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Review Article

The Case for Cannabidiol-Integration of Eastern and Western Medical Traditions and the Promise for the Future: A Narrative Review and Commentary

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ABSTRACT

Our intent in the following narrative review and commentary is to underscore the importance of critically re-exploring ancient and enduring medical traditions. We support a view that rediscovering and augmenting the elements of the past, especially in the context of Eastern traditions, will inform and strengthen the global future. In the absence of the historical and multicultural perspective, it could be argued that we have become rather myopic or focused within discrete silos; we seem continually to re-invent the wheel in successively refined form, without truly evaluating foundations, traditions, and history of use. This situation suggests that technologically sophisticated investigators and clinicians are not necessarily aware of the full spectrum of the safety, efficacy, clinical indications, and guidelines for the use of many naturally sourced pharmacologic formulations with a remarkably long history of widespread use, and with implications for valuable and innovative drug development. We discuss Cannabidiol (CBD) as illustrative of such an opportunity.

Keywords: Cannabidiol, CBD, Eastern Medicine, Traditional Medicine, Integrative Medicine.

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INTRODUCTION

Humans have been looking after their health in countless ways for thousands of years. From ensuring the balance of 'humors' in Ancient cultures to cold-water therapy in 19th-century England, our understanding of health and medicine has continued to shift and evolve. While health and ill health were initially thought to be dictated by the Gods, the ancient Greeks were the first to look at the body through the lens of human biology. They studied health by examining four bodily fluids or 'humors'-blood, black bile, yellow bile, and phlegm.

Today, Western medicine remains primarily founded on the principles established by the ancient Greeks. As Western medicine has evolved over the past 3,000 years, the key foundations of medical practice remain the same.

- Systematic and standardized inquiry and examination of the physical body and its symptoms.
- A scientific, evidence-based diagnosis of health or illness using clinically proven data collection methods and pathology management.
- Health is a fundamental human right that should be promoted and protected through compartmentalized instrumental and expressive care.

Eastern medicine, in contrast, refers to various organically integrated medical practices that originated throughout Asia. Although these practices have evolved over thousands of years, they still retain many of their original approaches to healing. Most Eastern medicine's philosophy is treating the whole person, not only the constellation of symptoms and clinical data. More than the Western bio-psycho-social perspective, Eastern medicine encompasses spiritual, social, and temporal health determinants and underscores aspects of illness prevention. Concretely, specific practices such as unani, homeopathy, naturopathy, and anthroposophy have searched for and discovered natural but, by Western scientific standards, vaguely defined methods and substances for healing and wellness. The Eastern pharmacopeia is vast, enriched with easily more than 2,000 medicines derived from various herbal, mineral, and animal sources.

Unani medications are often processed using classical or traditional preparation methods as originally described in Greco-Arabic

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medicine. Medicines are used singly or compounded with other substances to achieve synergistic, antagonistic, or detoxifying effects or simply as bases for putatively effective ingestion and assimilation.

The most common forms of Eastern medicine are:

- **Chinese medicine:** Dating back more than 2,000 years, Chinese medicine looks at the balance of energy in the body that runs through invisible 'meridians'. If a patient presents as unwell, a Chinese medicine practitioner will investigate where the flow of qi (pronounced 'chee')-or life force-may be blocked in the body by undertaking a tongue and pulse analysis. Patients may be prescribed herbal medicines, acupuncture, and remedial massage.
- **Ayurveda:** The ancient Indian practice of Ayurveda looks at the balance of three elemental energies-fire, water, and air-and where an individual might have an excess of one of these elements. Patients of Ayurveda are treated via changes to diet, massage, herbal medicine, and meditation.
- **Unani:** A form of medicine originating in Greco-Arabic regions. Unani formularies present combinations of various medicinal plants, minerals, animal products, a method of administration, various preservatives, indications and contraindications in different situations, restriction, avoidance, and abstinence of certain diets (*Parhez*), adverse drug effects; drug profiles; adverse drug-drug or food-drug interactions; guidelines for prescribing in extremes of age or in the presence of altered organ function or in the presence of pregnancy or lactation.[1]
- Eastern medicine treatments are more considered holistic, with the goal of restoring trusted balance through alternative treatments such as acupuncture, diet, and massage. However, it is important to recall that the key difference between Eastern medicine and Western medicine is that it aims to treat the whole person, which includes the spiritual and sociocultural context that defines the patient's conception of happiness and health. Western medicine seem to be recognizing the broad value of such an approach with the advent of "syndemics," or social determinants of health and disease.

METHODOLOGY

In preparation for the present commentary, we reviewed historical and ethnomedical databases associated with anthropological, archaeological, historical, and ethnomedical, and ethnobotanical subject matter, along with the literature of particular pathological conditions or diagnoses such as pain, anxiety, and sleep disorder. Our impression was that a significant portion of relevant studies and reports do not seem to have been identified in critical or systematic reviews using the usual keywords or search strings that include "cannabis" or "cannabinoids." Potentially illuminating work has thus been embedded in a variety of categories and published sources that were identified and accessed through review of selected works in history and the social disciplines. The process began with data aggregation on the cannabis and traditional Asian medicine landscape, that in turn, generated a preliminary list of pertinent articles and authors, that were, in turn, evaluated for quality and relevance through integrated review by a physician, a molecular biologist, and a toxicologist. Final selection of studies was guided by general adherence to Cochrane and PRISMA Criteria, (https://training.cochrane.org/handbook/current/chapter-03#section-3-2; https://www.prisma-statement.org), and full-text articles again, were evaluated by each author through the lens of their respective clinical and scientific disciplines.

BACKGROUND AND DISCUSSION

Thai Traditional Medicine

We highlight Thai Traditional Medicine (TTM) since it has drawn upon and integrated multiple ancient traditions, sustained them in a growing alternative and complementary medicine enterprise. According to the "Protection and Promotion of Thai Traditional Medicine Wisdom Act B.E. 2542," Thai Traditional Medicine (TTM) is defined as "the medical processes dealing with the examination, diagnosis, therapy, treatment, or prevention of diseases, or promotion and rehabilitation of the health of humans or animals, midwifery, Thai massage, as well as the preparation, production of Thai traditional medicines and the making of devices and instruments for medical purposes". TTM is characterized as a holistic and natural approach of health care that is derived from Buddhist beliefs, the observation of and respect for nature, and the wisdom of Thai ancestors.

In addition, traditional knowledge of TTM was also built through the processes of "selection", "adoption", "adaptation" and "utilization" of traditional medicine of some countries with which Thailand had contact in the past, e.g., India and China, to suit the Thai way of life. TTM knowledge was gradually developed, systematized, revised, recorded, and passed on from generation to generation throughout the country's history, from Sukothai to Ayutthaya (1350-1767), Thonburi (1767-1782), and the early Rattanakosin period (1782-1916), as a means of health care for the Thai people. After Burma destroyed Ayutthya in 1767, Kings Rama I-III of the present Chakri Dynasty played an important role in the revival of TTM. Over 1000 drug recipes and the body of knowledge of TTM regarding the origin of diseases and their treatments were gathered and inscribed on marble tablets and placed on the walls of two temples, namely Wat Po and Wat Raja Oros. The purposes of the Kings' orders were to compile collective knowledge of TTM that was partly lost or destroyed during the Burmese-Siamese War (1765-1767) and to give health education to the Thai people so that they could take care of their health using TTM. Unfortunately, the influence of Western medicine, which was introduced into Thailand by missionaries and Western

physicians during the reign of King Rama III (1787-1851), gradually increased and eventually led to the abandonment of the systematic teaching of TTM in the medical school in 1916. This sparked the decline in TTM acceptance, especially among people in urban areas, and the status of TTM practitioners in the country's healthcare system for over 60 years.

Ironically, collaboration between Indigenous and Western scientists honored as year's outstanding Science paper...celebrated as "giving a voice-literally-to the way other cultures and civilizations have done science so far..." Though, in this instance, the involved tribes included the Pueblo, Wichita, and Pawnee Nation, one could readily speculate how much could be brought to the laboratory bench from indigenous Eastern communities;[2,3] See also: https://www.science.org/content/article/scienceadviser-collaboration-between-indigenous-and-western-scientists-honored-year-s).

Avicenna

There is no better historical example of the increasingly appreciated integration of Eastern and Western tradition in the medical realm than the works of "Avicenna," to the Latin west, and "Ibn Sina" to the East. Avicenna's full name was Abu Ali Al-Hussein Ibn Abdullah Ibn Sina, from which the Arab world derived the nickname, Ibn Sina. A native of present-day Iran, Avicenna was born near the Samani kingdom's capital, Bukhara, in the year 980 AD.[4]

During his all too brief life, Avicenna occupied the "Golden period of Arab science", and claimed a significant place among the taught art and science of Medicine and Pharmacy.[5] He was known for identifying and cataloging naturally occurring substances mentioned in medieval medical literature that have, and may well continue to have, a crucial place in drug discovery. Avicenna`s Canon of Medicine was regarded as the first pharmacopeia and was used for almost 700 years following its creation by various medical schools and scientific institutions in both the East and the West.[6] Eight hundred drugs and 650 recipes of mixtures of different compounds from various sources are listed in the Canon, with extensive comments on the effectiveness of each drug or recipe for specific pathologic conditions.

Some of the agents suggested by Avicenna for treatment of inflammation and pain are now routinely prescribed drugs. And many of these compounds are under experimental or clinical investigations for putative therapeutic effects. However, most of these drugs remain largely unexamined. One obvious example is *Cannabis sativa*, which, according to the Canon acts as an anti-inflammatory with indications for "ophthalmitis, infectious wounds, gout, general edema, and uterine pain.[7] Apart from his acumen and foresight about the value of naturally occurring substances, Avicenna is said never to have lost a clear sense of the importance of harmonization of the disparate parts of health and illness in what must be among the first documented representations of the biopsychosocial approach to medicine that we at least aspire to in the West.

As to pharmacologic agents, it has been observed[8] that "Herbs are never simply medicine" in the Eastern tradition-they can be tonic or food. This belief supports a view that consumers and patients are sufficiently familiar with the raw materials and their effects such that the users may guide the development and indications for herbal remedies. However, their voices have certainly not always served to shape research and development. Throughout history, medical knowledge is usually documented or inherited by physicians, while the narratives of patients tend to be undervalued.[9] These narratives face the questions and mandates of the Western research paradigm that values data over faith in the agents derived from centuries of experience.

Herbal Medicine as a Driver of Western Science

Ge Hong (284-346 CE) is said to have prescribed the basis for an anti-malarial in his A Handbook of Prescriptions for Emergencies: "A handful of Qinghao immersed with two liters of water, wring out the juice and drink it all." This unique preparation inspired an approach that reduced extraction temperature was achieved by using ethyl ether.[10,11] The new sample of Qinghao ether extract showed 95-100% inhibition of rodent malaria. After this success, they began to isolate and purify the bioactive molecules in the extract. In 1972, an antimalarial compound was isolated, crystalized, and its structure determined in 1974. The same group used the basic structure of the molecule to create dihydroartemisinin with improved efficacy.[10,11] Artemisinin and its derivative dihydroartemisinin saved millions of lives threatened by malaria. This discovery was considered one of the breakthroughs in human health during the last century. Due to her tremendous contributions, Tu Youyou was awarded the 2011 Lasker Award for clinical research and the 2015 Nobel Prize in Physiology or Medicine.

This series of events illustrates the importance of herbal medicine in the context of science and that Western biomedical research took its cue from Eastern medicine to reveal both the mechanism of action and global clinical indications and potentials of a valuable agent.[8]

Now, with the augmented accessibility and legality of cannabinoids, herbal, and botanical compounds, increasing recognition and understanding that these elements and their historical narrative may represent powerful interactive variables for human health has become an important discussion that promotes innovative and much-expanded indications. Moreover, this discussion seems likely to yield a more complete and clinically meaningful approach to medical diagnosis and therapy.

East Meets West

Increasingly, we see examples of holistic or integrative medical care built upon Western approaches blended especially with

Traditional Thai and Chinese medicine, both in terms of personalized expressive and instrumental care. Modern Western interventions such a platelet rich plasma therapy are now complemented by traditional herbal treatments. Among the most widely used alternative therapies with roots in the ancient world is medical cannabis.

The 9th-century has been described as a rich time for cannabis medicine.[12] It seemed that Egyptian and Greek approaches crept unbidden into each other and diffused in all directions. The Persian physician, Sabur ibn Sahl cited use of cannabis various times in his formulary, Al-Aqrabadhin Al-Saghir, another very early Arabic pharmacopeia.[13] Ibn Sahl described a compound mixture of herbs, including "juice" extracted from cannabis flowers and seeds utilized to treat migraine and what amounted to gynecologic pain. This preparation was administered via instillation into the nostril of the afflicted patient, and likely represents an early mention of cannabis for migraine,[14] along with a then novel parenteral form of administration. It also highlights the biphasic nature of cannabinoid effects, such that early over-exposure may interfere with fertility and pregnancy while later, it was speculated that low dose cannabinoid effects may actually preserve reproductive function.[15]

Also, in the 9th century, the physician al-Kindi, wrote about the muscle relaxation properties of cannabis, supports Galen's assertions about easing the muscles of the limbs. Much later, O'Shaughnessy noted efficacy of cannabis extracts to produce survival in tetanus in India in 1839.[16]

Therapeutic cannabis represents a class of substances such as tobacco, ethyl alcohol, and caffeine (coffee and black tea), which have been and continue to be widely and regularly used by all humanity. Since 1940, when it was isolated by Roger Adams, extracted cannabinoids such as Cannabidiol (CBD) have been used both as monotherapy or in conjunction with mainstream prescription drugs depending upon indication and the individual needs and characteristics of the patient.

The major advance in the science behind CBD came in the 1960s from Raphael Mechoulam, the Israeli chemist who first identified CBD's structure. This discovery ultimately led to an understanding of the specific effects of individual cannabinoids in various combinations, doses, and routes of administration.

Interestingly, driven by myriad reports by non-medical and non-scientific users, global investigation of CBD in nonclinical and clinical settings, especially in the last decade, has spurred an enormous and diverse research effort.

Five years ago, relatively little was published in the academic mainstream about CBD and its therapeutic possibilities. Now, this component of an ancient class of drugs is seen by many patients and providers as a significant addition to the wellness world and medical management of various acute and chronic ailments and diseases.

(See Table 1 for a modern-era survey of *in vitro* and *in vivo* animal data suggestive of therapeutic anti-inflammatory actions by CBD).

The whole plant, Cannabis, was discussed in various texts as far back as 12,000 years ago in central Asia, and since then, cannabis seeds have accompanied the migration of nomadic peoples on several continents. It is often pointed out that evidence of the medicinal use of forms of cannabis appears in China, Egypt, and Greece, and later in the Roman Empire (Pliny the Elder, Dioscorides, Galen). In the 19th century, scholars such as Silvestre de Sacy, and Western physicians coming into contact with Muslim and Indian cultures, like O'Shaughnessy and Moreau de Tours, introduced the medicinal use of cannabis into Europe.[17]

Thailand enjoys a rich history of hemp and cannabis applications in formulae for managing depression, anorexia, insomnia, and various kinds of stress (see Figures 1 and 1a). In the mid-1600s, doctors that served the king united to compile a textbook of King Narai's medicines or Tamra Phra Osod Phra Narai, which was the first official textbook of Thai drug recipes. During the reign of King Rama V (1868-1910), the first medical textbook Tumra Paetsart Sonkrau and the first Thai national formulary called Tumra Paetsart Sonkhrau Chabub Luang as well as Tumra Vejasuksa, the first TTM textbook for medical students, were published. They are still official textbooks of TTM accepted by the Thai Food and Drug Administration (FDA) for the registration of traditional medicines…and these include prescriptions of traditional medicines that contain cannabis.[18]

Western style nonclinical and clinical evidence has shown that cannabinoids such as CBD can be safely and effectively used to reduce seizures, particularly in children with treatment-resistant epilepsy. Future bench research together with multicenter, placebo-controlled clinical trials will provide insight into cannabinoid function and the potential neuroprotective effects of modulating endocannabinoid tone. These findings will increase our mechanistic understanding of seizures and may provide novel, targeted therapeutics for epilepsy.[19]

The whole cannabis plant contains a complex mixture of compounds, including the major cannabinoids (i.e., Δ9-THC and CBD), as many as 150 minor cannabinoids, and terpenoids (limonene, myrcene, α-pinene, linalool, β-caryophyllene, caryophyllene oxide, nerolidol, and phytol). Importantly, it may be that the "entourage" of chemicals derived from the whole plant appears either more (or less) effective than any single cannabinoid for a given indication. In support of this view, there is evidence that CBD may potentiate the beneficial effects associated with Δ9-THC (analgesia, antiemesis, and anti-inflammation) and reduce the adverse effects of typical doses of Δ9-THC (impaired working memory, sedation, tachycardia, and paranoia).[20]

Mixtures, Combinations and Formulations

Some reports claim potential synergistic interactions of a mixture of phytocannabinoids and phytoterpenoids that may include therapeutic effects on pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal, and bacterial infections. However, proper characterization of any "synergistic" effects of multiple plant cannabinoids requires appropriately powered, randomized, placebo-controlled, trials of sufficient duration to yield robust demonstrations of effects that may be significantly greater or less than the sum of the parts.

Despite the number of challenges presented by complex botanical combinations for the Western regulatory landscape, what we also appreciate is that the Eastern approach actually illuminates the pharmacologic reality by suggesting in non-scientific terms that a desired effect of an herbal/botanical formulation is due to activation of multiple receptor families either as partial agonists which then trigger the signal transduction pathways that produce a clinical response. Thus, "the effects of Western drugs are often not as specific as proclaimed, and they do not [necessarily] act on the single receptor aimed for."[21]

Extracts of traditional Thai herbal combinations such as Tri-Pha-La and medicinal plants such as Fah-Talai-Jone are now utilized in commerce; a range of preparations designed for specific indications all contain CBD, which either augments or provides anti-oxidant (anti-inflammatory) and anti-microbial activity (see Figures 1 and 1a). Together with few or many other terpenoids, flavonoid glycosides, and other compounds such as the tocotrienols, the polyphenolic curcumin, NAD^+, and CBD, modern Thai medicine has suggested that aging itself, i.e., cellular senescence may be attenuated with exposure to these mixtures.

Contributing to the uneven and multifactorial impact of any complex botanical on human health is the traditional Eastern emphasis on understanding each individual patient's unique biopsychosocial, cultural, historical, and economic context. Examined and explored through this holistic perspective, the major cannabinoids present new therapeutic promise despite a very long history of human use.

Cannabidiol (CBD): Why Now?

CBD is the focus for the present commentary because it is the best studied exogenous cannabinoid, arguably with the most desirable side effect profile and the greatest versatility and efficacy in terms of indications. The emerging and exciting potentials of the medical cannabis landscape also serve to demonstrate that the most valuable pharmacologic agents may come from a deeper exploration of natural compounds that have always been with us…rather than from expensive and arbitrary bioprospecting for metabolites of exotics and extremophiles, or perhaps the synthesis of exciting but expensive monoclonals with less than ideal side effect profiles.

Overview of Mechanisms and Indications

CBD can modulate intracellular redox and inflammation signaling due to direct regulation of the generation of Reactive Oxygen Species (ROS) and agonistic/antagonistic effect on the activity of membrane receptors and modulating the metabolism of endocannabinoids. In nonclinical models, CBD shows

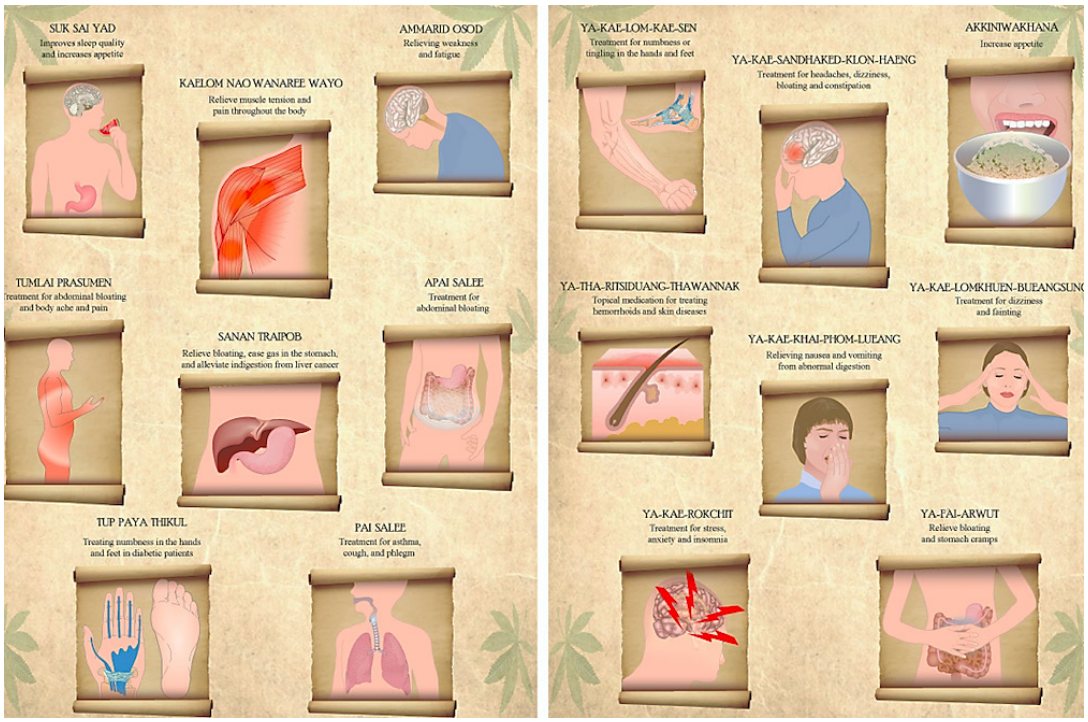

Figure 1 and 1a: Historically important Thai medicines containing Cannabis with traditional indications.

Table 1: *In vitro* and *in vivo* animal data suggestive of anti-inflammatory actions by CBD (adapted from Burstein 2015).

Response	Model
Reduces immune response	Rats subjected to pneumococcal meningitis
Prevents experimental colitis	Murine model of colitis
Reduced iNOS and IL-1β expression	Mouse model of Alzheimer's disease
Reduces β-amyloid-induced neuroinflammation	Cultured astrocytes
TNF-x and IL-1ß levels reduced	Murine collagen-induced arthritis
Decreases in PGE_2 plasma levels	Carrageenan paw injection in the rat
Reduced the extent of colitis	TNB mouse model of colitis
Inhibition of neutrophil chemotaxis	Human neutrophil migration
Effects on NF-κB, MAPK, ICAM-1, VCAM-1, TNF-α	Mouse model of type 1 diabetic cardiomyopathy
Enhanced IFN-**γ** and IL-2 production	Mouse splenocytes
Exacerbates LPS-induced pulmonary inflammation	Pulmonary inflammation in C57BL/6 mice
Reduced the TNF-α level in the frontal cortex	Pneumococcal meningitis in rats
Decreases hepatic ischemia-reperfusion (1/R) injury	Mouse model of hepatic 1/R
Reduced LPS-induced increase in TNFα and COX-2	Mouse model of sepsis-related encephalitis
Reduced effects of autoimmune encephalomyelitis	Immunized C57BL/6 mice
Reduces inflammation in Acute Lung Injury (ALI)	Mouse model of lipopolysaccharide-induced ALI

remarkable antioxidant activity on several cell types, such as UV-irradiated keratinocytes, skin fibroblasts, primary human keratinocytes, and murine microglial cells.[22]

Although there is structural overlap between CBD and THC, the conformational structures differ significantly. Whereas THC exists in an essentially planar conformation, CBD assumes a conformation in which the two rings are more or less at right angles to each other. This configurational difference may explain why CBD does not possess significant affinity for, or activation of the CB1 receptor, an action that THC is readily capable of effecting.

In mice with middle cerebral artery occlusion, CBD triggered a CB_1-independent decrease in reperfusion injury, inflammation, and death. This neuroprotective action may result from reduced myeloperoxidase activity, neutrophil migration, and microglia high-mobility group box 1 expression.[23] Additionally, CBD seems to activate peroxisome proliferator-activated receptor-γ, reduce NO and IL-β production, suppress gliosis, and decrease neuroinflammation in mice injected with amyloid β. Under oxidative conditions, CBD appears to interact with multiple receptor families and modulates intracellular pathways, regulating processes such as inflammation, differentiation, and apoptosis, in which oxidative signaling is involved. CBD directly changes the redox status of cells by affecting ROS generation due to interruption of free radical chain reactions, transition metal ions chelation, or activity of anti-/pro-oxidant enzymes.[24] Also, CBD can indirectly regulate the redox status through the modulation of the endocannabinoid metabolism (anandamide, the endogenous THC analog; AEA, and 2-arachidonoylglycerol, 2-AG) and the activity of membrane receptors, including Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) which "cooperate" with Nrf2 and NF-κB.[24]

The key role, then, of the Nrf2 system is the modulation of antioxidant defense and influence on the regulation of molecular signaling involved in apoptosis, ferroptosis, tumor differentiation, and transformation. That CBD appears to upregulate Nrf2 and downregulates its inhibitors BACH1 and Keap1 may prove to be a valuable pathway for ongoing research.

It is illuminating to examine one study utilizing the CANNUSE database for cannabis;[25] this contains over 2300 entries from 649 publications related to medicinal, alimentary, fibre and other uses from different geographical areas and cultures around the

world. In this dataset, the most commonly used plant parts were leaf (50.51%), seed (15.38%) and inflorescence (11.35%). The leaf was significantly associated with treatment of two categories: skin and subcutaneous tissue disorders and circulatory system and blood disorders; seed use was associated with musculoskeletal system disorders and traumas; while inflorescence use shows a statistical support for treatment of nervous system and mental disorders.

CBD may have myriad indications for non-inflammatory pathologies; even in the context of chronic idiopathic/functional disorders of hypermotility, it has been suggested that CBD indirectly activates (via Fatty Acid Amide Hydrolase (FAAH) inhibition) enteric CB1 receptors and thus attenuates motility/hypermotility. Inhibition of FAAH would thus elevate levels of anandamide, a well-documented CB1 ligand and potent anticholinergic.

CONCLUSION

History positions us to see patterns that might otherwise be invisible in the present. Similarly, the important traditions of a given culture are not written in italics; we must look closely enough to understand or at least recognize that something special may be occurring. This appears to be the case with much of what is subsumed under "Traditional Eastern Medicine."

Insights gleaned from an exploration of Eastern Medicine in its various forms may continue to provide increasingly valuable lines of research and development into novel delivery techniques and standardization of complex botanical and herbal medicines including cannabis-based medicines that have resurfaced in Western practice with newly developed but as yet incomplete evidence of safety and pleiotropic efficacy. Cannabis plants have been widely used in medicine since ancient times. In many traditional/indigenous settings, they are celebrated for their putative anti-diabetic, anti-inflammatory, neuroprotective, anti-cancer, anti-oxidative, anti-microbial, anti-viral, and anti-fungal activities. A growing body of evidence indicates that targeting the endocannabinoid system and various other receptors with cannabinoid compounds holds great challenges as well as potentials for addressing multiple medical conditions.[26,27]

We seem to be rediscovering ethnopharmacological research, with a focus on the most clinically intriguing compounds. As much as there is continued promise held out for *in silico* methods of risk assessment, we and others[28] stress the potential pitfalls of these methods and discuss the ongoing need for the application of modern but 'classical' *in vitro* and *in vivo* validation as an absolute requirement for beginning to establish risk assessment for traditional compounds that have never been tested to Western regulatory standards.

Perhaps we have rediscovered the wheel in terms of indigenous medicine with its thousands of years of human experience… rendered now into a scientifically refined, validated, and evidence-based framework…that expands indications, safety, and efficacy in ways that are likely to be of genuine clinical value. In the context of the exogenous cannabinoid spectrum, Cannabidiol (CBD), a 'non-psychoactive' component of *Cannabis sativa* L., is becoming one of the most studied compounds in developing pharmacotherapeutic approaches to treat oxidative stress-related diseases such as cardiovascular, metabolic, neurodegenerative, and neoplastic diseases.

Pathologic stressors shift the redox homeostasis of cells toward the oxidative state and, in the process, activate Nrf2-a redox sensor-to mediate a host of integrated and cytoprotective responses, including antioxidation, detoxification, anti-inflammation, and autophagy. The fact that hormetic (subthreshold) doses of cellular stressors generate the ROS required to create an oxidative state and signal the activation of Nrf2 suggests that Nrf2-mediated cytoprotection and resiliency are regulated by a hormetic, biphasic dose-response relationship in which low doses are associated with stimulation and high dose ranges are linked with inhibition.[29]

After all is said and done, the full potential of medical cannabinoids in general may lie in what has been learned, tested, and adjusted for thousands of years in the Eastern medicine tradition... Innovation and "disruption" in the best sense of the term may be operationalized in mixtures of standardized formulations of botanical and herbal extracts informed by centuries of use, and now adjusted not only to novel indications but to specific patient characteristics, genomic profile, and lifestyle. We will soon come to more fully understand the spectrum of pleiotropic effects of individual and combined cannabinoids, of favorable as well as adverse interactions with the endocannabinoid system, and of adjustments in product formulation and route of administration. And it is here that the future may lie in the improved recapitulation of ancient Eastern approaches married to modern Western technology with randomized controlled trials and notions of personalized medicine informed by ancient experience.

LIMITATIONS

The primary limitation of the present discussion is in the Eastern traditional medicine literature subject itself, which across the centuries is unapologetically not evidence-based. Our hope was to begin to conceptualize fertile intersections of Eastern and Western medical traditions for subsequent highly focused hypothesis-development and testing in rigorously desined randomized controlled trials. While this trend has begun, we utilize the example of cannabis to suggest that important gaps exist.

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CONFLICT OF INTEREST

Pressman and Hayes are paid scientific advisors to Vectura Fertin Pharma; Hoeng is a full time employee of Vectura; Warinhomhoun is a paid consultant to DR CBD, and Padmindra is the CEO and founder of DR CBD. The opinions and commentary expressed in the present manuscript are solely those of the authors and do not necessarily represent those held by Vectura or DR CBD.

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ABBREVIATIONS

CBD: Cannabidiol; **THC:** Tetrahydrocannabinol; **TTM:** Traditional Thai Medicine; **FDA:** Food and Drug Administration; **ROS:** Reactive Oxygen Species; **AEA:** *N*-arachidonoylethanolamine; **PPAR:** Peroxisome Proliferator-Activated Receptor; **FAAH:** Fatty Acid Amide Hydrolase.

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