NPC Natural Product Communications

Integration of Traditional and Western Medicine in Vietnamese Populations: A Review of Health Perceptions and Therapies

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Received: March 30th, 2016; Accepted: June 16th, 2016

In Vietnam, two types of traditional medicine (TM) are practiced: *thuoc nam*, medicine of the South, and *thuoc bac*, medicine of the North, both of which are largely based on herbal drugs used by different Vietnamese ethnic groups. This review presents recently published information from various databases regarding TM, especially herbal drugs, and its integration with Western medical practices outside and inside Vietnam. We first discuss the integration of traditional and modern health concepts by Vietnamese immigrants living outside Vietnam. Next, we describe native and emigrated health education and practices of pharmacy students, health professionals, and citizens living in Vietnam. Finally, we report the recent biological validation of medicinal plants and non-herbal therapies emerging from Vietnamese TM and their current and potential medical uses as identified by Western approaches. The main example described here involves utilization of the tree *Artocarpus tonkinensis* by the ethnic minority of Black Hmong in northern Vietnam, who use a decoction of its leaves to treat arthritis and backache without apparent adverse effects. Our comprehensive review emphasizes that, although Vietnam has a very rich collection of TM practices (particularly the use of herbal drugs), these therapies should be biologically and clinically validated with modern Western methods for optimal integration of Western and traditional medicine in global populations.

Keywords: Vietnam, Natural products, Artocarpus tonkinensis, Thuoc nam, Thuoc bac, Herbal medicine, Traditional medicine.

Traditional medicine (TM) refers to the knowledge, skills, and practices based on theories, beliefs, and experiences of an indigenous culture used to maintain health and prevent, diagnose, or treat physical and mental illness. TM spans diverse therapies and practices that vary by country and region, including drugs composed of herbs, animal extracts, and/or minerals. Additionally, TM employs non-pharmacological treatments, such as acupuncture, manual therapies, and spiritual practices [1].

In Vietnam, two types of TM coexist. The first, *thuoc nam* ("medicine of the South"), is indigenous Vietnamese traditional medicine (VTM) and is based largely on folk herbal knowledge. During Chinese rule in Vietnam, Chinese doctors introduced the second type of TM, traditional Chinese medicine (TCM), now referred to as *thuoc bac* ("medicine of the North"). Numerous medical exchanges between China and Vietnam occurred during the Song, Jin, and Yuan periods, resulting in the integration of herbs, spices, and perfumes in both Vietnamese and Chinese practices. For example, in China near the Sino-Vietnam border, people now commonly chew betel, whose use has been recorded in Chinese medical texts [2]. In contrast, the Buddhist scholar and monk, the founder of VTM, promoted the national application of *thuoc nam* in Vietnam. Tue Tinh's literary legacy stands as a comprehensive corpus of Vietnamese knowledge of TM theory (*materia medica*)

and clinical practice. Collected in eleven volumes, one work describes more than 630 remedies of plant, animal, and/or mineral origin, over 500 of which are uniquely Vietnamese. Tue Tinh's two best known works are still viewed as the fundamental texts of VTM and related pharmacology: *Nam Duoc Than Hieu (The Miraculous Effectiveness of Southern Medicines)* and *Thap Tam Phuong Gia Giam (The Thirteen Modified Classic Formulas for Traditional Drug Combinations)* [3].

Although TM is a mainstream Vietnamese practice, growing interest in additional forms of complementary and alternative medicine (CAM) exists. A survey assessing the knowledge, attitudes, and practices of CAM therapies of 312 physicians at Vietnamese Oriental medicine hospitals suggested that Oriental herbal medicine and acupuncture were more commonly used than Vietnamese folk medicine. In general, the physicians employed a broad range of CAM methods, particularly chiropractice, diet supplements, and dietary therapy, as well as numerous Western medical approaches, in their daily practice [1].

Interest in TM continues to thrive in both developing countries and in the West, as countries want to exploit these "natural" remedies for improved therapeutics with low toxicity. Here, we summarize recent biologically validated findings regarding the efficacy of TM

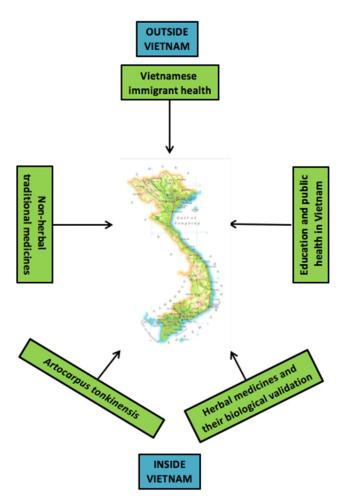


Figure 1: Schematic of review scope. In this review, we considered articles related to VTM outside and inside Vietnam, including the influence of Vietnamese immigration on VTM integration in other countries and the status of education and public health, biological validation of herbal medicines, use of *Artocarpus tonkinensis*, and non-herbal traditional medicines within Vietnam.

drugs and related therapies used in Vietnam to facilitate the successful integration of traditional and Western medicine.

We analyzed and summarized articles published in the last 5 years with the terms "Vietnam" and "Traditional Medicine" in their titles and/or abstracts to generate a comprehensive view of TM among Vietnamese populations. Here, we describe the effect of Vietnamese immigrants on TM in developed countries. We then focus on TMrelated issues within Vietnam, including TM health education of Vietnamese students, medical doctors, and citizens, and the influence of Western medical practices brought into Vietnam. We also report biologically validated studies of herbal and non-herbal TM drugs, paying specific attention to ethnopharmacological studies of *Artocarpus tonkinensis*, a northern Vietnam tree used by the ethnic Hmong minority to treat arthritis and backache (Figure 1).

Outside Vietnam: Integration of traditional and Western medicine by Vietnamese immigrants in developed countries

Interest in TM and CAM practice is increasing in developed countries. In the United States, 38.3% of adults and 11.8% of children have used some form of CAM, and many physicians in Europe and North America have referred their patients for acupuncture (43%), chiropractice (40%), and/or massage therapy (21%) [1]. Due to the increasing use of TM and CAM in Western

countries, we considered how Vietnamese immigrants navigate the Western health system and if they integrate VTM practices with Western health concepts. For successful integration, it is important to first translate TM knowledge into Western terms for descendants of immigrants (i.e., second- or third-generation) and Western natives. To this end, the World Health Organization (WHO) published a compendium entitled "WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region," which defines 3259 terms commonly used in VTM, traditional Chinese Medicine (TCM), Japanese Kampo medicine, and Korean traditional medicine. The text includes the basic theories, diagnostics, diseases, and therapies associated with TM and provides English wording for 153 manuscript titles of TM classical texts published in China, Vietnam, Japan, and Korea. The correct usage of standard TM terminologies is necessary to convey accurately their scientific importance, especially to audiences unfamiliar with TM practices [4].

Because Vietnamese immigrants may be reluctant to speak with Western practitioners about their traditional practices, a written survey was conducted to determine how beliefs among firstgeneration immigrants affected their health-care habits. The survey revealed that the participants embraced both traditional and Western medicine, partly due to scarcity of convenient TM products [5]. Furthermore, the study results did not identify any dangerous health practices followed by the respondents. Notably, their beliefs mirror those of many Americans about "natural" and dietary supplement products. Notably, respondents often used VTM as a supplement or for disease prevention rather than as a replacement for Western medical treatment. Pharmacists should also note that Vietnamese patients may avoid ingesting traditional and Western medicines at the same time [5].

Health beliefs among Vietnamese immigrant communities have been investigated mainly by surveys on mental illness, diabetes, women's health, drug use, and infectious disease. Asian patients preferentially seek mental health care from their primary care providers but are unlikely to receive it [6]. Thus, primary care providers need culturally informed strategies for addressing stigmatizing illnesses. In a study aimed at improving communication and health care relationships between physicians and Vietnamese-American patients, 11 Vietnamese-American participants described their experiences with depression with respect to: (1) stigma; (2) social functioning and the role of family; (3) traditional healing and beliefs about medications; and (4) language and culture, suggesting physicians should tailor their interviewing style to an increasingly diverse patient population [6]. Mental illness-related stigma is a major barrier to health care, but little is known about the effects of this stigma on Vietnamese populations or how emigration and acculturation processes affect their traditional views. To address this question, focus group discussions were conducted with Vietnamese-Americans in New Orleans, LA, USA, and with Vietnamese nationals in Bui Chu, Vietnam, who share historical and cultural backgrounds. Results showed significant differences in mental illness perceptions between Vietnamese-Americans and Vietnamese nationals, whereas mental illness-related stigma and lack of understanding of mental illness characterized both groups [7].

Ethnically diverse diabetes patients also face significant challenges in disease self-management, ranging from cultural expectations to inequalities in health care. A phenomenology-based study analyzed self-management support across three groups of 28 ethnically diverse Australian diabetes patients: Arabic-speaking (n=11), English-speaking (n=9), and Vietnamese-speaking (n=8). Two major themes emerged regarding the poor quality of their selfmanagement information and challenges in negotiating traditional consultation styles. In particular, participants believed they knew more about diabetes self-management than their doctors but felt unable to influence the consultation or communicate their changing needs in self-management support. Thus, the health care needs of ethnically diverse patients continue to be marginalized [8].

Regarding women's health, Pap testing behavior among Vietnamese-American women was investigated using a communitybased survey of 265 women, aged 18 or above, in five United States cities: Houston (TX), Springfield (MA), Camden (NJ), Charlotte (NC), and Falls Church (VA). Having health insurance was the most important predictor of Pap testing, so interventions should focus on improving financial access to this test among Vietnamese-American women. Results also suggest communication programs should emphasize preventive practices and work to change traditional attitudes and misconceptions related to Pap testing among minority women [9].

When health behaviors and beliefs among ethnic Vietnamese intravenous drug users in Australia were investigated, participants commonly reported attempts to treat heroin overdose by withdrawing blood (*rut mau*), a practice derived from cultural beliefs about the role and function of blood in the body and its relationship to illness and health. Participants drew on a range of beliefs and etiologic models, particularly TCM and VTM, to understand their health [10]. Thus, Vietnamese immigrants living abroad represent an ideal model for determining how to achieve optimal integration between VTM and Western medicine.

Inside Vietnam: Education and public health

Integration of TM and Western medicine in Vietnam often starts with locally or internationally sponsored education programs for students and medical doctors. For example, Vietnamese pharmacy programs offer various degree programs and specializations in drug management and supply, drug development and production, pharmacology and clinical pharmacy, TM and pharmacology, and drug quality control. Despite these options, pharmacy education in Vietnam generally remains product-oriented [11].

As part of the "ASIA-LINK" postgraduate medical student program, the European Community has supported the development and implementation of a psychosomatic training curriculum for medical doctors in China, Vietnam, and Laos. Health care in these countries is characterized by the coexistence of traditional and Western medicine. However, significant social, economic, and cultural changes in these countries have led to increased psychological and psychosomatic problems, including disorders without adequate medical or psychological treatment. To address this limitation, regional training centers were formed in Shanghai (China), Ho Chi Minh City and Hue (Vietnam), and Vientiane (Laos), and improved training in psychosomatic medicine for postgraduate medical doctors is now available. To promote traditional and Western medicine integration, the transferability of Western concepts should be tested locally and then adapted as necessary [12].

Regarding perceptions of infectious diseases, attitudes regarding prevention, screening, and treatment of hepatitis B virus infection were explored in Chinese, Korean, and Vietnamese communities using a qualitative assessment issued to 12 adult focus groups (n=113). Participants reported using CAM when Western medicine fails or is unaffordable. The results suggested that improved education related to both TM and Western medicine is necessary for

patient understanding of infectious disease [13]. In 2008, crosssectional survey data were collected from 329 mothers of children under 6 years old in Khanh Hoa province (Vietnam) to identify their perceptions of the transmission and treatment of pneumonia. An important issue identified is the need to provide more information about the symptoms and treatment of childhood pneumonia in urban and rural Vietnamese communities [14].

Traditional Vietnamese culture places women in a subordinate and often disadvantaged position with respect to sexual health and contraceptive decision-making. Data from 4632 married women collected in the 2005 Vietnam Population and AIDS Indicator Survey revealed relationships between women's sociodemographic characteristics, self-efficacy in sexual activity and condom use, and consistency of condom use. The availability of condoms for disease prevention should continue to be widely promoted, and women should be educated and encouraged to assert their need for protection against HIV infection [15].

Depression is a common psychiatric condition that significantly contributes to the global disease burden. A narrative review was conducted to measure factors influencing depression screening, diagnosis, and treatment among the Vietnamese population. Findings indicate the importance of considering somatic symptoms during depression screenings and using culturally adapted and dimensional screening instruments. Vietnamese patients displayed a tendency to seek VTM- and meditation-based therapies when experiencing emotional distress [16].

With regard to alcohol use in Vietnam, four homemade (artisanally manufactured and unrecorded) and seven commercial (industrially manufactured and taxed) alcohol products from Vietnam were chemically analyzed for toxicologically relevant substances. One homemade sample, commonly used in TCM, consisted of pickled snakes and scorpions and contained 77% (v/v) alcohol. However, insufficient evidence exists to conclude that alcohol quality, beyond the effects of ethanol, strongly influence health in Vietnam [17].

Workplace health and safety further challenges TM and Western medicine in Vietnam. A recent study indicates that the Participatory Action-Oriented Training program, focused on improving workplace health and safety at work, produces better outcomes in small- and medium-sized enterprises than a traditional Vietnamese method [18].

Furthermore, maintaining traditional practices while integrating them with established Western health education concepts at multiple levels may promote improved workplace health and safety in Vietnam with the aim of importing Western medicine practices. Finally, organ transplantation in Vietnam is not common because few people donate their own organs or those of their relatives after death according to the traditional Vietnamese belief that "as a man lives, so shall he die". Thus, additional measures are necessary to develop the practice of organ transplantation in Vietnam, despite traditional beliefs that discourage such Western medical practices [19].

Herbal medicines and their biological validation

Table 1 provides a summary of medicinal plants, their utilization in TM, and their potential future therapeutic uses. Herbology is a central practice of VTM and, along with acupuncture, is the most commonly used VTM method [1]. Therefore, validating the efficacy of medicinal plants using biotechnological methods is important. Many VTM herbal drugs come directly from ethnopharmacological traditions of various ethnic minorities across Vietnam. To determine

Herb	Traditional medicine treatment	Potential new treatment based on biological validation	References
Stefania rotunda	Asthma, headache,	Malaria, cancer	[24]
(Menispermaceae) Eryngium foetidum	fever, diarrhea Burns, earache, fever, hypertension, constipation, fits, asthma, stomach-ache, worms, infertility complications, snakebites, diarrhea, malaria	Parasitic trypanosomes, nematodes, fungi, and bacterial infections in humans and other mammals	[25]
Paederia foetida, Paederia scadens	Inflammation, piles, diarrhea	Antinociceptive, anti- inflammatory, anti- diarrheal, anti-tussive and antitumor activities	[26]
Palatiferum (Acanthaceae)	Hypertension, diarrhea, arthritis, hemorrhoids, stomach-ache, tumors, colitis, bleeding, wounds, constipation, flu, colon cancer, nephritis, diabetes	Diabetes and antimicrobial activities	[27, 28]
Pseuderanthemum palatiferum	Inflammatory diseases	Anti-oxidant and anti- inflammatory properties	[27, 29]
Lotus (<i>Nelumbo</i> nucifera)	Anti-inflammatory, antioxidant	Phenolic compounds research	[33, 34]
Tram, Voi, and Gac	Anti-inflammatory, antioxidant	Supplements for human health	[35]
Mallotus	Antioxidant, cytotoxic activities	Antioxidant activity	[36, 37, 38, 39]
Crinium latifolium	Anti-cancer (treatment of prostate cancer and lymphoma) and antiviral activity	Potent antioxidant, anti-inflammatory, and anti-cancer activities	[40, 43]
Wedelia biflora	Various symptoms/cancer	Unknown	[41]
Zanthoxylum avicennae	Hepatocellular carcinoma	Hepatocellular carcinoma	[42]
Cnidium monnieri (Osthole)	Vasodilating and antihypertensive	Antihypertensive and potential anti-diabetic activities	[44]
Gynostemma pentaphyllum (Cucurbitaceae), Anemarrhena asphodeloides (Liliaceae), and Angiopteris evecta (Marattiaceae)	Anti-diabetic activity	Unknown	[45, 46, 47, 48, 49]
<i>Aconitum</i> genus (Ranunculaceae)	Rheumatic fever, joint pain, endocrinal disorders	Immunosuppressive activity	[50]
<i>Tinospora</i> species (Menispermaceae)	Acute hepatitis	Hepatitis treatment	[51]
Artocarpus tonkinensis	Arthritis, backache, taeniasis	Potential anti-cancer activity	[52, 53, 54, 55, 56, 57]

the appropriate use of herbal drugs, strategies must be established for identifying new medicinal plants and determining the most efficient methods for isolating their active compounds. Whether natural drug discovery programs should rely on wild plants collected "randomly" from the environment or should focus on plants collected based on their potential TM use is debated. One study addressed this question by exploring if plants with ethnomedical uses in Vietnam and Laos have a higher hit rate in bioassay testing than plants collected from a national park in Vietnam to maximize taxonomic diversity. Plants with ethnomedical uses exhibited a higher rate of activity in drug discovery screening [20].

After plant medicines (or other non-herbal traditional drugs and practices) are identified, their efficacy must be validated by rigorous testing. To this end, the use of Western biological methods of scientific validation is critical. For isolating active compounds, methods must be standardized for each herbal sample. For example, high-performance liquid chromatography was used to simultaneously quantify five major bioactive constituents in the stems of resiniferous *Dracaena* plants from China and Vietnam and related plants used in TCM preparations [21].

From a clinical perspective, VTM is largely non-evidence-based, but subclinical research data from past decades do support the traditional use of many herbal VTM drugs. However, knowledge of possible adverse reactions and herb-drug interactions is necessary for safe use of these materials. Although the Vietnamese government supports further scientific development of VTM and its integration with Western medicine [22], TM often competes with evidence-based practices in some geographic areas. In northern Vietnam, however, primary health care staff can sometimes translate Western knowledge into practice. In addition, the Vietnamese health care system tries to promote the scientific validation of VTM therapies when possible [23].

Multi-disease herbal medicines. Stephania rotunda Lour. (Menispermaceae) is an important TM plant grown in Southeast Asia. Its stems, leaves, and tubers are used in Cambodian, Laotian, Indian, and Vietnamese folk medicine to treat various ailments, including asthma, headache, fever, and diarrhea. Notably, pharmacological investigations have validated many folk uses of *S. rotunda*, leading to its potential use in other applications, such as malarial and cancer research [24].

Eryngium foetidum L. is a biennial herb cultivated in India, Vietnam, and Australia and used extensively as a medicinal plant in many tropical regions. *E. foetidum* possesses a wide range of ethnomedicinal uses, including treatment for burns, earache, fevers, hypertension, constipation, seizures, asthma, stomach-ache, infertility complications, snakebites, diarrhea, and malaria. A significant constituent of the plant's essential oil is E-2-dodecenal ("eryngial"), a fraction of which is the subject of a US patent application for its effectiveness against parasitic trypanosomes, nematodes, fungi, and bacterial infections in humans and other mammals [25].

Paederia foetida, grown mainly in China, Bangladesh, India, and Mauritius, is used in folk medicine for treatment of inflammation and diarrhea. The related species *P. scadens* is also used in folk remedies in southern China, Vietnam, India, and Japan for treating joint aches, jaundice, dysentery, and dyspepsia. Studies of their TM uses and their phytochemistry, pharmacology, toxicology, and clinical application suggest these two species possess anti-nociceptive, anti-inflammatory, anti-diarrheal, anti-tussive, and anti-tumor properties [26].

Pseuderanthemum palatiferum (Nees) Radlk (Acanthaceae) was discovered in northern Vietnam and subsequently used throughout the country in VTM. The leaves of the plant are used to treat various diseases, including hypertension, diarrhea, arthritis, hemorrhoids, stomach-ache, tumors, colitis, bleeding, wound injury, constipation, flu, colon cancer, nephritis, and diabetes [27]. Treatment of normal and streptozotocin-induced diabetic rats with an 80% ethanolic leaf extract of *P. palatiferum* showed a beneficial

effect in hyperglycemic rats and prevented some complications of diabetes [27]. In addition, lignins, betulin, and lupeol, isolated from the plant's roots, show cytotoxic and antimicrobial activities [28]. In addition, specifically, RAW264.7 macrophages treated with *P. palatiferum* showed decreased oxidative stress and reduced iNOS and COX-2 protein levels, suggesting the plant possesses strong anti-oxidant and anti-inflammatory properties [27, 29].

Many microbial pathogens of humans are indigenous to Vietnam, making its environment optimal for identifying plants with novel antimicrobial activity. One example involves a genetic variant of the H5N1 influenza virus (subclade 2.3.2.1) which is found in Vietnam and Laos, but was first identified in Bulgaria. Several cases of human infections with this virus have been identified [30]. In addition, the chloroquine-resistant Vietnam Smith/RE strain of *Plasmodium falciparum*, the causative agent of malaria, has been utilized for screening flora of the Lake Victoria region for antimicrobial activity. Fifty-four unique organic extracts from seven plant families were individually tested for anti-plasmodial activity against chloroquine-sensitive [Sierra Leone (D-6)] and chloroquineresistant [Vietnam (W-2)] strains [31, 32].

Anti-inflammatory and antioxidant herbal medicines. The traditional use of lotus (*Nelumbo nucifera*) leaves and rhizomes as an anti-inflammatory and antioxidant remedy relies on its phenolic compounds [33]. An optimized separation procedure was developed to analyze diverse *N. nucifera* samples collected in Vietnam, each of which displayed significant qualitative and quantitative differences in bioactivity based on its cultivation area and growth season. The most potent flavonoids include quercetin 3-glucoside (isoquercetin), quercetin-3-O- β -glucuronide, nelumboside, and quercetin 3-galactoside (hyperoside) [33, 34].

Edible plants grown in Vietnam are of interest to food chemists as ideal sources of natural medicinal chemicals. Methanol extracts of three edible Vietnamese-grown plants, Tram, Voi, and Gac, investigated using a 2,2-diphenylpicrylhydrazyl assay showed antioxidant and anti-inflammatory activities. Together with their total phenolic contents, these extracts may be potential supplements for improving human health [35].

Some *Mallotus* species are common sources of TM compounds in Vietnam and China, many of which exhibit antioxidant and cytotoxic activities [36-38]. A method was developed to identify *Mallotus*-derived compounds responsible for the plant's antioxidant activity [39].

Anti-cancer medicines. Several VTM folk remedies have shown potential anti-cancer activity in controlled studies. Crinum latifolium L. leaf extracts are traditionally used in Vietnam and now globally for treatment of prostate cancer. Specifically, C. latifolium extracts and its alkaloid fraction inhibit proliferation of lymphoma cells [40] and contribute to the recovery of the immune function [43]. The plant Wedelia biflora has also been used in Indian and Vietnamese TM to treat various conditions, and data suggest that some compounds isolated from W. biflora are effective against some cancers [41]. Another traditional Vietnamese herb, Zanthoxylum avicennae, inhibits proliferation of HA22T human hepatocellular carcinoma cells via PP2A activation [42].

Cardiovascular compounds. Osthole is a coumarin extracted from *Cnidium monnieri* (L.) Cusson, a medicinal plant widely used in Vietnamese and Chinese TM as a vasodilating and antihypertensive agent. Data indicate that osthole is a vascular Ca(v)1.2 channel antagonist that stabilizes the channel in its inactivated state. This

mechanism may account for reduced systolic blood pressure induced by osthole in hypertensive animals, identifying it as a lead candidate in the search for novel anti-hypertensive agents [44].

Anti-diabetes medicines. Although the prevalence of type 2 diabetes in developing countries is increasing, several plants are used to treat this disease in Vietnam. A study in which eight VTM herbs were screened for hypoglycemic effects found that extracts of Gynostemma pentaphyllum (GP) Makino (Cucurbitaceae), Anemarrhena asphodeloides Bunge (Liliaceae), and Angiopteris evecta Forst. Hoffn. (Marattiaceae) reduced blood glucose and inhibited increased blood glucose after glucose challenge in healthy mice [45]. The traditional Vietnamese herb GP tea (Giao co lam) also improved insulin sensitivity in drug-naïve type 2 diabetics [46] and, together with sulfonvlurea, was an alternative treatment for type 2 diabetes in 25 drug-naïve patients [47]. Another study explored the anti-diabetic effect of GP in 24 drug-naïve type 2 diabetic patients and found that GP induced a prompt improvement of glycemia and insulin sensitivity [48]. Furthermore, GP tea may exhibit protein tyrosine phosphatase 1B inhibitory activity, suggesting a possible mechanism for its anti-diabetic activity [49].

Adverse effects. Specific attention must be paid to the safety of herbal drugs to minimize their adverse effects. Two relevant examples are Aconitum (Ranunculaceae) herbs and Tinospora crispa (Menispermaceae). Several Aconitum herbs are popular for their treatment of rheumatic fever, joint pain, and some endocrinal disorders in Indian, Vietnamese, Korean, Japanese, Tibetan, and Chinese medicine. Unfortunately, the herbs have a narrow therapeutic range, although their toxicity can be potentially reduced [50]. Toxic effects of *Tinospora* species, often used in South Asian medicine, have also been described. For example, acute hepatitis associated with long-term daily use of high doses of *T. crispa* was reported in a 49-year-old male in Vietnam with chronic low back pain, further highlighting the potential risks of some traditional herbal remedies [51].

Utilization and validation of Artocarpus tonkinensis

A. tonkinensis A.Chev. ex Gagnep (Moraceae) (Figure 2) is a tree found in northern Vietnam used in VTM by the Hmong ethnic minority to treat arthritis and backache. In Laotian folk medicine, this breadfruit tree is used in the treatment of taeniasis resulting from infection with the dwarf tapeworm *Hymenolepis nana*. This use was validated when an ethanol extraction from the tree showed anti-parasitic activity in mice experimentally infected with *H. nana* [52]. Another recent study investigating the use of *A. tonkinensis* for arthritis treatment via activity-guided fractionation found that an *n*-butanol extract from the tree's leaves led to isolation of the auronol glycosides maesopsin 4-*O*-glucoside and alphitonin-4-*O*glucoside.

Both compounds demonstrated immunosuppressive activity in a lymphocyte stimulation test [53]. The ethyl acetate extract from this plant was also tested for anti-inflammatory properties; intraperitoneal injections of *A. tonkinensis* extract decreased both arthritis incidence and severity and delayed disease onset in rats with collagen-induced arthritis. *In vitro*, an extract induced apoptosis in lymph node cell cultures, inhibited mitogen-induced T-cell proliferation, and induced apoptosis of activated LN-derived lymphocytes [54]. In addition, four individual active components isolated from *A. tonkinensis* have anti-inflammatory effects, which correlate with the tree's inhibition of mitogen-induced T-cell proliferation. These extracts also inhibited production of cytokines, such as tumor necrosis factor- α and interferon- γ , in mitogen-stimulated T cells. The authors postulated that suppression of T-cell

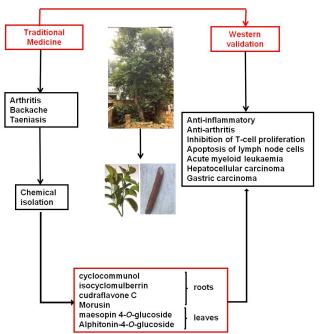


Figure 2: Progression of *Artocarpus tonkinensis* from traditional therapeutic utilization to biological validation. New chemical compounds have been isolated from leaves and roots of *A. tonkinensis*, and novel therapeutic uses beyond TM-based treatments have been identified through biological validation studies.

proliferation and cytokine production by *A. tonkinensis* flavonoids contribute to reduced arthritis severity after experimentally-induced arthritis [55].

A. tonkinensis compounds were also tested for anti-cancer activity, revealing that maesopsin 4-*O*- β -D-glucoside (TAT-2) has anti-proliferative effects on acute myeloid leukemia cells and modulates expression of 19 genes, including hemeoxigenase-1 (HMOX-1), sulphiredoxin 1 homolog (SRXN1), and breast carcinoma amplified sequence 3 (BCAS3) [56]. TAT-2 has also *in vivo* anti-cancer effect [57]. Other compounds isolated from *A. tonkinensis* roots, such as cyclocommunol, isocyclomulberrin, cudraflavone C, and morusin, also exhibited cytotoxicity against hepatocellular carcinoma (SMMC-7721) and gastric carcinoma (BGC-823 and SGC-7901) cell lines [58]. Thus, the success of *A. tonkinensis* use shows TM can maintain its ethnocultural identify while capitalizing on Western scientific approaches (e.g. chemical isolation of active compounds and their biological validation) to ascertain its efficacy and safety.

Non-herbal TM in Vietnam

Frog skin. The study of the interrelationships between humans and animals in their environment has prompted numerous applications of animal-derived products in medicine. Frog skin, for example, is used in Vietnamese and South American TM as a biological dressing to encourage wound healing. One study of mice showed that frog skin secretions from *Rana ridibunda* effectively promote wound healing, demonstrating its potential for clinical application in wound care [59].

Earthworms. Earthworms have provided ancient cultures with sources of both food and medicinal cures. Renewed interest in their

therapeutic uses in Ayurveda, TCM, and medical practices in Japan, Vietnam, and Korea, grew serendipitously from an extensive analysis of the earthworm's innate immune system, replete with leukocytes and humoral products that exert credible health benefits. Earthworms are inexpensive, ethically non-controversial, and uncommon disease vectors but are not pests whose numerous ecological, environmental, and biomedical benefits substantiated by comprehensive investigations have been recognized [60]. For example, histopathological studies have revealed that earthworm paste is more effective than ranitidine in preventing gastric lesion formation, suggesting its potential as an anti-ulcer agent [61].

Conclusion: The health policy of Vietnam focuses on integration of Western medicine and VTM, a promising framework for Vietnam and other developed countries. Traditional health concepts, practices, and drugs must meet the validation standards of Western countries for this successful integration.

In this review, we have summarized findings from recent studies that validated drugs derived from traditional Vietnamese cultures, which continuously change due to their interactions with Western health concepts and practices. We first evaluated the modification of traditional health perceptions by Vietnamese immigrants within Western countries, who represent an interesting experimental population, and found a persistence of VTM melded with newly acquired Western health practices. We then discussed health education disseminated at different levels (citizens, medical students, and practicing doctors) within Vietnam, showing how Oriental and Western medicine further interact and can improve health of the general population.

Within this framework, we analyzed the contribution of VTM in establishing improved medical standards via the biological validation of ethnically-derived remedies. Our paradigmatic example describes A. tonkinensis, whose leaf extracts are used to treat arthritis and backache by the ethnic minority of black Hmong, who live in the mountains of northern Vietnam near China. The remedy was brought to the attention of the Vietnamese Academy of Science and Technology, who isolated the plant's active compounds that were later validated in collaboration with our research group in Italy. The story of A. tonkinensis will conclude when pre-clinical studies and clinical trials enable approval of the drug for general Thus, biological validation of traditional medicines, use. particularly characterization of their active components, will hopefully prompt development of novel drugs, reveal new drug targets, and uncover pathogenic mechanisms of various diseases. Additionally, because many TM therapies have been used for a long time, ideal compounds have already been selected based on their efficacy and low toxicity profile and could be utilized in Western medicine after appropriate validation. The findings in this review indicate that successful integration of Western and Oriental medicine can improve public health perceptions and available medical treatments to cultures around the world.

Acknowledgments - We thank BioScience Writers for editing assistance. This work was supported in part by Italian Ministero degli Esteri e della Cooperazione Internazionale, AIRC (Associazione Italiana Ricerca sul Cancro), and Vietnamese MOST (Ministry of Science and Technology).

References

- [1] Pham DD, Yoo JH, Tran BQ, Ta TT. (2013) Complementary and alternative medicine use among physicians in oriental medicine hospitals in vietnam: a hospital-based survey. *Evidence-Based Complementary and Alternative Medicine*, Article ID 392191.
- [2] Liu QX, Dai M. (2012) Medical exchanges between China and Vietnam during the Song, Jin and Yuan Periods. Zhonghua yi shi za zhi, 42, 18-20.

- [3] Dung TN, Bodeker G. (2001) Tue Tinh: founder of Vietnamese traditional medicine. *Journal af Alternative and Complementary Medicine*, 7, 401-403.
- [4] Choi SH, Chang IM. (2010) A milestone in codifying the wisdom of traditional Oriental medicine: TCM, Kampo, TKM, and TVM-WHO international standard terminologies on traditional medicine in the western Pacific region. *Evidence-Based Complementary and Alternative Medicine*, 7, 303-305.
- [5] Nguyen S, Miller DR, Dingel MJ. (2010) Traditional medicine use in a Vietnamese-American community. *Annals of Pharmacotherapy*, 44, 769-770.
- [6] Fancher TL, Ton H, Le Meyer O, Ho T, Paterniti DA. (2010) Discussing depression with Vietnamese-American patients. *Journal of Immigrant and Minority Health*, 12, 263-266.
- [7] Do M, Pham NN, Wallick S, Nastasi BK. (2014) Perceptions of mental illness and related stigma among Vietnamese populations: Findings from a mixed method study. *Journal of Immigrant and Minority Health*, 16, 1294-1298.
- [8] Rose VK, Harris MF. (2015) Experiences of self-management support from GPs among Australian ethnically diverse diabetes patients: A qualitative study. Psychology, Health & Medicine, 20, 114-120.
- [9] Do M. (2015) Predictors of cervical cancer screening among Vietnamese-American women. *Journal of Immigrant and Minority Health*, 17, 756-764.
- [10] Maher L, Ho HT. (2009) Overdose beliefs and management practices among ethnic Vietnamese heroin users in Sydney, Australia. Harm Reduction Journal, 6, 6-15.
- [11] Vo TH, Bedouch P, Nguyen TH, Nguyen TL, Hoang TK, Calop J, Allenet B. (2013) Pharmacy education in Vietnam. American Journal of Pharmaceutical Education, 77, 114-126.
- [12] Fritzsche K, Scheib P, Ko N, Wirsching M, Kuhnert A, Hick J, Schüßler G, Wu W, Yuan S, Cat NH, Vongphrachanh S, Linh NT, Viet NK, ASIA-LINK Workgroup. (2012) Results of a psychosomatic training program in China, Vietnam, and Laos: Successful cross-cultural transfer of a postgraduate training program for medical doctors. *BioPsychoSocial Medicine*, 6, 17-30.
- [13] Hwang JP, Roundtree AK, Suarez-Almazor ME. (2012) Attitudes toward hepatitis B virus among Vietnamese-, Chinese-, and Korean-Americans in the Houston area, Texas. Journal of Community Health, 37, 1091-1100.
- [14] Kaljee LM, Anh DD, Minh TT, Huu Tho L, Batmunkh N, Kilgore PE. (2011) Rural and urban Vietnamese mothers' utilization of healthcare resources for children under 6 years with pneumonia and associated symptoms. *Journal of Behavioral Medicine*, 34, 254-267.
- [15] Do M, Fu H. (2011) Is women's self-efficacy in negotiating sexual decision making associated with condom use in marital relationships in Vietnam? *Studies in Family Planning*, 42, 273-282.
- [16] Niemi M, Malqvist M, Giang KB, Allebeck P, Falkenberg T. (2013) A narrative review of factors influencing detection and treatment of depression in Vietnam. *International Journal of Mental Health Systems*, 7, 15-24.
- [17] Lachenmeier DW, Anh PT, Popova S, Rehm J. (2009) The quality of alcohol products in Vietnam and its implications for public health. International Journal of Environmental Research and Public Health, 6, 2090-2101.
- [18] Nguyen TP, Khai TT. (2014) An evaluation of the Participatory Action-Oriented Training (PAOT) program in small enterprises in Vietnam. Journal of Occupational Health, 56, 309-316.
- [19] Ledinh H. (2011) Landmarks in clinical solid organ transplantation in Vietnam. Transplantation Proceedings, 43, 3408-3411.
- [20] Gyllenhaal C, Kadushin MR, Southavong B, Sydara K, Bouamanivong S, Xaiveu M, Xuan LT, Hiep NT, Hung NV, Loc PK, Dac LX, Bich TQ, Cuong NM, Ly HM, Zhang HJ, Franzblau SG, Xie H, Riley MC, Elkington BG, Nguyen HT, Waller DP, Ma CY, Tamez P, Tan GT, Pezzuto JM, Soejarto DD. (2012) Ethnobotanical approach versus random approach in the search for new bioactive compounds: Support of a hypothesis. *Pharmaceutical Biology*, 50, 30-41.
- [21] Fan LL, Tu PF, Chen HD, Cai SQ. (2009) Simultaneous quantification of five major constituents in stems of *Dracaena* plants and related medicinal preparations from China and Vietnam by HPLC-DAD. *Biomedical Chromatography*, 23, 1191-1200.
- [22] Woerdenbag HJ, Nguyen TM, Vu DV, Tran H, Nguyen DT, Tran TV, De Smet PA, Brouwers JR. (2012) Vietnamese traditional medicine from a pharmacist's perspective. *Expert Review of Clinical Pharmacology*, 5, 459-477.
- [23] Eriksson L, Nga NT, Hoa DP, Persson LA, Ewald U, Wallin L. (2011) Newborn care and knowledge translation: Perceptions among primary healthcare staff in northern Vietnam. *Implementation Science*, 6, 29-38.
- [24] Desgrouas C, Taudon N, Bun SS, Baghdikian B, Bory S, Parzy D, Ollivier E. (2014) Ethnobotany, phytochemistry, and pharmacology of Stephania rotunda Lour. Journal of Ethnopharmacology, 154, 537-563.
- [25] Paul JH, Seaforth CE, Tikasingh T. (2011) Eryngium foetidum L.: A review. Fitoterapia, 82, 302-308.
- [26] Wang L, Jiang Y, Han T, Zheng C, Qin L. (2014) A phytochemical, pharmacological, and clinical profile of *Paederia foetida* and *P. scandens*. *Natural Product Communications*, 9, 879-886.
- [27] Padee P, Nualkaew S, Talubmook C, Sakuljaitrong S. (2010) Hypoglycemic effect of a leaf extract of *Pseuderanthemum palatiferum* (Nees) Radlk in normal and streptozotocin-induced diabetic rats. *Journal of Ethnopharmacology*, 132, 491-496.
- [28] Sittisart P, Chitsomboon B. (2014) Intracellular ROS scavenging activity and downregulation of inflammatory mediators in RAW264.7 macrophage by fresh leaf extracts of *Pseuderanthemum palatiferum*. *Evidence-Based Complementary and Alternative Medicine*, 2014, Article ID 309095.
- [29] Mai HD, Minh HN, Pham VC, Bui KN, Nguyen VH, Chau VM. (2011) Lignins and other constituents from the roots of the Vietnamese medicinal plant *Pseuderanthemum palatiferum*. *Planta Medica*, 77, 951-954.
- [30] Xu L, Bao L, Yuan J, Li F, Lv Q, Deng W, Xu Y, Yao Y, Yu P, Chen H, Yuen KY, Qin C. (2013) Antigenicity and transmissibility of a novel clade 2.3.2.1 avian influenza H5N1 virus. *Journal of General Virology*, 94, 2616-2626.
- [31] Ye Z, Van Dyke K, Rossan RN. (2013) Effective treatment with a tetrandrine/chloroquine combination for chloroquine-resistant falciparum malaria in *Aotus* monkeys. *Malaria Journal*, 12, 117-122.
- [32] Ayuko TA, Njau RN, Cornelius W, Leah N, Ndiege IO. (2009) *In vitro* antiplasmodial activity and toxicity assessment of plant extracts used in traditional malaria therapy in the Lake Victoria region. *Memorias do Instituto Oswaldo Cruz*, 104, 689-694.
- [33] Lin HY, Kuo YH, Lin YL, Chiang W. (2009) Antioxidative effect and active components from leaves of lotus (Nelumbo nucifera). Journal of Agricultural and Food Chemistry, 57, 6623-6629.
- [34] Do TC, Nguyen TD, Tran H, Stuppner H, Ganzera M. (2012) Quantitative determination of phenolic compounds in lotus (*Nelumbo nucifera*) leaves by capillary zone electrophoresis. *Planta Medica*, 78, 1796-1799.
- [35] Sone Y, Moon JK, Mai TT, Thu NN, Asano E, Yamaguchi K, Otsuka Y, Shibamoto T. (**2011**) Antioxidant/anti-inflammatory activities and total phenolic content of extracts obtained from plants grown in Vietnam. *Journal of the Science of Food and Agriculture*, **91**, 2259-2264.
- [36] Tistaert C, Dejaegher B, Nguyen HN, Chataigne G, Riviere C, Nguyen TH, Chau VM, Quetin-Leclercq J, Van der Heyden Y. (2009) Potential antioxidant compounds in Mallotus species fingerprints. Part I: Indication, using linear multivariate calibration techniques. *Analytica Chimica Acta*, 652, 189-197.

- [37] Tistaert C, Dejaegher B, Nguyen Hoai N, Chataigné G, Rivière C, Nguyen Thi Hong V, Chau Van M, Quetin-Leclercq J, Van der Heyden Y. (2009) Potential antioxidant compounds in Mallotus species fingerprints. Part I: Indication, using linear multivariate calibration techniques. Analytica Chimica Acta, 649, 24-32.
- [38] Nguyen Hoai N, Dejaegher B, Tistaert C, Nguyen Thi Hong V, Riviere C, Chataigne G, Phan Van K, Chau Van M, Quetin-Leclercq J, Van der Heyden Y. (2009) Development of HPLC fingerprints for *Mallotus* species extracts and evaluation of the peaks responsible for their antioxidant activity. *Journal of Pharmaceutical and Biomedical Analysis*, 50, 753-763.
- [39] Tistaert C, Dejaegher B, Chataigné G, Rivière C, Hoai NN, Van MC, Quetin-Leclercq J, Van der Heyden Y. (2012) Potential antioxidant compounds in *Mallotus* species fingerprints. Part II: Fingerprint alignment, data analysis, and peak identification. *Analytica Chimica Acta*, 721, 35-43.
- [40] Nguyen HY, Vo BH, Nguyen LT, Bernad J, Alaeddine M, Coste A, Reybier K, Pipy B, Nepveu F. (2013) Extracts of Crinum latifolium inhibit the cell viability of mouse lymphoma cell line EL4 and induce activation of anti-tumour activity of macrophages in vitro. Journal of Ethnopharmacology, 149, 75-83.
- [41] Thu NT, Ha le T, Nga VT, Tuyen PN, Quang TT, Daniellee FR, Lawrence P, Phung NK. (**2013**) Six new phenolic glycosides and a new ceramide from the flowers of *Wedelia biflora* and their cytotoxicity against some cancer cell lines. *Natural Product Communications*, **8**, 367-372.
- [42] Dung TD, Chang HC, Binh TV, Lee MR, Tsai CH, Tsai FJ, Kuo WW, Chen LM, Huang CY. (2012) Zanthoxylum avicennae extracts inhibit cell proliferation through protein phosphatase 2A activation in HA22T human hepatocellular carcinoma cells in vitro and in vivo. International Journal of Molecular Medicine, 29, 1045-1052.
- [43] Jenny M, Wondrak A, Zvetkova E, Tram NT, Phi PT, Schennach H, Culig Z, Ueberall F, Fuchs D. (2011) Crinum latifolium leaf extracts suppress immune activation cascades in peripheral blood mononuclear cells and proliferation of prostate tumor cells. Scientia Pharmaceutica, 79, 323-335.
- [44] Fusi F, Sgaragli G, Ha le M, Cuong NM, Saponara S. (2012) Mechanism of osthole inhibition of vascular Ca(v)1.2 current. European Journal of Pharmacology, 680, 22-27.
- [45] Hoa NK, Phan DV, Thuan ND, Ostenson CG. (2009) Screening of the hypoglycemic effect of eight Vietnamese herbal drugs. *Methods and Findings in Experimental and Clinical Pharmacology*, 31, 165-169.
- [46] Huyen VT, Phan DV, Thang P, Hoa NK, Ostenson CG. (2013) Gynostemma pentaphyllum tea improves insulin sensitivity in type 2 diabetic patients. Journal of Nutrition and Metabolism, 2013, 765383.
- [47] Huyen VT, Phan DV, Thang P, Ky PT, Hoa NK, Ostenson CG. (2012) Anti-diabetic effects of add-on Gynostemma pentaphyllum extract therapy with sulfonylureas in type 2 diabetic patients. Evidence-Based Complementary and Alternative Medicine, 2012, Article ID 452313.
- [48] Huyen VT, Phan DV, Thang P, Hoa NK, Ostenson CG. (2010) Anti-diabetic effect of *Gynostemma pentaphyllum* tea in randomly assigned type 2 diabetic patients. *Hormone and Metabolic Research*, 42, 353-357.
- [49] Hung TM, Hoang DM, Kim JC, Jang HS, Ahn JS, Min BS. (2009) Protein tyrosine phosphatase 1B inhibitory by dammaranes from Vietnamese Giao-Co-Lam tea. Journal of Ethnopharmacology, 124, 240-245.
- [50] Nyirimigabo E, Xu Y, Li Y, Wang Y, Agyemang K, Zhang Y. (2015) A review on phytochemistry, pharmacology, and toxicology studies of Aconitum. The Journal of Pharmacy and Pharmacology, 67, 1-19.
- [51] Langrand J, Regnault H, Cachet X, Bouzidi C, Villa AF, Serfaty L, Garnier R, Michel S. (2014) Toxic hepatitis induced by an herbal medicine: *Tinospora crispa. Phytomedicine*, 21, 1120-1123.
- [52] Rasfon K. (1991) [The anticestodal activity of preparations made from the breadfruit]. *Meditsinskaia Parazitologiia i Parazitarnye Bolezni*, 5, 49-52.
- [53] Thuy TT, Kamperdick C, Ninh PT, Lien TP, Thao TT, Sung TV. (2004) Immunosuppressive auronol glycosides from Artocarpus tonkinensis. Die Pharmazie, 59, 297-300.
- [54] Ngoc DD, Catrina AI, Lundberg K, Harris HE, Ha NT, Anh PT, Larsson P. (2005) Inhibition by Artocarpus tonkinensis of the development of collagen-induced arthritis in rats. Scandinavian Journal of Immunology, 61, 234-241.
- [55] Dang DT, Eriste E, Liepinsh E, Trinh TT, Erlandsson-Harris H, Sillard R, Larsson P. (2009) A novel anti-inflammatory compound, artonkin-4'-O-glucoside, from the leaves of Artocarpus tonkinensis suppresses experimentally induced arthritis. Scandinavian Journal of Immunology, 69, 110-118.
- [56] Pozzesi N, Pierangeli S, Vacca C, Falchi L, Pettorossi V, Martelli MP, Thuy TT, Ninh PT, Liberati AM, Riccardi C, Sung TV, Delfino DV. (2011) Maesopsin 4-O-beta-D-glucoside, a natural compound isolated from the leaves of Artocarpus tonkinensis, inhibits proliferation and up-regulates HMOX1, SRXN1, and BCAS3 in acute myeloid leukemia. Journal of Chemotherapy, 23, 150-157.
- [57] Thuy TT, Thien DD, Quang Hung T, Tam NT, Anh NT, Nga NT, Cuc NT, Mai le P, Van Sung T, Delfino DV, Thao do T. (2016) In vivo anticancer activity of maesopsin 4-O-β-glucoside isolated from leaves of Artocarpus tonkinensis A. Chev. Ex Gagnep. Asian Pacific Journal of Tropical Medicine, 9, 351-356.
- [58] Ma JP, Qiao X, Pan S, Shen H, Zhu GF, Hou AJ. (2010) New isoprenylated flavonoids and cytotoxic constituents from Artocarpus tonkinensis. Journal of Asian Natural Products Research, 12, 586-592.
- [59] Mashreghi M, Rezazade Bazaz M, Mahdavi Shahri N, Asoodeh A, Mashreghi M, Behnam Rassouli M, Golmohammadzadeh S. (2013) Topical effects of frog *Rana ridibunda* skin secretions on wound healing and reduction of wound microbial load. *Journal of Ethnopharmacology*, 145, 793-797.
- [60] Cooper EL, Balamurugan M, Huang CY, Tsao CR, Heredia J, Tommaseo-Ponzetta M, Paoletti MG. (2012) Earthworms dilong: ancient, inexpensive, noncontroversial models may help clarify approaches to integrated medicine emphasizing neuroimmune systems. *Evidence-Based Complementary and Alternative Medicine*, 2012, Article ID 164152.
- [61] Prakash M, Gunasekaran G. (2010) Gastroprotective effect of earthworm paste (*Lampito mauritii*, Kinberg) on experimental gastric ulcers in rats. *European Review for Medical and Pharmacological Sciences*, 14, 171-176.