] Piperine is isolated from black pepper, which is used as a bioavailability enhancer. It is present in *Trikatu*, a component found in multiple medicinal formulations described in Ayurveda.

Translation of concepts for P4 systems medicine. Establishing the relationship of phenotypic classification of Ayurveda with modern genomic analysis has led to an emergence of the new field of Ayurgenomics.^[69,70,90,91] Large cohort studies in multiple populations are being undertaken^[66] toward understanding the biology of health and disease for its global applicability.

Discussion

Toward further recognition?

Despite unconventional aspects of TKBM that could trigger distrust and reluctance among people who are used to conventional medicine, the popularity and use of TKBM has been rising in the past few years. The number of WHO Member States providing policy on TKBM increased from 25 in 1999 to 69 in 2013, whereas the number of Member States regulating herbal medicines increased

from 65 to 119 in the same timeframe (out of the 195 Member States). The main reason explaining the difficulties to establish regulatory policies is the lack of research data for 105 of the Member States.^[92] However, efforts are being made to add scientific results and evidence to the existing TKBM. The purpose is of course to increase credibility among the scientific community and to build up suitable patterns and limits to the use of TKBM. Among the possible options to improve TKBM acknowledgment is the rather recent concept of evidence-based practice (EBP), which claims “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research.”^[93] An improvement of the personalized aspects of medicine is clearly evoked.^[94–96] The rules of EBP are still discussed although a common consensus is available,^[97] and may be applied to TKBM.^[98] However, EBP relevance may sound controversial because TKBM always referred to empirically based observations on individuals.^[99] A second option is the conduct of well-designed clinical trials and studies, providing scientific proof of the positive effects of TKBM either on lone use,^[24,100] or coupled in an integrated manner with conventional WM.^[101,102] Understanding of the TKBM biological effects and philosophy could thus be improved in an easier manner although the observation and conclusion from providing one drug to a group of patients could be challenging for a methodology that prioritizes the individualization of treatment at the single patient level. The third option is the proper identification of the TKBM drug compounds and molecular targets with current omics technologies.^[90,103,104]

To date, the role and efficiency of TKBM is assessed in the modern context of many diseases, such as discussion about the use of TKBM in Autism Spectrum Disorders,^[105,106] the efficiency of Kambo formulas in the context of atopic dermatitis,^[37] or Ayurveda in cancer inflammation,^[76] rheumatoid arthritis,^[107] weight loss,^[108] or TCM in cancer.^[109,110]

A major mistrust of TKBM is triggered by the potential presence of harmful components within the preparations. Lead, mercury, or arsenic poisoning is found to be rare but nevertheless occurs.^[111–113] As in the case of several treatments in WM, some Ayurvedic medications include potentially dangerous components, which harmful effects may be dependent on dose, time of administration, and organism's response to treatment.^[114,115] Even though the TKBM market regulation is growing worldwide, particular attention should be taken as to the source and nature of the drugs used.

Two different approaches

The options offered above are challenging to adopt in the context of TKBM because of its intrinsic features, which differ from conventional medicine. WM is based on the assumption that the administration of one particular synthetic and chemical drug is necessary and sufficient to efficiently eradicate the causes or symptoms of the pathology, whether it be a pathogen organism, such as virus or bacteria, or a molecular dysfunction due to a reaction of the patient organism to stress hits from lifestyle factors (such as poor nutrition) or the outside environment.^[116] A particular treatment is assigned to each particular disease (usually gold standards proposed by medical societies), “one drug fits all,”^[117] and the attention is especially focused neither on the patient's genotype or phenotype, nor on his/her acceptance of and response to the chemicals (cases of intolerance and allergy apart), thus resulting in either enormous variation in the efficiency of treatments,^[118] possibly due to poor carriage and processing of drugs throughout the

body,^[119] or various important side effects.^[120] WM aims at relieving the patient suffering by focusing on symptoms and single organs, whereas TKBM aims to assist the whole organism to regenerate, adapt, and regain a balanced state, which can be described as a “health continuum.”^[116] The focus is aimed not only addressing the underlying cause of diseases, but also dealing with the consequence of physiological imbalances with a proper management of patient health and wellness. Unlike WM, TKBM relies on raw natural products, from plants, minerals, or animals with single intakes or mixture preparations. WM also includes natural-based products, but mostly chemically synthesized, thus eliminating the supposed synergistic interactions between the components of a herbal remedy. WM does not systematically include psychological therapy to evaluate and improve patient wellness, whereas TKBM diagnosis is also based on patient listening and evaluation of possible psychological alteration. The methodology used in TKBM places the patient at the center of the action, requiring more involvement from her/him, now in a participative medicine that could inspire the ongoing transition from reactive to proactive medicine in modern health-care systems. The comparison between WM and TKBM remains a challenging task because the 2 philosophies are conceptually very different (Table 3). A systems biology approach will help to advance medicine by embracing all forms of effective interventions, no matter where their origins are.

From ignorance to mutual understanding

Despite the fact that several aspects of TKBM seem far from Western culture, and belong to Eastern countries sovereign histories and cultures, there are similarities that may help in further acceptance of TKBM. At some point in its history and development, WM also had a humor-based medicine,^[121] and elaborated *Materia Medica*.^[122,123] Even though those concepts are considered as belonging to a revolved era, the indisputable advances of WM

lost in the process the benefits of personalized medicine and the patient wellness.

On the one hand, the matter is the definition of equilibrium in the organism. In WM, human biology has been described as universal: we all are composed of the same molecules, produced from the same type of genetic framework, which composition differs to allow an infinity of combinations, thus resulting into multiple phenotypes. Gene expression differs in intensity, but basically, genes are here and the medications will target particular known gene products: proteins in the form of a receptor, carrier, enzyme, structural protein, ion channel, etc., whether it be those of the host or a pathogen. The underlying belief is that the same drug will work on the same biological target, no matter how different the patient phenotypes are. This will result in improved efficiency when it actually works, but with potential side effects. WM seeks to abruptly restore homeostasis—that is, the universally known biological functioning of an organism—even though the level of homeostasis is unique for every patient. The drug dose may be similar although the response will be different, causing excess perturbation for some and lack for others. In this context, it seems useful to categorize and anticipate the common patterns of patients. This is what TKBM suggests, by defining the patient constitution, and the deviance amplitude triggered by a disease on this particular constitution, or by matching predefined patterns to a particular formula. Even though the universality of the body molecular components are known and understood in TKBM, the response of an organism to a treatment will be rationalized and adapted at a personalized level, providing the organism with the necessary components to recover as much as possible on its own, smoothly reaching homeostasis. In both approaches, the definition of equilibrium in an organism is similar. The methodology to restore homeostasis after a disease-induced variation or intervention is different (Figure 2).

On the other hand, an important question raised is the definition of a disease.^[124] What is supposed to be the normal functioning of

TABLE 3.
Conceptual Comparison Among Allopathic, Conventional WM, and holistic TKBM

WM	TKBM
Targets symptom, medications aim at eradicating pathogen or molecular imbalance to treat disease on specific part of the body	Targets general imbalance of the body; medications aim at reversal of disease process
Explanation of disease: mostly biological	Explanation of disease: biological, psychological, linking external environment with internal imbalance
Focus on disease eradication (for infectious and communicable diseases)	Focus on disease reversal through medicine and diet exploiting the healing potential of an individual
One drug fits all	One drug fits one pattern of disease in an individual
Efficiency tested and proven with state-of-the-art clinical trials	Efficiency empirically mastered through medicine history and few modern evidence
Diagnoses focus on family antecedent and genetic background	Diagnoses also focus on environment and surroundings history, perfected through practice and patient feedback in addition to baseline variability in health
Specifically targets body parts	Targets the diseased part with consideration of impacts in the whole body
Active compounds from chemicals (usually single molecules with single targets)	Active compounds from natural products, multiple components of low concentration
Regulatory authority functions through approvals (FDA, etc...)	Variable regulations (strict regulation of TCM, Kampo, Sa-sang, and Ayurveda)
Patented products, out-of-reach knowledge	Open access, available to everyone and practiced prior art
No self-medication, strictly apply doctors' treatment	Preventive through self-care and patient participation encouraged, physician prescription required for disease treatment
Several side effects	No or few side effects

Both WM and TKBM philosophies are distinct. Each has its proper conveniences, advantages, and drawbacks. However, complementarity is found in health improvement.

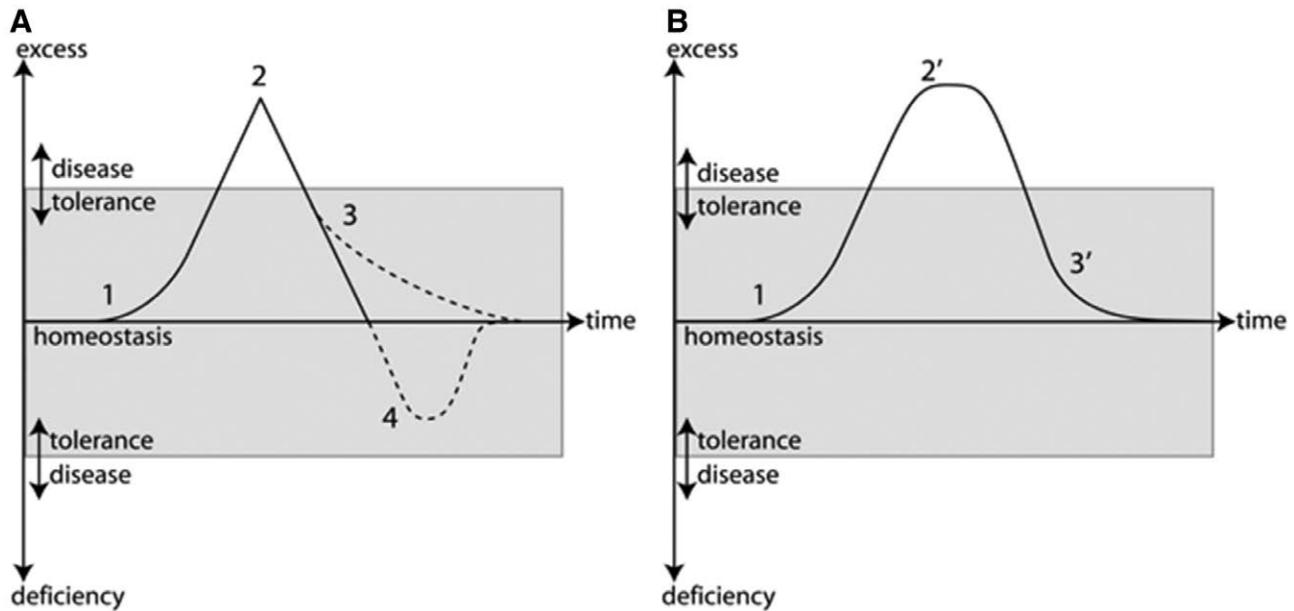


Figure 2. Non-linearity and homeostasis in biology.

a human organism that corresponds to a healthy/well-being state? Definition of a disease evolves over time; the acceptance of new social rules removes diseases from official lists, whereas the development of drugs may create new pathologies to match the needs. Where is the limit between normal and healthy aging and a state of dysfunctions, which can lead to a disease? Is a genetic predisposition enough to consider the patient as bearer of a disease? WM and TKBM may consider the limit of illness at a different level regarding the patient phenotypic pattern, and adapt a treatment in consequence.

In the context of the recently emerging systems approaches to biology and medicine, the analogy could be made with TKBM trying to focus on how the whole organism–environment system is functioning, how the organism and environment interacts with each other, and how interventions are capable of providing solutions to assist the organism (both mind and body) to recover homeostasis. In both approaches, the whole body is believed to be self-sufficient and functioning as a network of repressed-activated circuits of its various biological systems.

Conclusions

We covered a comprehensive description of WM, TCM and its Japanese and Korean derivatives, Kampo and Sa-sang, and traditional Indian medicine. It is noteworthy that an exhaustive description of TKBM would not be limited to these but would by instance include Native American, South American, African, Aboriginal, or Indonesian traditional medicines. As stated in Toward further recognition? section, as of 2013, 69 out of 195 WHO Member States provide policy on TKBM, and 119 regulate herbal medicines. TKBM may play a major role in the coming years to help create a modern medicine that considers the patient's wellness during treatment and the prevention of diseases. As the evolution of medicine will be grounded on a more predictive, preventive, personalized, and participatory approach,^[94] and with the support of modern technology such as connected medical devices, the consideration of the phenotype variation of a patient before treatment will increase. Besides the rich history and cultural elements of TKBMs, some of which may be found irrelevant in the current and modern context, their application in WM methodology as a complementary approach to assist

disease treatment efficiently with reduced side effects should prove helpful. The lack of regulation toward TKBM use and application may be slowing the process of acceptance in Western societies, and open the door to marginal processes, far beyond the core of medicine. The supreme purpose of medicine is to prevent diseases and relieve a patient from suffering, with a spectrum of approaches that is traditionally organ- and symptom-centric in WM or with a focus on underlying whole-body mechanisms in TKBM.^[98] There is only one universal science, the understanding of nature—effective western and eastern medicine techniques should merge to form a modern form of medicine, that is preventive, predictive, personalized, and participatory. In modern medicine, patients should be empowered to understand their own health trajectory and have access to all effective interventions to prevent and treat diseases.

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