

A Review of Medicinal Plant Patents

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Abstract: Medicinal plant formulations have been used in traditional medicines for thousands of years. Plant-based medicine is still a major source of new drug leads and herbal treatments are highly lucrative in the international marketplace. The intellectual property issues for medicinal plant formulas are complicated for numerous reasons. Many of the patents are attempting to emulate the pharmaceutical model of composition patents that as we will discuss, is usually not an appropriate approach for medicinal plants. This paper does not seek to be an exhaustive review but rather provide an overview of the many aspects of medicinal plant patents, a topic of considerable future growth. Our experience has been that the merging of modern and traditional knowledge leads to unexpected correlations, elucidations and insights with tremendous potential for patentable discovery. A continuation of the dialogue on indigenous intellectual property rights will benefit from the inclusion of an increased diversity of voices that have the ability to recognize the mutual and often complementary abilities of traditional and modern sciences. The question is not how to simplify the complexity but rather how to embrace the complexity from the traditional medicine worldview with the tools of science.

Keywords: Medicinal plant patent, traditional medicine, herbal medicine, biopiracy.

INTRODUCTION AND OVERVIEW

Medicinal plant formulations have been used in traditional medicines for thousands of years. The intellectual property (IP) issues for medicinal plant formulas are complicated for numerous reasons. Many of the patents are attempting to emulate the pharmaceutical model of composition patents, which as we will discuss, is usually not an appropriate approach for medicinal plants. Rather than exploring potential strategies for circumventing the obstacles for medicinal plant-based patents, we hope to propose a framework of why the usual IP approach of the synthesized and highly purified molecule of western pharmaceuticals may not be the best model to emulate. The unique challenges of bringing scientifically-supported traditional medicines into modern healthcare practice not only offer unique IP opportunities but ultimately serve the larger intent of IP legal theory in service to humanity.

All authors of this paper are members of the Global Institute for Tibetan Medicine [1], a research group dedicated to the preservation and continued evolution of Traditional Tibetan Medicine. From our perspective on the challenges of R&D, regulation, and IP-based financial incentives to support the advancement of traditional medicine, we shall give a review of market demand, regulatory considerations, and challenges of IP that create advances in the art with financial incentives that can help support those advances. Finally, we review a number of patents to identify current trends and highlight current challenges on which we can focus on

improving as a scientific community. This paper does not seek to be an exhaustive review but rather provide an overview of the many aspects of patents of medicinal plants, a topic of considerable future growth.

PUBLIC HEALTH OPPORTUNITIES PRESENTED BY MEDICINAL PLANTS AND TRADITIONAL MEDICINES

Chronic diseases are among the most common, costly, and preventable health problems in the United States and the burden of this care is enormous [2]. The National Center on Aging reports that 75 percent of health care costs stem from chronic conditions [3]. National healthcare spending exceeded \$2.3 trillion in 2008 and was projected to surpass \$2.5 trillion in 2010; the majority of these expenses were for care of chronic conditions [4]. This phenomenon is quickly spreading to the rest of the world as modern lifestyles and diet are adopted. Though modern western biomedicine has considerable success with acute injuries and treatment of infectious diseases, it remains burdened in its care of chronic disabling conditions. New approaches are needed for understanding and caring for the body, approaches that are simple, cost-effective and with minimal side effects.

THE DIFFERING AND COMPLEMENTARY APPROACH OF USING MEDICINAL PLANTS FROM TRADITIONAL MEDICINES

The complexities of chronic diseases such as diabetes, heart disease, neurological disorders, and cancer demonstrate the interplay of systems of the body and have shown in general that a single pharmaceutical compound does not work for the treatment and management of a particular chronic disease. The use of drug cocktails is gaining acceptance in

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allopathic treatments, most notably for HIV and cancer. The use of combined drugs is similar in concept to the use of complex medicinal plant formulas in traditional medicines, although the allopathic theory is still one of combating pathology versus restoring homeostasis (balance) in traditional medicine.

THE WORLD HEALTH ORGANIZATION (WHO) STATES [5]

“Traditional medicine (TM) is the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses. Traditional medicine that has been adopted by other populations (outside its indigenous culture) is often termed alternative or complementary medicine. Herbal medicines include herbs, herbal materials, herbal preparations, and finished herbal products that contain parts of plants or other plant materials as active ingredients.”

MARKET DEMAND

According to the WHO, in some Asian and African countries traditional medicine is the dominant form of primary health care with 80% of the population depending on it. In many developed countries, 70% to 80% of the population has used some form of alternative or complementary medicine (e.g. acupuncture) [5].

Herbal treatments are the most popular form of traditional medicine and can be highly lucrative in the international marketplace. Annual revenues for herbal treatments in Western Europe reached (all figures USD) \$5 billion in 2003-2004 [5]. In China, sales of herbal products totaled \$14 billion in 2005. Herbal medicine revenue in Brazil was \$160 million in 2007. In the US, the rollercoaster growth and shrinkage of the market annual sales from a high of 120% in 1996 to a low of negative 19% in 2000, has shown steady improvement of 5% in 2009 to just over \$5 billion [6] with the mainstream (drug stores, supermarkets, discount chains) providing a larger portion of the growth at 14% for the same time period demonstrating a trend toward mainstream acceptance. The post-1996 drop in the U.S. was driven by a series of negative articles in the popular press pertaining to quality issues with Asian Ginseng and St. John’s wort and the market withdrawal of Ephedra for weight loss, which led to an overall distrust of dietary supplement (DS) quality and safety.

The international marketplace did not experience this precipitous drop in sales as did the US and according to a January 2011 report by Global Industry Analysts, global sales of herbal supplements are projected to hit \$93 Billion by 2015 [7]. The report further cites the rationale for optimistic growth rates being an aging “Baby-Boomer” population and an increasing confidence in quality and safety with the implementation of Good Manufacturing Practice (GMP) requirements and better regulatory oversight in the US and internationally. These drivers for robust future growth projections point to the need for innovation in processes, machines and manufactures not just composition of matter.

SYSTEMATIC TRADITIONAL MEDICINE

Not all systems of traditional medicine are equal in their levels of theory and documentation. We identify a select subset of Traditional Medicine (TM), as “Systematic Traditional Medicine”(STM) which is:

A written, standardized complete medical system with a comprehensive theory and practice, a system of documentation and improvement including theory, hypothesis and experimentation, standardized education, ongoing history of traditional use and evolved independently from allopathic (conventional western) medicine.

Examples are Traditional Tibetan Medicine, Traditional Chinese Medicine, Ayurveda, and Eclectic medicine. The above characteristics make these traditional systems more like, and more compatible with, modern research-based medicine, although traditional practice relies more on empirical observation than biological and pharmacological elucidation.

We have chosen to focus our research efforts on Traditional Tibetan Medicine (TTM). Due to its geographical location and continuous historical support, TTM has been able to integrate the best traditional science of its neighbors in India, China, Persia, and classical Greece (the foundation of western medicine) into a highly coordinated and state-supported integrative TM. The systematic evolution of TTM is progressing to this day in Tibet and with the exiled government of Tibet, headquartered in Dharamshala, India, with a stated goal of appropriate integration with western science and medicine. Modern Tibetan medicine is a historically integrative medicine with elements of each of the above systems and a unique pulse diagnosis, urine diagnosis, and herb-mineral formulations to improve quality of life and restore the body to balance. Because of this we see TTM as an exceptionally robust TM and are actively engaging classically trained TTM practitioners in the modernization and integration of western medicine and TTM.

The complementary strengths and weaknesses of our current allopathic medical system and STM and DS, would benefit both systems if appropriate scientific integration could be achieved:

Allopathic

- Excels in acute and traumatic treatment
- Excels in reductionism elucidation of specific pathology/pharmacology
- Highly definable/reproducible
- Suited to mass production /dispensing
- Generally expensive

STM & DS

- Excels in long term health maintenance
- Excels in understanding of complex treatments utilizing a systems theory
- Long history of use co-evolutionary biochemistry
- Highly individualized
- Generally inexpensive

Although any TM system has the potential for a starting point for medical innovation leading to IP, we think that STM holds unique promise because of its theoretical capability to be integrated into the western medical system. The innovations that help achieve this are fertile grounds for IP development. Modern whole systems innovations are developing as part of an integrated modern healthcare system such as Functional Medicine [8]. The medical approaches of Functional Medicine also take a systems view and provide a natural link for the integration of traditional and western medical views.

The question arises: With such an economic and social incentive, why is there so little support for the scientific research necessary to truly integrate the potential contributions of TM and DS into our current medical system?

THE HISTORICAL TREND AWAY FROM NATURAL COMPOUNDS TO ULTRA PURIFIED AND SYNTHETIC COMPOUNDS

The first American Pharmacopeia in 1820 contained about 70% botanical drugs. That declined to 5.3% by 1960 [9]. A market and public resurgence of interest in plant based botanical medicine and dietary supplements in the last two decades has led to an increase in quality standards in the United States Pharmacopeia (USP) resulting in the necessity of a new separate volume, the USP Dietary Supplement Compendium, published in 2009 [10]. These are standards for existing public domain DS, not new drugs.

The USP, National Formulary (both now combined under the USP) and the Homeopathic Pharmacopeia of the United States (more on Homeopathic in subsequent sections) are the "Official Compendiums" of the United States. Once the USP develops a drug standard and it becomes official, it is enforceable by the U.S. Food and Drug Administration (FDA), and all manufacturers of a drug must comply with the USP standard if they wish to import it to or market it in the United States. Dietary supplement manufacturers in the U.S. may voluntarily choose to meet USP standards but are not required to do so. Most "New Drugs" as recognized by the U.S. Food, Drug and Cosmetic Act, are required by Section 505 of the Act to apply to the FDA for authorization. However, the Dietary, Supplement Health and Education Act (DSHEA) regulates DS as foods; hence Section 505 does not apply. Although some botanicals may qualify as drugs if submitted to the FDA for approval as drugs, the FDA in the Guidance for Industry: Botanical Drug Products (2004) [11], recognized the inherent differences between most synthetic and or purified drugs and botanicals:

"Botanical drug products have certain unique characteristics that should be taken into account in the application of FDA regulations and guidance. Botanical drugs are derived from vegetable matter and are usually prepared as complex mixtures. Their chemical constituents are not always well defined. In many cases, the active constituent in a botanical drug is not identified, nor is its biological activity well characterized. Therefore, the CMC documentation that should be provided for botanical drugs will often be different from that for synthetic or highly purified drugs, whose active constituents can be more readily chemically identified and quantified."

Plant-based medicine is still a major source of new drug leads as indicated by David J. Newman and Gordon M. Cragg in the *Journal of Natural Products* [12] who state in the area of cancer drugs 73% are other than synthetic and 47% are actually or directly derived natural products. They further state that the current crisis in a lack of productivity of truly new and novel drugs would be well served to expand the exploration of natural compounds for new drug leads and possible elucidation of previously unknown biosynthetic pathways.

The current patent environment that helped to foster such a healthy market and hence the supporting research and development funding for highly purified and synthesized compounds, many originating from plant based therapeutics, does little to support TM in its natural state. This is due to a phenomena the industry calls "borrowed science."

THE IP DIS-INCENTIVE FOR RESEARCH SUPPORT OF TM AND DS

Let's assume an ethnobotanist with informed consent [13] of the originating culture, researched a plant based traditional medicine that is effective for a condition she recognizes as diabetes. She spends twenty million dollars, a very modest amount by modern drug development standards, carefully reproducing the traditional propagation and processing of the material and utilizes modern scientific methodology to develop a well-defined and consistent extract. She does toxicology studies and a series of high quality double blind clinical studies with a total of five-hundred patients who respond 95% positively with no significant side-effects. She publishes her results in a number of respected peer-reviewed journals. The popular press picks up the research results and her traditional medicine is in demand. She launches the product as a dietary supplement because the US has no market category for traditional medicines. Her product has no patent protection because products of nature are not patentable and the traditional literature constitutes prior art. Because of her rigorous farm to shelf quality control system, the amortized cost of twenty million dollars in R&D, and her ethical commitment to pay royalties to benefit the traditional culture of origin [14], her product retails for \$75 per bottle; a fraction of the comparative Rx product with better results and no negative side-effects. This includes \$5 per bottle for advertising and promotion allotment.

A competitor buys the least expensive botanical raw materials in the open market, although the quality is questionable and there is no verifiable connection to the quality of the material in the clinical trial except it is the correct genus, species, and plant part. He can retail the product for \$35 per bottle even with a \$20 per bottle marketing allotment. He is allowed to use all of the published research and publicity to support his product (borrowed science) with no restrictions, royalties or licensing required. The market not only does not differentiate between products, rather, it heavily favors the less expensive product, due to better promotional support and the in-store draw of a discounted popular product. After he successfully puts the inventor out of business with more promotion and a huge price advantage, other competitors enter the market competing on price and the quality invariably slides. A follow-up meta analysis is done by a university

on the products now flooding the market that bear little or no resemblance to the original high quality material used for the clinical trials, and it is published that the originally reported 95% positive clinical trial results are in actuality, no better than placebo and a number of the products have been found to contain high levels of adulterants.

Although a hypothetical example, this conundrum plays out often with a significant difference. Because of the borrowed science disincentive, the original R&D investments are not made. The lack of scientific research and support for TM and DS is often cited as proof of their inferiority, "If it worked someone would have invested in the research." What this is really proof of is a system of IP and insurance reimbursement that is stacked against scientific research and support for TM and DS. There are ways to improve this anti-investment incentive in quality and research through improved and market recognized standards and clever use of existing IP incentives.

RAPIDLY IMPROVING BOTANICAL MEDICINE AND DS QUALITY STANDARDS

With the resurgence of interest in TM and DS in the early 1990s, some members of congress and the FDA felt it necessary to gain control by creating a regulatory framework for market approval and label claims modeled after drugs. Because of the research disincentive of borrowed science for non-patentable TM and DS it became apparent that the net result of this proposed legislation would be that sufficient R&D and proof of concept would never be funded, essentially outlawing most TM and DS. Public perception of their basic rights to manage their health being infringed by this perceived regulatory overreach was ignited by a 1992 FDA raid on the offices of Dr. Jonathan Wright for utilizing FDA banned L-tryptophan and vitamin therapies. The number of letters to congress in favor of market availability for TM and DS was second only to opposition to the Vietnam War, eventually leading to the adoption of the Dietary Supplement Health and Education Act (DSHEA) of 1994 [15]. DSHEA recognizes an empirical assumption of safety based on traditional use as foods ("foods" also includes traditional medicines). For TM this assumption of safety is legitimate, however, it assumes that the marketed products are the same as used in the tradition, which is not a codified requirement. Characterizing TM as a food also sidesteps the issues of its intended therapeutic use. DSHEA has recently clarified its requirements for Good Manufacturing Practices (GMP) for DS. Leading pharmacopeias have also increased efforts in standards such as the United States Pharmacopeia (USP) with its new Dietary Supplement Compendium, The European Pharmacopeia, The German Commission E monographs and the Codex Alimentarius, to name a few. Although in the US compliance with USP monographs are a requirement for OTC and Rx drugs, no such requirement exists for TM or DS. An encouraging international trend in science-based regulation is the development of a third category between food and drugs for traditional medicines and therapeutic DS such as the Australian Therapeutics Goods Act 1989 where "complementary medicines" are regulated as medicines; in Canada, as Natural Health Products (under OTC drug regulations) and in the EU-Member States, as Traditional Herbal Medicinal Products or Well-Established

use Medicinal Products (both under drug regulations). The well-worn path of traditional medicine only as a source of biochemical leads for synthetic patentable drug compounds will continue; however, this is not where we see the best IP opportunities. As we move toward a more scientifically based regulatory system with appropriate technologies for capturing the complexity of natural products with "drug-like" reproducibility, safety, and efficacy, the opportunities and financial rewards of technology to support TM can be realized.

PATENTS AND MEDICINAL PLANTS

The body of U.S. patent law and corresponding international law that has arisen from medicinal plant patents is complex and nuanced; however, the basic principles important to researchers and engineers are consistent. Patents do not grant a positive right, the right to sell an invention; rather they confer a negative right, blocking others from utilizing your invention for a specific period of time (for utility patents, usually 20 years from date of application) after which it goes into the public domain. The intent of granting this time-limited monopoly is to create incentive for invention and innovation. Patents that are granted for "inventions" that are in actuality restatements of traditional knowledge without any real novel contribution subvert this process by turning the patent system into unfair business advantage without the balancing public benefit of advancement to the art.

For something (inventions or discovery of any new and useful process, machine, manufacture, or composition or matter, or any new and useful improvement thereof [16], that we shall just call inventions) to be patentable it must pass all three tests of utility, novelty and non-obvious [17].

Utility is the easiest hurdle for most inventions. An invention must convey a current beneficial use to the public. A functional therapeutic by its definition passes this test. It is not however sufficient to say that an invention may have some future or undiscovered utility. Provided in the Table is a sampling of utility patents relevant to medicinal plant formulas. We later review in more detail some of the medicinal plant utility patents (Table 1).

Novelty is a requirement that the invention is new and not already known in the public domain. Public domain includes if the inventor discloses the invention, such as in an academic article or promotional materials, for more than a year prior to the filing of a patent application.

The public domain also includes all *Materia Medica* (medical body of knowledge) including oral knowledge. This is the area of most IP difficulty for TM formulas. TMs are marketed in the US as Dietary Supplements under DSHEA. TMs marketed prior to 1994 are grandfathered under the assumption that materials that have an ongoing use in a traditional system of medicine have an empirical assumption of safety. International law differs but often employs a similar logic. If a proposed patentable formulation is close enough to a traditional formulation and relies on a traditional use to claim, the assumption of safety to market it without the process of applying for approval as a new food, ingredient or medicine, then by definition it is likely not patentable. If it is unique enough to be considered novel, then by definition it cannot be assumed to be safe by way of traditional use.

Table 1. Examples of Utility Patents Pertaining to Medicinal Plants

Patent Type	Inventors	Patent Name	Patent #	Date
A. Process	Raju GG, Raju, Subbaraju GV, Venkateswarlu S	Pharmaceutically Active Extracts of Vitex Leucoxyon, A Process of Extracting the Same and a Method of Treating Diabetes and Inflammatory Diseases Therewith	US7780997B2	8/24/2010
	Huh GH, Kim YH, BM Kim	Promoter for the High Level Expression in Plant-Tissue Culture and Vector Using the Same	US20100100986A1	4/22/2010
	Ritali-Nurmi A, Rischer H, Oksman-Caldentey K-M, Rui M	Plant Cell Lines Established from the Medicinal Plant <i>Veratrum californicum</i>	US20090305338A1	12/10/2009
	Hylands PJ, Nicholson JK, Holmes E, Dunn J	Process for Quality Control and Standardization of Medicinal Plant Products	US6806090B1	10/19/2004
	Lei J	Process of Powder for Bath from Natural Plants	US6541163B1	04/01/2003
	Schierstedt D	Medicinal Plant Dry Extracts	US6472439B1	10/29/2002
	Blanchette RA, Heuveling van Beek H	Cultivated Agarwood	US20020194780A1	02/26/2002
	Durance TD, Yousif AN, Kim H-O, Scaman CH	Process for Drying Medicinal Plants	US6128831	10/10/2000
	Kwak W-j, Han C-k, Kim H-s, An J-s, Kim T-s	Process of Extracting and Purifying Biologically Effective Ingredients from Combined Medicinal Plants and their Extract Composition	US5910307	06/8/1999
	Staba J	Production of Diosgenin by Plant Tissue Culture Technique	US3628287	10/20/1969
B. Machine	Farmer EJ, Hovey DJ	Device for Monitoring a Magnetic Field Emanating from an Organism	US005458142A	10/17/1995
	Cordes HP	Apparatus for Separating Food Articles from Field Debris	US4082189	04/04/1978
	Baker JG	Improvement in Tincture Presses	US220112	09/30/1879
C. Method	Dadala VK, Rhagavan KV	Novel Method for Chromatographic Fingerprinting and Standardization of Single Medicines and Formulations	US 232706	09/17/2009
	Leung AY, Pennyroyal G	System and Method for Assessing Traditional Medicine	WO2009036387A1	03/19/2009
	Xu R	Methods and Compositions for Treating or Preventing Neurodegenerative Disease	US131528A1	06/05/2008
	Dadala VK, Rhagavan KV	Method for Standardization of Chemical and Therapeutic Values of Foods and Medicines using Animated Chromatographic Fingerprinting	US288217A1	12/13/2007
	Charron D	Method and Topical Formulation for Treating Headaches	US20060165812A1	07/27/2006
	Last B	Method of Preparing Dioscorea Tincture and Uses Thereof	US6156897A	04/06/2006
	Majeed M, Badmaev V, Bammi RK, Prakash S, Natarajan S	Method of Increased Bioavailability of Nutrients and Pharmaceutical Preparations with Tetrahydropiperine and its Analogues and Derivatives	US006849645B2	02/01/2005
	Hinz HR	Method for purifying 20(S)-camptothecin	US20060073224A1	12/05/2000

(Table 1) contd....

Patent Type	Inventors	Patent Name	Patent #	Date
D. Formula/ composition	Rao JM, Sampathkumar U, Sastry BS, Yadav JS, Raghavan KV, Palit G, Bhalla DN, Rai D, Varier PM, Muraleedharan TS, Muraleedharan K	Herbal Composition for the Treatment of Gastric Ulcer	US7651705B2	01/26/2010
	Chou WH, Chou V	Herbal Compositions and Methods for Enhancing Vital Energy and Athletic Performance	US20090274783A1	11/05/2009
	Chan HLH	Herbal Formulation for Treatment of Depression and Other Related Disorders and Method of Preparing the Same	US7318939B2	01/15/2008
	Shane M	Medicinal plant compositions of matter and method of preparation	US7306816	12/11/2007
	Liu Z, Qi W, Fu T, Zou W, Ji Y, Li B, Huang Y	Pharmaceutical Composition Containing Steroidal Saponins, The Preparation Method and use Thereof	US20070254847A1	11/01/2007
	Zhang Y, Wu X, Yu Z, Zhu Y, Chen L, Lou S	Composition Containing Total Triterpenoid Saponins extracted from Bamboo, and the Preparation Method and Use Thereof	US20060148733A1	06/06/2006
	Seipel TA	Herbal Compositions for the Prevention or Treatment of Urinary Incontinence and Overactive Bladder	US20060040004A1	02/23/2006
	Dreyer LR	Homeopathic Formulations Useful for Treating Pain and/or Inflammation	US20040180101A1	09/16/2004
	McClung JH	Composition for Topical Application to Skin	US6579543	06/17/2003
	Niazi SK	Pharmaceutical Preparation for the Treatment of Gastrointestinal Ulcers and Hemorrhoids	US6365198B1	04/02/2002
Masiello D	Composition and Method for Treating Herpes Simplex	US5834443	11/10/1998	

There is also specific precedent for products of nature. Products of nature, including naturally occurring compounds produced by plants, are not patentable. To avoid this issue, it is a common industry practice to synthesize the naturally occurring compound in a way that the molecular structure is unique and different enough from the original substance, yet retains the benefits and does not introduce unacceptable new unintended side effects. The classic example of this was in 1898, when chemists working at Bayer AG produced a synthetically altered version of salicin, known as aspirin (Salicin is a naturally occurring compound found in Willow (*Salix spp.*) and Meadowsweet (*Spiraea ulmaria*) traditionally used as an analgesic an antipyretic). Another approach is to create a highly purified version of the active principals in the naturally occurring material. Just purification is not usually enough to make the compound patentable; it must also show unexpected results, physiologically or otherwise, in its highly purified state [18]. A recent example of this is GlaxoSmithKline's Lovaza[®], (a.k.a. Omacor[®]) a highly puri-

fied, chemically altered Omega-3 ethyl esters standardized fish oil indicated for treatment of high triglycerides [19-21].

Non-obvious expands on the concept of being novel in that an invention must not only be new and not already known but also requires that the invention not be obvious to persons having ordinary skills in the art.

The USPTO states: “

“... if the difference between the subject matter sought to be patented and the Prior Art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” [20]

In the case of STMs, this includes traditional practitioners, biochemists, nutritionists etc. If an inventor was to take a traditional formula for improved eyesight and add lutein and vitamin A, both well known for prophylactic protection from macular degeneration and overall eye health, though

the particular combination may not appear in any known prior art, the outcome of supporting healthy eyesight or even the more specific claim of macular degeneration would be anticipated by those having ordinary skills in the art.

This is a situation apparently overlooked in some patents we reviewed that appear to patent a traditional formula. Alternately, in some patents the traditional formula is altered which would then suggest a new food, ingredient, or drug while still relying on the *Materia Medica* for safety and efficacy. In short, the inventor cannot have it both ways. The granting of a patent does not guarantee its defensibility. We suspect that this is exacerbated in the case of traditional formulations because the literature (often not in English) is not well-indexed or known to patent application examiners.

Of the three major categories of patents (design, plant, and utility) the utility patent is the most common and clearly the most applicable for TM patents.

A **design patent** consists of the visual ornamental characteristics of a functional item and is not considered in this paper.

Plant patents, although commonly misconstrued to offer protection for plant-based medicines, only protect invention or discovery of asexually reproduced, distinct, and new varieties of plants, other than a tuber propagated plant or a plant found in an uncultivated state. This does not include discoveries of a new application for an existing variety of plant or a previously unknown therapeutic substitute for a traditionally used plant.

Prior to the Plant Protection Act (PPA) of 1930, new varieties of plants were considered not patentable due to the "Products of Nature" exclusion. IP protection for plant varieties was further expanded with the Plant Variety Protection Act (PVPA) of 1970, which is not administered by the PTO and is not considered a patent.

In 1980 the Supreme Court held that genetically engineered bacterium could be patented as utility patents, not plant patents. Companies pursuing IP protection for genetically modified plants have successfully argued that genetically modified plants fall under utility patents as manufactures rather than the less restrictive (hence offering more protection to the inventor), protection afforded by plant patents or the PVPA [21]. In essence, this approach portrays the genetically modified plant as a mechanism that produced a unique product. This is an emerging and controversial area as it relates to the modernization of medicinal plant use; however, it does not qualify as traditional medicine. Hence, products of genetic engineering should be subject to the new drug requirements for pre-market approval from the FDA.

Utility patents are by far the most common patents and are generally what are thought of as patents. Utility patents fall into four general categories: *Process, Machine, Article of Manufacture, and Composition of Matter*. In most instances of the medicinal plant patents that we reviewed, the patent overlaps with at least two of the utility categories; e.g. overlap of new process and new machine in a single patent, overlap of new composition and new method of delivery in a patent. Provided in the Table is a sampling of utility patents relevant to medicinal plants.

Utility: Process patents for medicinal plants relate to many different aspects of the plant process including cultivation, harvesting, drying, and extraction.

Cultivation

As medicinal plants are integrated into western medicine and the demand increases, there will be need for new methods of medicinal plant cultivation to meet demand. An example of a cultivation patent is Blanchette & van Beek, Cultivated Agarwood [22]. This patent describes a way to provide agarwood from cultivated trees by forming an artificial wound into the xylem and providing means for aeration and improved production. Ideally future such patents would include a mechanism whereby to evaluate the medicinal grade or cosmetic quality of the substance cultivated.

Another possibility is plant tissue culture. As early as 1969 patents were filed in this area: J Stabe, Production of Diosgenin by Plant Tissue Culture [23]. A few other examples of medicinal plant tissue culture are in collaboration with Korea, Huh *et al.* Promoter for the High Level Expression in Plant-Tissue Culture and Vector Using the Same [24] and in collaboration with Finland and Canada, Ritala-Nurmi *et al.* Plant Cell Lines Established from The Medicinal Plant *Veratrum californicum* [25]. These patents discuss ways to propagate plants in the lab in a controlled way to express certain medicinal substances. This is a way to increase in concentration compounds used in the further synthesis or purification of drug compounds. Although highly useful for the claimed application, this type of concentration of "active compounds" in traditional medicine would need to be considered with caution because it is rare that the therapeutic action is actually from a single active compound (if it were it would be purified or synthesized for a drug) and the effects of possible synergistic compounds are not generally known.

Drying

Harvesting and drying protocols for medicinal plants are very detailed in traditional medicine knowledge. The harvest season and time of day depends on the type of plant. The method of drying also relates to its growing environment. There are many factors to take into account and the collaboration of traditional knowledge enhances outcome.

Durance, Yousif, Kim, and Scaman have patented a Process for Drying Medicinal Plants [26]. This method applies "...power to plant materials in a chamber under reduced pressure to reduce the moisture content without significantly reducing (oxidizing) the concentration of active medicinal component in dried plant materials, thereby producing a dried medicinal plant product which more closely approaches the medicinal properties of the fresh plant than those of the dried products produced by conventional drying processes." Medicinal plants are highly enriched in compounds with conjugated double bonds that are particularly susceptible to oxidative damage. The use of microwaves, however, adds the potential to break and create new bonds, both issues with microwaved food and irradiated herbs (a very common practice although not always compliant with current regulations) and worth noting here.

Extraction

Patents for the extraction processes of medicinal plants are relatively abundant and date as far back as 1879 with JG Baker's Improvement in Tincture Presses [27]. This paper does not seek to be an exhaustive review of the many tincture presses and extraction devices since then, but the extraction method of medicinal plants is critical to their final medicinal effect. A new process for the extraction of medicinal plants can be patented without a new machine but our experience and review indicates that usually a new machine is patented that requires new process. In other words, new machine often leads to new process though new process can occur without new machines.

Utility

Machine patents for medicinal plants include cultivation and harvesting machines, tincture presses and better extraction machines, and devices for monitoring the effects of medicinal plants in the lab on cells and in the body.

Harvesting

The cultivation of plants in a field more closely replicates the environments of nature than does plant tissue culture. Large-scale cultivation can accommodate better harvesting. One patent in this area is by Cordes on an Apparatus for Separating Food Articles from Field Debris [28]. This apparatus separates food debris from an admixture of articles and uses responsiveness to a photoelectric cell to assist with ejection of debris. More efficient cultivation and harvesting methods will enhance profit for the final product.

Devices

New devices for the study of medicinal plants include those for monitoring the effects of plant extracts on cells in the lab and those for monitoring the whole person. Regarding the latter is the patent of Farmer *et al.* device for Monitoring a Magnetic Field Emanating from an Organism [29]. This device measures extremely low level, low frequency electromagnetic fields of the whole person and cites Traditional Medicine knowledge as the basis of the device invention. Such a device could be used to monitor the clinical effects of TM and medicinal plants.

Utility

Methods patents for medicinal plants include ways to characterize and standardize a formula, better ways for processing and quality control. This has advanced to include genomics and gene arrays to study the chemical compositions of plant formulas and identify key markers, and for studying the effects of medicinal plants, both on cells in the lab and in the human body. An example of a patent pending co-invented by co-author of this paper, Pennyroyal, is a System and Method for Assessing Traditional Medicines, a process for deriving drug-like consistency from complex natural products [30]. Abstract: Methods of defining a standard for a traditional medicine are provided. A method can comprise obtaining at least two samples of the traditional medicine that have been authenticated by qualitative profiling as representing a control positive; quantitatively profiling each of

the at least two samples using at least two physicochemical analyses.... Methods of certifying a test sample of a traditional medicine are also provided. ...A certified traditional medicine comprises a traditional medicine certified by these methods.

This pending patent is limited to the process of creating a high level of quality control utilizing mutually reinforcing modern analytical techniques. The "control positive" in this invention are samples of traditional therapeutics that have been determined as high quality by traditional practitioners. Not only does this approach not try to circumvent the contribution of traditional knowledge but acknowledges it as the foundation on which the invention is built and by very definition acknowledges the contribution of traditional knowledge as verified by those trained in the art of the tradition.

A Process for Quality Control and Standardization of Medicinal Plant Products utilizes Nuclear Magnetic Resonance spectroscopy and a computer-based pattern recognition technique to characterize medicinal plants in a manner similar to differentiating wines based on their origin [31].

Two patents by Dadala and Rhagavan reviewed the vata-pitta-kapha tridosha and earth-water-fire-wood-metal five element theories of Ayurvedic and Traditional Chinese Medicines as prior art to their inventions of fingerprinting medicinal plants for quality control: Method for Standardization of Chemical and Therapeutic Values of Foods and Medicines using Animated Chromatographic Fingerprinting [32]. Novel Method for Chromatographic Fingerprinting and Standardization of Single Medicines and Formulations [33].

Utility

Composition of matter patents are chemical compositions and may include mixtures of ingredients as well as new chemical compounds. This is what is most commonly thought of with patented pharmaceuticals and by extension what is most commonly thought of as patentable in traditional medicine. Because of the issues of prior art and products of nature not being patentable, composition of matter may not yield the best potential IP and contribution to the art in the appropriate advancement of traditional medicine, although this is the area that gets the most research attention. The approach and research framework for composition of matter depends largely on the go-to-market goals. If the primary go-to-market goal is the isolation of chemicals from TM, composition of matter is clearly the appropriate approach; however, if IP opportunities in the advancement of bringing TM to market is the market goal, other patent types will likely yield the best results.

There are many composition patents for medicinal plant formulas, but as we have reviewed in this paper, we emphasize the need to truly understand the complete context as known by traditional medicine practitioners. Furthermore, the *Materia Medica* of STM is extensively documented. Many composition patents list herbs from *Materia Medica* and the patent is potentially invalid if contested. We will review two such cases. This is a regulatory gray area as we evolve in the modernization of traditional medicine. The WHO acknowledges that this discussion must occur but it has yet to happen [14]. It is a topic beyond the scope of this paper and it is our hope that this will encourage further dia-

logue of how to integrate traditional and modern medical knowledge in a way that benefits both traditional originators and modern inventors including a compensation and royalty system.

In our opinion, future areas of focus for research leading to patents relevant to medicinal plants are better methods for characterization, processing, and formulation of products. This as an integrated field is just emerging. The patenting of formulas, however, remains a complicated issue that requires ongoing dialogue amongst researchers and traditional medicine practitioners. With all of the attention that is given to traditional medicine as an alternate resource for composition of matter patents, we see the potential of processes, machines, and articles of manufacture as having the greatest unmet potential for advancing the area and producing marketable IP.

ISSUES OF PLANT-BASED TRADITIONAL THERAPEUTICS

Traditional medicine and medicinal plants have been used in defined population groups for thousands of years. There are challenges as new populations and cultures adopt traditional medicine practices.

Traditional Expertise

Traditional medicine practices have been adopted in different cultures and regions without the parallel advance of international standards and methods for evaluation. There has been a scientific and regulatory trend to view TM as western drugs manufactured by plants, ignoring important differences in traditional quality control, processing, dispensing, cultural beliefs, diagnostic and therapeutic outcomes, and selective population based differences in diet, lifestyle, genetics, and relevant health issues. The entire summation of the practice, theory, and environmental factors must be understood with a truly qualified traditional expert who is steeped in the culture and tradition as opposed to an outsider seeing the TM through the lenses of their own education and cultural paradigm. The practice of traditional medicine is also usually highly patient specific as opposed to standardized to the population like most western mass-products drugs.

Many Tibetan formulations for example, contain 30-60 different ingredients which can have undesirable effects unless carefully matched to the individual patient's functional imbalances and need to be monitored carefully by a trained Tibetan doctor. Some formulations that tend to be simpler, are known to be safe for general use in the population more as a supplement than a therapeutic. It is concerning when western researchers want to utilize traditional medicines when they see positive results without understanding the entire system that supports the healing process. One would not engage in a western medical practice if not properly trained and western researchers need to include properly trained traditional professionals if they are going to utilize traditional therapies.

National Policy and Regulation

Regulations for traditional medicines have recently emerged with wide variations as to the acceptance of tradi-

tional use for safety and efficacy as noted above. Regulating traditional medicine products, practices, and practitioners is difficult due to variations in definitions and categorizations of traditional medicine therapies and application. A single herbal product could be defined as either a food, a dietary supplement or an herbal medicine depending on the country. This disparity in regulations at the national level has implications for international access and distribution of products.

There is also a growing consensus on the inappropriateness of "mining" traditional cultures for their knowledge. The term "biopiracy" is often used to describe the misappropriation of knowledge and/or biological materials from traditional communities [34]. The cultural understanding of community knowledge has as a core concept the dissemination of knowledge as a means of supporting the community and sustaining the life dependent ecosystem. This is at odds with the western view of IP which emphasizes exploitation and individual ownership as an incentive to commercialization [35]. International minimum standards for many forms of IP are set forth in the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) which is administered by the World Trade Organization (WTO), which currently does not specifically protect traditional knowledge. There are however, specific international agreements directly impacting traditional knowledge IP such as [34]:

- Universal Declaration of Human Rights (UDHR) (1948)
 - Article 27:
 - "Everyone has the right ... to share in scientific advancement and its benefits ... to the protection of the moral and material interests resulting from any scientific, literary or artistic production ... to share in scientific advancement and its benefits."
- International Covenant on Economic, Social and Cultural Rights (ICESCR) (1976)
 - Article 15:
 - "... Recognize the right of ...everyone To enjoy the benefits of scientific progress and its applications;"
- Convention on Biological Diversity (CBD), 1993
 - Article 8(j):
 - "... preserve and maintain knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity and promote their wider application with the approval and involvement of the holders of such knowledge, innovations and practices and encourage the equitable sharing of the benefits arising from the utilization of such knowledge..."
- International Labor Organization Convention No. 169 (1989)
 - Article 15 (1):
 - "The rights of the peoples concerned to the natural resources pertaining to their lands shall be specially safeguarded. These rights include the right of these peoples to participate in the use, management and conservation of these resources."

- Draft Declaration on Indigenous Rights (2007)
 - Article 29:
 - “Indigenous peoples are entitled to the recognition of the full ownership, control and protection of their cultural and intellectual property. They have the right to special measures to control, develop and protect their sciences, technologies and cultural manifestations, including human and other genetic resources, seeds, medicines, knowledge of the properties of fauna and flora, oral traditions.”

There are patents approved that in our opinion do not meet these standards. For example, a widely used medicinal plant is patented for traditional uses, or many plants are patented for the assembly of possible formulas. In both instances, prior art is often overlooked regarding the traditional medical source of the knowledge.

A patent that is often cited as an alleged example of bio-piracy is that of the multinational chemical corporation WR Grace Company:

United States Patent 5,124,349, Carter *et al.* June 23, 1992 Storage stable azadirachtin formulation (EP0436257) [36] and Locke *et al.* and United States Patent 5,298,251 Locke *et al.* March 29, 1994: Fungicide compositions derived from neem oil and neem wax fractions [37]. Abstract: “Novel fungicide compositions prepared from neem seeds are disclosed. Two distinct neem derived fungicides obtained non-polar, hydrophobic solvent neem seed extracts which are substantially free of azadirachtin, by removing the hydrophobic solvent and cooling the resulting neem oil to separate a semi-solid neem wax fraction and a clarified neem oil fraction.” [38]

WR Grace dismissed any claim for co-inventorship and royalties for the contribution of thousands of years of use for neem as a medicine and insecticide as “Folk Medicine.” Under challenge of prior art, in March, 2005, the European Patent Office revoked the European Patent EP0436257. The US patent is still in place.

WR Grace’s claim was that their novel extraction process improved extraction efficiency and shelf life of the product, both true, however, their claims extended to the use of neem as a pesticide with no acknowledgement or compensation of the contribution of traditional knowledge.

Commenting on the legal challenge to the Grace patents, Vandana Shiva in *Biopiracy: The Plunder of Nature and Knowledge* [39] is critical of W. R. Grace’s claim that their extraction process constitute a genuine innovation or patented compositions and processes were sufficiently novel of the well documented traditional use as a natural pesticide and medicine. He concludes that the granting of the requirement of being novel and not disclosed in prior art, was due to ignorance in the West of the existence of traditional literature documentation and widely known traditional knowledge in India. The Indian Central Insecticide Board chose not to register neem products under the Indian Insecticides Act of 1968 because they understood that neem had extensive use in India as an insecticide and traditional medicine for centuries.

It is our opinion that WR Grace would have fared better in the European courts and in the “Courts of public opinion” if they had followed the principals of recognizing contribution and joint inventorship [40] of traditional knowledge and limited their claims to the improved process for extraction, storage and application, a valid genuine contribution to the art, and recognized the holders of the traditional knowledge in a cooperative commercial exploitation of a traditional method and composition.

Another example is United States Patent 5,401,504 Das, *et al.* March 28, 1995, Use of turmeric in wound healing [41]. Abstract: Method of promoting healing of a wound by administering turmeric to a patient afflicted with the wound. The patent application makes no mention of prior art related to Turmeric for wound healing and cites only American and European references none past 1983. An examiner with experience in TM would have been suspect that such a mainstay of traditional Asian medicine as turmeric should have more traditional references.

The Indian Council for Scientific and Industrial Research (CSIR) successfully challenged and overturned this patent in 1996. The US PTO ruled the patents were anticipated and obvious by the demonstration of thirty-two prior written references, some in ancient Sanskrit [42].

Unique Aspects of Homeopathy

Although the majority of homeopathic remedies are of botanical origin, homeopathy poses a unique set of challenges for IP. The term “drug” is defined in U.S. law with the Food Drug and Cosmetic Act (FDCA) in Section 201(g)(1) FDCA, 21 U.S.C. §321(g)(1), as:

“...articles recognized in the official United States Pharmacopoeia, Official Homeopathic Pharmacopoeia of the United States, Official National Formulary or any supplement to any of them. . .”

Hence, homeopathic remedies (the term for homeopathic drugs) are classified as drugs. However, unlike most allopathic drugs, which are required by section 505 of the FDCA to go through an FDA premarket approval process, just inclusion in the Official Homeopathic Pharmacopoeia is enough to qualify the remedy as a legal drug. Homeopathic theory is also a challenge to describe with currently accepted western scientific models. One of the core homeopathic theories is the concept of “potentisation” (making physiologically stronger) by diluting the actual plant, mineral, animal or chemical-based extract in a series of highly prescribed steps that included a percussive action. The net resulting remedy often contains no original molecules of the original therapeutic agent (diluted beyond Avogadro’s constant) but is said to have higher biological action. Most theoretical explanations center around the concepts of energetic medicine where some form of electromagnetic energy is transferred into the medium and contains the physiologically active principle. Without going into the hotly debated arena of the scientific validity of homeopathy, this is another example of a medical system with a very specific theory being reviewed by examiners with little knowledge. One of the authors of this paper, Pennyroyal, had the direct experience of having a

proposed patent for measuring homeopathic efficacy and potency rejected on all claims because the patent reviewer refused to acknowledge any difference between herbal extracts and homeopathic remedies. Regardless of the belief in the validity of homeopathy, the difference between these is obvious, especially for those remedies that are diluted beyond Avogadro's constant.

Safety, Effectiveness and Quality

Many people believe that because medicines are herbal (natural) or traditional they are inherently safe (or carry no risk for harm). However, traditional medicines and practices can cause harmful, adverse reactions if the product or therapy is of poor quality, or it is taken inappropriately or in conjunction with other medicines. Increased patient awareness about safe usage is important, as well as more professional training, collaboration and communication among providers of traditional and other medicines.

Scientific evidence from studies conducted to evaluate the safety and effectiveness of traditional medicine products and practices is limited by the financial disincentive and limited appropriate technologies and methodologies. While evidence shows that acupuncture, some herbal medicines and some manual therapies (e.g. massage) are effective for specific conditions, further study of products and practices is needed. Requirements and methods for research and evaluation are complex. For example, it can be difficult to assess the quality of finished herbal products. The safety, effectiveness and quality of finished herbal medicine products depend on the quality of their source materials (which can include hundreds of natural constituents), and how elements are handled through production processes. The work reviewed of co-author, Pennyroyal, System and Method for Assessing Traditional Medicines [32], is a patent-pending process for deriving drug-like consistency from complex natural products and promises great reliability and reproducibility of medicinal plant products.

Knowledge and Sustainability

Traditional knowledge is the information that people in a given community, based on experience and adaptation to a local culture and environment, have developed over time, and continue to develop. This knowledge is used to sustain the community and its culture and to maintain the genetic resources necessary for the continued survival of the community.

Herbal materials for products are collected from wild plant populations and cultivated as medicinal plants. The expanding herbal product market could drive over-harvesting of plants and threaten biodiversity. Poorly managed collection and cultivation practices could lead to the extinction of endangered plant species and the destruction of natural resources. Efforts to preserve both plant populations and knowledge on how to use them for medicinal purposes is needed to sustain traditional medicine. This is not only addressed in the Convention on Biological Diversity (CBD), but also by CITES (Convention on International Trade in Endangered Species of Wild Fauna and Flora, 1975) which is a voluntary international agreement between governments.

Its aim is to ensure that international trade in specimens of wild animals and plants does not threaten their survival.

There is also a trend toward certification of environmental and social responsibility as evidenced by the International Organization for Standards, Geneva, Switzerland, which is known for its manufacturing quality standards, also verifies a Social Responsibility Standard, ISO 26000, which amongst other guidelines measures compliance against UN Global compact, ISO 28000 supply chain management and BS 8904 Sustainable development [43].

SUMMARY AND CONCLUSION

The clinical research that is evolving for studies of medicinal plants reflects a need to re-evaluate how to design such studies, taking into account the theoretical framework of the STM and the whole person view. Concurrent with this examination of how to study traditional medicine with a systems view, are many inventors with patents or ideas for patents to study medicinal plants at varying stages of the clinical trial process. Dialogue with traditional practitioners will facilitate development and a level of understanding that will not only ensure safe effective products, but also lead to deeper possibilities for discovery. Our experience has been that the merging of modern and traditional knowledge leads to unexpected correlations, elucidations, and insights with tremendous potential for patentable discovery. A continuation of the dialogue on indigenous intellectual property rights will benefit from the inclusion of an increased diversity of voices that have the ability to recognize the mutual and often complementary attributes of traditional and modern sciences. The question is not how to simplify the complexity but rather how to embrace the complexity from the traditional medicine worldview with the tools of science.

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ABBREVIATIONS

CBD	=	Convention on Biological Diversity (1993)
CITES	=	Convention on International Trade in Endangered Species (1975)
CMC	=	Chemistry, Manufacturing and Control
DS	=	Dietary Supplement
DSHEA	=	Dietary Supplement Health and Education Act (1994)
EU	=	European Union
FDA	=	Food and Drug Administration
FDCA	=	Food Drug and Cosmetic Act (1938)
GMP	=	Good Manufacturing Practices

ICESCR	=	International Covenant on Economic, Social and Cultural Rights (1976)
IP	=	Intellectual Property
OTC	=	Over-the-counter (drugs)
PPA	=	Plant Protection Act (1930)
PTO	=	Patent and Trademark Office (US)
PVPA	=	Plant Variety Protection Act (1970)
R&D	=	Research and Development
Rx	=	A medical prescription
STM	=	Systematic Traditional Medicine
TM	=	Traditional Medicine
TTM	=	Traditional Tibetan Medicine
UDHR	=	Universal Declaration of Human Rights (1948)
USD	=	United States Dollar
USP	=	United States Pharmacopeia
WHO	=	World Health Organization

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