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The rise of the holobiont and the return of ancient medicines

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Abstract
Historically, there are many types of alternative forms of medicines falling into the category of traditional complementary and alternative medicines (TCAM): traditional Chinese medicine (TCM), Unani, traditional Japanese medicine (TJM), Ayurveda, etc. In the West, one tradition stands out for its use across the millennia: Western Constitutional Medicine (WCM), i.e., Greek-Roman medicine as the foundation of Western medicine. As per traditional Eastern medicine, although difficult to scientifically demonstrate, the principles of WCM through have been experimented on for more than two millennia. Recently a new paradigm shift has rocked the world of biology and promises to change the landscape of medicine too: the concept of the holobiont. Humans are now seen as metaorganisms, a multicellular eukaryote inseparable from its integrated consortia of myriad of species of microbes, mingling together. Among the many applications of this reality view of humans is the idea of eubiosis, or equilibrium of all the species of microorganisms that occupy a specific niche in our body (resident microbiota). The loss of this equilibrium is defined as dysbiosis and results in disease and is akin to the dyskrasis (disequilibrium) of ancient medicine (although different names and systems are used, all are concordant in the path to follow). All treatments devised by TCAMs have the ultimate goal of restoring the natural equilibrium in each individual's own body (eubiosis of the holobiont). A rebalancing of the interconnected body-mind-spirit systems in each of these ancient medicines is achieved through the use of various systems but mostly through nutrition. It is herewith proposed that TCAM were much closer to the truth about our biology than is modern medicine. A new medicine (such as personalized medicine) must therefore take on the challenge of integrating this new view of biology. Failure to do so would irreparably separate modern medicine from reality, leaving the path free to TCAMs to fill in this void.

Keywords: Failure, systems, irreparably, medicine

1. Introduction
Complementary and alternative medicine (CAM) is a socially and culturally constructed concept to identify any medical systems, treatments or therapies that do not currently fall into accepted mainstream or conventional medicine [1]. Indeed, CAM proposes the use of natural remedies for all ailments, as alternative to and with fewer perceived side effects than conventional medicine [2, 3]. In CAM, therapeutic modalities are generally separated into three main domains; herbal, spiritual, and physical, where the former includes herbs or herbal remedies, such as homeopathy or Chinese herbs or teas; special diets or nutritional remedies, vitamins, or supplements [4].
But this tradition of using non-pharmacologic therapeutic techniques has actually a long history. Traditional medicine is the sum total of the knowledge, skill and practices based on theories, beliefs and experiences, indigenous to different cultures, developed over the centuries in both Eastern and Western societies [5]. Some traditional medicine systems have produced over the centuries huge volumes of literature and records of the theoretical concepts and practical skills, whil others pass down from generation to generation through verbal teaching [6]. In the East, traditional Chinese Medicine (TCM) and traditional Indian Medicine (TIM) dominate the scene and are used amply in both regions of Asia by well-trained practitioners [7]. In the West, the stage was dominated by Hippocratic Greek medicine which was adopted by Romans to become Greco-Roman medicine (GRM or traditional Western Medicine [TWM]) which was then spread throughout the West (Americas) and the Mediterranean region (Unani Tibb) [8, 9]. Together, all three (TCM, TIM and Unani Tibb or TWM) form the three major whole medical systems recognized by the WHO, that is, complete systems of theory and practice that have evolved independently over time in different cultures and apart from conventional (modern) medicine or Western medicine [10]. Many more traditions and TCAMs exist in various countries throughout the World, among which are traditions in Korea and Japan (Kampo) being serviced Vis a Vis with modern biomedicine, African traditions, being rediscovered and increasingly used [11, 13].
While in many Countries in Asia, Africa, and Latin America traditional and indigenous medical practices dating back many centuries continue to be used, in the West (Europe and North America, where biomedicine had developed), CAM are being resorted to for various reasons [14]. It is nevertheless clear that TCAM is not understood by modern medical science in terms of theoretical framework and clinical practice. So much so that emergent research practices is attempting to provide sustainable forms of knowledge from indigenous science, which has been previously limited by polarized views of legitimacy and validity, since it was expected to conform to the conventionality and rationality of "acceptable" Western science–based research protocols [15]. But, it might just be that modern science had not caught up with TCAMs and that it needed a new paradigm shift to finally understand ancient medicine. This paradigm shift may have been

provided by biology. Indeed, this postmodern synthesis of various biological concepts have originated the concept of the holobiont, which represents a dramatic revolution in perspective in life sciences [16].

Medicine is just now starting to get in touch with this reality and the consequences seem to be earth-shaking [17]. A new paradigm has risen in medicine: personalized medicine. Modern medicine is now moving towards a new individualized health-care model that reflect the thinking of patient-centred care with biological–psychological–social–environmental–spiritual characteristics [18]. Ancient medicines have always been closer to the holistic nexus which is being discovered by science as time passes. Newer theories at the forefront of 21st century science are being developed, such as metabolomics and systems biology, resemble TCAMs in many aspects such as study method and design [19]. The recent adoption of these theories to analyse TCAMs have greatly enhanced our knowledge of the scientific connotations of these ancient medicines further paving the way for an increased understanding of the holistic nature of health [20, 21].

Yet, another revolution in biology promises to completely change the way we think of medicine, altogether. The emerging understanding of the critical role played by microbiota in human health and disease is pushing the boundaries of clinical medicine towards a new paradigm and to new and previously undiscovered territories [22]. By reviewing this concept, a new vision of medicine will emerge that will aid in the understanding of ancient traditions and how much more modern they are with respect to conventional biomedicine.

The Holobiont

Investigated scientific literature was too vast to comprehensively or feasibly review and selected manuscripts were chosen. From the analysis of recent literature on prebiotics, a key concept keeps manifesting again and again: the human being is a holobiont [23]. A holobiont is an individual with an emergent phenotype composed of both his or her own genome and cells (eukaryotes) and the resident microbiota's genetic material and cells/viruses at any given point in time, forming the hologenome [24, 25]. The macrobe (the host) has different forms of interactions (opportunistic, competitive or cooperative) with all of its associated microbiota, including bacteria, archaea, viruses, protists, fungi, and microscopic multicellular animals such as nematodes [26]. This new vision of biology, emerging from the ground-breaking researches on the universality and diversity of microorganisms (microbiology), affords a holistic view of biological complexity of human beings [27]. Diet, by providing substrates for the bacteria in the colon (the densest and probably the most important of the host-associated microbial communities), contributes to influencing all aspects of human biology and health [28]. A summary of this analysis is hereafter presented.

The Emerging Holobiont

The hundreds of trillions of microbes that colonize our intestine (an amount of cells that vastly outnumbers our own by orders of magnitude) are now considered critical to human health after having been deemed just opportunistic bystanders [29]. The bacterial cells in the holobiont (between 3.7 and 4.4 x 10^{13}) are thought to outnumber human eukaryote cells (between 3.0 and 3.7 x 10^{13}) by almost a factor of 2 [23]. Most of our commensal bacteria belong to four main phyla (Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria) and are in the colon, where the concentration is the highest as is the diversity [30]. This community of microbes consists of a large variety of bacterial species that collectively influence numerous aspects of human nutrition and health by supplying an arsenal of carbohydrate-active enzymes (CAZyme) [31, 32]. Bacterial CAZymes are important constituents of the human holobiont as they are required to digest most of our complex repertoire of dietary polysaccharides, which we are unable to hydrolyse and thus utilize [33]. Indeed, the combined genomes of all resident bacteria, the microbiome, contain more than 5 million genes, thus outnumbering the host's genetic potential by two orders of magnitude [34].

A growing number of studies in recent years highlight how functions related to the metabolism, immunity, and environmental adaptation of animal, plant or fungal life are accomplished by a host-specific microbiome [35, 38]. There is a sophisticated and intricate molecular crosstalk among the multiple components of the holobiont that has to be maintained in order to achieve health [17]. Resident microbes perform very important functions that humans need. For example, bacterial fermentation in the human colon of enzyme-resistant carbohydrates produces molecules that have wide-ranging impacts on host physiology: the short-chain fatty acids (SCFAs) [39]. SCFA (e.g., propionate, acetate, butyrate) are the principal by-products of the fermentation of complex carbohydrates by gut microbiota [40].

SCFA are involved in numerous physiological processes ranging from energy, lipid metabolism, to immunity and inflammation [29]. Some of these, like maintaining the luminal pH, inhibiting the growth of pathogens, influencing the bowel motility, and act as signaling molecules reducing production of proinflammatory cytokines are important homeostatic functions [30].

Apart from being practically vital for the complete digestion of food, the gut microbiome also functions as a barrier against pathogens [41]. Good microbes literally "fight" against pathogens in a competition for the limited food sources. Commensal microbial communities produce antimicrobial substances, occupy ecological niches and compete for nutrients thus defending the host against pathogen colonisation [42].

Having a health gut microbiome has been recognized as being important in all stages of life especially at the beginning. Resident microbial communities seem to play an important role in the development of immune tolerance to innocuous antigens and microorganisms [41]. Commensal microbes release also a variety of metabolites including essential vitamins, which influence locally and/or systemically host physiology [34]. Gut microbiota also must be present in early stages of life for metabolic and immune system pathways to develop optimally for long-term health [43].

The Complex Holobiont

It has thus been amply documented in literature that we, as humans, are not monogenomic organisms, but rather are beings living as holobionts. Human holobionts are symbiotic consortia of numerous diverse microbial communities (ecosystems), cooperating together (symbiosis)

rather than competing (to form the biome called human) [44]. In this sense, we humans are superorganisms, a term coined to identify how different species associate, transiently (mutualism, parasitism) or permanently (symbiosis, commensalism), to do things of ecological import [45]. And we are indeed made up of different species, so that we are anatomical, physiological, developmental, immunological, and biological units, emerged from a shared relationship between different kingdoms of life [46].

It is now recognized that mutualistic symbioses between microbial communities and their multicellular host, forming the holobiont, is the norm in nature (ubiquitous) and not an exception [47]. From these mutualistic interactions comes a state of healthy conditions for the holobiont. On the other hand, in diseases states, from these same interactions emerges the pathobiome, i.e., the pathogenic microbiome of an unhealthy holobiont, which modulates pathogenesis at a community microbial level [48]. For the holobiont, human pathobiome can be viewed as a subset of its microbiome centered on pathogens and their interactions with other microbes of the same or different kingdoms of life [49].

Because many host-associated microbes are uncultivable outside their hosts, environmental genomics approaches have been successfully applied to unravel the diversity and roles of microbes in non-model and model organisms and in all ecosystems [50]. Both animals and plants are thus holobionts, functioning as distinct biological entities, anatomically, metabolically, immunologically, and this is the hallmark of eukaryotic life [51]. We cannot anymore call ourselves as individuals (or insular individuality), neither anatomically nor physiologically, as in fact we are symbiotic complexes of many species (symbionts) living together [52]. Current studies have revealed that the blood of healthy humans is not a sterile environment as previously supposed but instead is the niche for a diversified microbiome, with likely an important physiologic role [53].

Symbiotic microbiota (symbionts) are thus so intimately connected to the host in the holobiont that any form of disruption will have negative consequences in terms of health [54]. A consequence of the complex conglomerate of the host (made up of eukaryotic cells) with microbiota (microbial eukaryotes, archaea, bacteria and viruses) dwelling in defined ecological niches inside and on the metaorganism is the redefinition of what constitutes the biological individual [55]. As multicellular organisms (or metaorganisms), we rely on our associated microbes for many aspects of our function and biology which include basic life history traits such as longevity, developmental pace and epigenetic programming [42, 56]. So fundamental are the interactions between the microbial associates, symbionts, and the microbial community that these driving forces in ecosystems are increasingly deemed modulators of host phenotype, providing heritable variation to future generations (epigenetics) [57].

The human holobiont concept has originated from the realization of a multitude of microbic niches within and on our body. Resident bacteria have been identified in the intestines, but not just on the surface: even within a few millimetres from the surface between the enteric cells [58]. Many species have been discovered in the stomach of healthy individuals [59]. Living microbes have been found with recent high-throughput techniques in the previously thought sterile brain and blood [60, 61]. A proper, personalized and commensal microbiome has also been recognized thriving on the skin, in the mouth and esophagus, in the testes and seminal fluid, and also in the uterus and placenta where they are responsible for maintaining homeostatic maternal-foetal interactions [62, 66].

In the end, the concept of the holobiont or metaorganism focuses on the intimate relationship between the host and its consortia of commensal microorganisms. When the functional association between them breaks down, a dysbiotic state occurs, leading to grave effects on animal health [67]. The recognition that humans are holobionts has led many researchers to reassess their views about various processes and concepts that are foundational in biological thinking [26]. Medicine is still very much behind in this re-evaluation process.

Dysbiosis

Dysbiosis is a common problem that originates when the microbiota is perturbed [68]. In these instances, several diseases may arise including obesity, diabetes and general inflammation (with consequential GI disorders) [69]. It is also likely that the majority of the population is affected by dysbiosis and have persistent low-grade inflammation [70, 71]. Dysbiosis is also accelerated by the consumption of normal carbohydrates (starches) which favours pathogenic microorganisms with respect to the useful ABO-aligned resident gut bacteria [72, 73]. Dysbiosis then translates in series of intestinal disorders, such as inflammatory bowel disease, and extra-intestinal disorders, including metabolic and cardiovascular diseases [74]. The opposite of such an altered state which is closely related to systematic inflammations and the metabolic syndromes, is normobiosis and is connected with an under-growth of the Proteobacteria, and/or increased Bacteroidetes [30]. Substantial literature also suggests that dysbiosis can cause gut epithelial barrier dysfunction, and thereby provide a point of entry into the body by microorganisms, including the blood, resulting in atopobiosis (translocation into regions not normally colonized by that species) [75].

Diet can also have direct impact on immune and inflammatory responses at a tissue level (contact of foodstuff with the epithelial cells). It has been shown extensively that certain carbohydrate structures (called glycans), that act as antigens, elicit immune responses upon contact [76, 77]. These dietary glycans resist enzymatic attack during digestion and either interact with human lectins on the GI linen [73, 78, 79] or are utilized selectively by our gut bacteria, thus impacting on health and disease [80, 81].

In conclusion, there is a vast collection of recent literature on the health benefits of prebiotics that need not to be summarized but scantly here. Ample in-depth reviews are already available and are referred to although these cannot possibly bring justice to the hugeness of the literature available [82, 84].

TCAMs

TCAMs can be variously known as ethno-medicine, traditional medicine, folk medicine, native healing, or CAM and are broad and diverse being culture-bound methods of healing and the oldest form of health care system [12]. While modern medicine (biomedicine) has achieved a lot through its wonder treatments, complete or partial cure is still not achievable for many diseases and treatment is largely symptomatic, with sometimes serious adverse events [85]. Hence, the resurgence of TCAMs has been hailed as a way

to avoid adverse reactions and treat at least partially the uncurable diseases.

Philosophically, all TCAMs and ethnomedicines are similar among each other with a scope that is largely different from modern biomedicine. Particularly, TCAMs, like TCM, focus more on health maintenance rather than symptomatic relief and emphasizes on enhancing the body's resistance to diseases, which is especially helpful in early intervention and in personalized and combination therapies [18].

In Asia, TCM is the system with the longest history, developed through thousands of years of empirical testing and refinement, and has spread in many other Asian countries influencing their respective philosophies to align them more to TCM [86].

Kampo and TCM are very similar in theory and practice (Kampo being the herbal system used in China that developed during the Han dynasty) and are fully integrated into the healthcare system in Japan and China respectively [87].

Sasang constitutional medicine (SCM) is a unique form of traditional Korean therapeutic medicine, based on the Yin and Yang theory and on Confucianism, where humans are classified into four constitutions depending on their physical and psychological characteristics [13].

Maybe the largest ensemble of systems of medicines is TIM. TIM has six recognized systems of medicines: most originated from the Indian continent (Yoga, Ayurveda and Siddha) others have been absorbed from outside (Unani, Homeopathy, Naturopathy), apart from a large number of unsystematised medicines that don't belong to any category [88].

In TIM, not only Ayurveda but also Unani Tibb forms part of the system of medicine practised in India [85].

Traditional Persian medicine (TPM), is a system of medicine developed in Persia from Greek humoral medicine, as a famous medical school is based on four humors (bile, blood, phlegm, black bile) and is considered to be very similar to Unani Tibb [89].

Iranian traditional medicine (ITM) is one of the oldest medical schools with more than 1000 years of history and has a good level of similitude with TWM since both have a basis on humoral theory [90]. These two systems of medicines can be considered one and the same. Indeed, non-conventional medical schools, practiced primarily in the Muslim community, ITM or Persian medicine, are also called Hikmat and their practitioners [91].

Most of these medicines can be considered humoral medicines. In Western humoral medicine (TWM), a balance of the four humours (blood, phlegm and yellow and black bile) was believed to determine health and disease [92]. Each person has a natural complexion, which is his or her own normal distribution (admixture, individual temperament) of the four humours (and related qualities like hot and cold), which changes depending on further variables such as age, sex, customary nutrition, climate, season and the type of daily activities [93].

Many other ethnomedicines consider illness and health are strongly influenced by spiritual and religious factors, whereby human beings are in an integral and interactive relation with the universe around him/her, seen as both nature and society [94].

Equilibrium in TCAMs

The concept of equilibrium is fundamental in all TCAMs. It is possible to find this concept everywhere in all TCAMs.

Starting from TCM, the healthy human body is viewed as an entity in equilibrium — the ultimate goal of any treatment in TCM is to restore the qi (energy) and yin-yang (balance) of this complex system [86]. Hence, the holistic adjustment to pursue a system balance in the human body seen as a dynamic state of the yin and yang, the five elements and the qi is the basic principle of TCM [18]. Even more so, according to the theories of TCM, everyone has a unique natural balance, called an individual's harmonious constitutional nature, which, in the context of disease, becomes disturbed and the person develops disease [95].

Similarly, in SCM, different constitutions decide the equilibrium state of internal organ function (seen as visceral group pairs) and so disharmony (loss of regulation) brings about disease [13].

Kampo too, in TJM, regards the disease state as an imbalanced state, and the process of healing is undertaken to correct this imbalance or to help the individual patient return to the equilibrium state [96].

In TIM, Ayurveda defines disease as "any disturbance in the equilibrium of tissue elements known as Dhatus" (eight in number) resulting in three types of diseases; endogenous, exogenous and psychic [85]. In this sense, the optimum state of health in an individual is state of ideal equilibrium among the three Indian doshas, proper to that person.

In ITM, the term mizaj (temperament) describes the normal biochemical equilibrium of the body as a whole (as cells, tissues, organs) while any change in this equilibrium is termed as su-e-mizaj or derangement of temperament (dystemperament) [97]. Similarly, in TPM any imbalance in humoral equilibrium (dystemperament) may result in organ or system disorder (for example gastrointestinal system) [89].

We have seen that all TCAMs have this underlying knowledge of equilibrium and homeostasis, which when perturbed generates disease. In TCM, a disease is conceptually similar to that in Western medicine (though the two systems have their own disease classification system) and consists in a diagnosis of disequilibrium among the subsystems: wherefore TCM advocates restoring an equilibrium to help the organism heal itself (self-healing) [98]. In early western humoral medicine, illness occurs when the balance of humors is upset (dyscrasis), which may be caused by a deficiency, excess or uneven distribution of one or more of the four humors [93]. A restoration of the equilibrium (eukrasis) of the humors is always sought in humoral theories [92].

Therefore, all TCAMs essentially utilize multimodal interventions to achieve a rebalancing of the interconnected body-mind-spirit systems [98]. For all ethnomedicines, health is attributed to the equilibrium or balance between forces of nature (and society in a psychosocial view of human beings), while illness is the disequilibrium of these forces [94].

Conclusions

With the new era of personalized medicine, the old paradigm of a one size fits all concept of medicine (with its synthetic medications that often elicit many adverse events) is definitively ended [18]. Although it may still take a lot of time for the common physicians to catch up with the latest research, a new medicine that embraces the holistic approach of ancient traditions is now on the horizon.

Herbal remedies remain at the forefront of any CAM. To

date, in some parts of the world, the majority of the population continue to rely on their own traditional medicine to meet their primary health care needs [6]. But, the future is not an easy one for all TCAMs. For certain TCAMs, such as TIM, traditional skills and wisdom have almost entirely disappeared or are in the process of disappearing as the knowledge has not been documented properly or standardized (as the language is often Sanskrit or regional), rendering systematisation a difficult task [85].

It has been shown that there is a fine-tuned and resilient equilibrium within the members of the microbiota and between them and the host, and this is what constitutes health for the holobiont [17].

The holobiont is a metaorganism made up of cells from immensely diverse species. The holobiont share more affinities with communities than they do with organisms or integrated individuals [26]. The host's microbiota is increasingly being recognized for its major role on host health, in the prevention and therapy of diseases and in treatments restoring altered microbiota [50]. And this occurs not just at the phenotype but also at the genomic level. Quite a few scientists have argued that hologenomes might exist as hierarchically nested, although not necessarily integrated, levels of genomes in which all levels of selection are in play [24].

It is important to note that ancient medicines did understand how the personal condition of each individual defined the unique state of health and disease. Indeed, all people are categorized in to different categories based on their psychosomatic constitution (thus displaying unique characteristics), that often can be grouped into defined constitutions [88]. Whilst each of the major medical system has its own number of humors, they all nevertheless recognize an equilibrium and disequilibrium state. Balance (or homeostasis) of energy or humors in TCM is a state that has a parallel with the well-understood scientific concepts of metabolism and immunity in the western scientific world [86]. Similarly, minor medical systems, ethnomedicines, still use traditional methods (e.g., plants) to re-establish the pre-illness equilibrium [99].

The restoration of the equilibrium (eubiosis) is the ultimate scope and purpose of any interventions on the holobiont. Restoration of equilibrium has also always been the scope of all traditional CAMs (88, 100). In the light of the holobiont, thus, we have a new understanding of the truth of all traditional CAMs, whether they are of Indian, and Chinese, Middle Eastern or European origin [101, 102].

Modern medicine must take on the challenge of biology and integrate the new paradigm into its own matrix. Modern medicine must learn to see the patient through the lens of the holobiont: a multicellular eukaryote together with its inseparable colonies of persistent symbionts forming a critically important unit of anatomy, physiology and immunology [103]. Personalized medicine may be able to pick up the challenge develop a new theory which integrates personalized dietary suggestions (nutrition) and the microbiota-host holobionts system [104, 105]. Medicine should learn to piece together metabolomic, metagenomic, transcriptomic, and epigenomic data (multi-omics approach) to investigate optimal functioning of the holobiont (with diet being the archetypal environmental variable) and its microbiota–nutrient metabolism–epigenetics axis [106, 107]. Failure to do so would likely spell doom to modern medicine leaving the path to a resurgence of ancient medicines and TCAMs. These medicine systems, with their arsenal of natural remedies and concepts akin to that of the biologic holobiont, would rapidly fill the void left by modern medicine.

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