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Herbal medicines: old and new concepts, truths and misunderstandings

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Abstract: Men have been using herbal medicines for thousands of years. The advantages of this type of therapeutics include good availability, local cultural aspects, individual preferences, the increasing demand for natural and organic products, and the already validated synergistic effects of herbal medicines. However, ethically, the scope and limits of these drugs need to be established not only by ethnopharmacological evidences but also by scientific investigations, which confirm the therapeutic effects. With this study, we propose to discuss the possible advantages of using herbal medicines instead of purified compounds, the truth and myths about herbal medicines, drug discovery, and the implications for medical education and health care.

Review

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Introduction

Chemical substances derived from animals, plants, and microbes have been used to treat diseases since the dawn of medicine (Koehn & Carter, 2005; Schmidt et al., 2008), while plant-derived products have dominated the human pharmacopoeia for thousands of years and have provided endless source of medicine (Schmidt et al., 2008). Although the medicinal use of willow (*Salix* sp.) dates back 6000 years (DerMarderosian & Beutler, 2011), it was only in 1897 that the first synthetic drug, aspirin, was created out of the salicylic acid extracted from willow barks. This discovery led to an era dominated by the pharmaceutical industry, characterized by the concept of mono-drug therapeutics to treat complex diseases and synthetic drug development by the advent of structure activity-guided organic synthesis and high throughput screening (HTS). Therefore, the use of natural products in drug discovery has been reduced. Synthetic pharmacology broke the connection between plants and human health, making modern medicine primarily dependent on medicines based on single synthetic or naturally-derived molecules, with a single mechanism of action (Raskin & Ripoll, 2004). Undoubtedly, this approach greatly improved medical care, human health, thus extending human life. Simultaneously, physicians started seeing the use of herbal medicines as an "alternative," unqualified, primitive, non-scientific health-care practice for those without access to "real" medical care. However, according to the World Health Organization (WHO), 70-95% of the world's population rely on traditional medicine for their primary health care, and most of these practices include the use of plant extracts or their active components (Sardesai, 2002; Robinson & Zhang, 2011).

Therefore, there is a huge gap between current "best medical practices" and the way people are actually treated all over the world. Sadly, the use of herbal medicines, aka phytotherapics, is hardly accepted by health care providers, mostly based on lack of knowledge. In this article we aimed to discuss the main aspects related to the use of herbal medicines, its acceptance by the medical community, potential advantages, and future directions.

Potential advantages of herbal medicines

Isolated compounds versus herbal extracts

Usually, the natural product is extracted from the source, then concentrated, fractionated and purified, yielding essentially a single biologically active compound (Koehn & Carter, 2005). It still is routine practice for scientists to investigate medicinal plants just to find the single chemical substance responsible for the therapeutic effect (Williamson, 2001). Considering that the biological activity may be the result of the combination of several compounds, the isolation process may lead to its loss or reduction (Raskin & Ripoll, 2004). In fact, it is already well known that sometimes complex mixtures of compounds

in herbal medicines, aka phytocomplexes, have greater effects than isolated compounds (Gomez Castellanos et al., 2009). Information gathered from trials evaluating the action of whole plant extracts versus the action of purified preparation showed that, in many cases, the potency of the later declines as purification of the extract continues into more isolated fractions or single compounds (Cravotto et al., 2010). Thus, one of the advantages of herbal medicines is their complex composition. Their components have multiple activities that result in a greater total activity (Schmidt et al., 2008). Possible explanations include synergy, enhanced bioavailability, cumulative effects, or simply the addictive properties of the constituents, but further research is required (Williamson, 2001).

Exointeractions (interactions with substances not present in the extract) and endointeractions (interactions between substances present within the extract) may have a profound effect on human health. Phytochemical interactions may explain the health effects of regional diets (like Mediterranean), undesirable side effects of drugs, and inconsistent performance of dietary supplements (Lila & Raskin, 2005). Endointeractions have already been demonstrated in tomatoes (lycopene), β-carotene, broccoli (sulforaphane), soy (isoflavones), St. John's wort (hypericin, hyperforin), and cranberries (flavonoids), just to name a few (Lila & Raskin, 2005). A very good example can be found in the study by Capasso et al, who have shown that a standardized extract of *Cannabis sativa* is superior to its main compound, cannabidiol, in inhibiting both rat and human bladder contractility (Capasso et al., 2011).

Isolation and purification of the active principles from an exceptionally complex matrix are the major bottlenecks affecting drug discovery from natural sources, and this reductionist approach may lead to inconclusive findings in clinical trials (Williamson, 2001; Raskin & Ripoll, 2004). Other reasons for not always isolating or fractioning a plant extract are the possible presence of unstable or unknown active constituents and the presence of a range of active compounds, rather than only one (Williamson, 2001).

The "herbal shotgun" approach: a multi-targeted approach

Modern medicine advocates that an ideal therapeutic intervention should act on single, specific targets, like inhibiting an enzyme or binding to a receptor. Medical students are taught that the so called "silver bullet approach" (Williamson, 2001) is the more elegant, desirable, "right-way-to-do" pharmacotherapy. The alleged potential advantages of using a single molecule to treat diseases rely on the fact that it's easier to study its pharmacokinetic and pharmacodynamic properties, mechanisms of action, interactions, and adverse effects. Also, the likelihood of an allergic reaction is potentially lower. The same authors described the use of herbal medicines as an "herbal shotgun" approach, due to the high number of chemical compounds present within the extracts (Williamson, 2001). We believe this is actually an advantage: although the use of a single molecule as treatment may fit the pathophysiology of some diseases, it may not for many others. Diseases with a multifactorial etiology, as well as those with a high incidence of resistance, or variable response to treatments, are usually treated using a combination of different drugs, aiming different targets. Examples include systemic arterial hypertension, atherosclerosis, type-2 diabetes mellitus, tuberculosis, cancer, infections by multi-resistant bacteria, heart failure, and septic shock (Williamson, 2001). Combination of chemotherapy has been the mainstay of cancer treatment for over 40 years. It is reasonable to assume that a mixture of compounds (phytochemicals or synthetic) would have greater bioactivity than a single compound because a mixture of bioactive compounds has the ability to affect multiple targets (Schmidt et al., 2008). Indeed, current guidelines for the treatment of several clinical conditions (*e.g.* septic shock) recommend the use of "bundles" of therapeutic interventions. These interventions have only been proven beneficial when used in association, and failed to show benefits when used alone (Nguyen et al., 2007; Coba et al., 2011). Therefore, the combination of several therapeutic agents or drugs, aiming at different therapeutic targets, is actually already being advocated and practiced by modern medicine, and it is also the most claimed advantage of herbal medicines. In addition, it may be cheaper (Raskin & Ripoll, 2004).

Natural synergism

Modern medicine has only recently learned how rapidly pathogens and cancer cells can develop resistance to single ingredient drugs, and that led to the administration of complex drug cocktails to circumvent or delay the resistance. Plants learned this strategy very early in their evolution in order to survive. By relying on combinations of pleiotropic, multi-targeted molecules, plants may have perfected interacting phytochemical complexes to accomplish many complementary tasks (Koehn & Carter, 2005; Lila & Raskin, 2005). Natural products significantly differ from synthetic drugs by the frequency of different atoms, radicals and spatial configuration (Koehn & Carter, 2005). They have less nitrogen, phosphorus, sulfur, halogens, and more overall molecular complexity, scaffold variety, stereochemical richness, ring system diversity, and carbohydrate constituents (Schmidt et al., 2008). Also, natural products have the capacity to modulate or inhibit protein-protein interactions. As a result, these molecules are effective modulators of cellular processes such as the immune response, signal transduction, mitosis and apoptosis (Koehn & Carter, 2005). Any natural

product isolated from a plant is usually part of a "mini-combinatorial library" of biochemically related analogues, precursors and catabolites that may have overlapping pharmacological activities (Raskin & Ripoll, 2004). While the functions of most secondary metabolites synthesized by plants are still obscure, a significant proportion of these metabolites play a role in defense and cell signaling both on cellular and organic levels. Thus, it is not surprising that mixtures of plant secondary metabolites could be more biologically active than individual components or a random combination of them (Lila & Raskin, 2005).

Synergism between natural products and synthetic compounds

Resistance of microorganisms to multiple antibiotic drugs has also stimulated investigations on synergism between antibiotics and substances isolated from plants. Many studies have shown that the bioavailability of phenolic compounds like epigallocatechin gallate (EGCg), isolated from *Camellia sinensis* (Takahashi et al., 1995; Suresh et al., 1997), tellimagrandin I, present in *Rosa canina* (Shiota et al., 2000), and corilagin, isolated from *Arctostaphylos uva-ursi* (Shimizu et al., 2001), increase the inhibitory effect of commercially available antibiotics on the growth of microorganisms. Moreover, there are reports of potentiated antibiotic effects when associated with plant extracts like the ethanolic extract of *Mangifera indica.* These associations led to a 4-fold reduction on the MIC of tetracycline and erythromycin (Souto et al., 2011). Another example is the *Tectona grandis* methanolic extract. When associated with tetracycline, it has promoted a synergistic effect resulting in a 2-fold reduction on the MIC against *Salmonella typhimurium* strains, and a 4-fold reduction against *Klebsiella pneumoniae* (Purushotham et al., 2010). Synergism between phenolic compounds hydroxytyrosol, verbascoside, tyrosol and gallic acid isolated from Olive Mill Wastewater showed antimicrobial activity, at 100 μg/mL, against *Streptococcus pyogenes, Staphylococcus aureus, Escherichia coli,* and *Klebsiella pneumoniae* (Tafesh et al., 2011). Pseudolaric acid isolated from plants used in traditional Chinese medicine showed synergistic effect with fluconazole against several *Candida* species (Yan et al., 2012). *In vitro* studies on the association of soybean-derived genistein and tamoxifen showed a synergistic effect on the inhibition and growth of some breast cancer lineages (Tanos et al., 2002), similarly to the synergistic effect observed between curcumin (from *Curcuma longa*) and cysplatin (Notarbartolo et al., 2005). Besides those, quercetin, EGCg, thearubigins, and catechin also exhibit synergistic effects with the main chemotherapeutic medicines available (HemaIswarya & Doble, 2006).

The mechanisms of synergism among the compounds present in a single herbal extract are mainly related to two factors: the simultaneous solubility of a group of substances with different polarities, and the multiplicity of targets that these substances can act on, including enzymes, receptors, ion channels, transport proteins, antibodies, and many others (Wagner & Ulrich-Merzenich, 2009)

Real and alleged limitations of herbal medicines

Phytomedicine is not well accepted by the medical community and pharmaceutical industry because of a belief that it lacks safety and efficacy validation and regulations, as well as concerns on poor standardization and quality control, mistakes in nomenclature (Houghton, 1998), difficulties in identifying active ingredients and determining their complex modes of action (Raskin & Ripoll, 2004).

Lack of effect

It's a common belief that, in herbal medicines, the amount of supposedly active constituents is too low to have any relevant therapeutic effect at all. This assumption has led skeptics to dismiss these medicines as placebos (Williamson, 2001). This is not true. In a recent report of the American Association of Poison Control Center (AAPCC) on data from 1983-2009, in the United States, more than 2 million plant ingestion exposures were reported, and only 18.5% of them could be categorized as nontoxic. The remaining cases were categorized as gastrointestinal irritants, skin irritants, anticholinergics, hallucinogens, depressants, and stimulants. Also, plant ingestion resulted in 45 deaths (0.002%) (Krenzelok & Mrvos, 2011). These findings clearly show that the ingestion of plants or herbal extracts can undoubtedly have significant biological effects.

Lack of specific regulations

The indications and posology of plant-derived products vary widely across nations and continents, according to socioeconomic and cultural aspects, as well as to regulations. For example, ginger (*Zingiber officinalis*) can be used as medicine in Europe, as food supplement in the United States, and as tea in Brazil, where until recently, it was not considered medicine. Since 2004, herbal medicines are FDA-regulated and defined as "complex extracts from a plant to be used for the treatment of disease." They are clinically evaluated for safety and efficacy just as conventional drugs, but the process for botanical drugs can be expedited when there is history of safe human use (Raskin & Ripoll, 2004; Schmidt et al., 2008). Recently, Brazil has taken large steps towards

better regulations on botanical drugs, starting in 2006 with the "National Policies on Medicinal Plants and Herbal Medicines." In the last few years, several regulations were published, addressing the use of botanical drugs (as infusions) without medical prescriptions (Anvisa, 2010a), the use herbal medicines with simplified registration (Anvisa, 2008), and other important issues. Brazil has also recently published an updated national pharmacopeia (Farmacopeia Brasileira, 2010) and a national herbal formulary (Anvisa, 2011). The new definitions brought by these regulations made nomenclature more clear (Chart 1).

Chart 1. Definitions according to the Brazilian regulations.

Word	Definition
Herbal medicine	Any medicine obtained exclusively from vegetal raw material, with well-known efficacy, side effects and toxicity, as well as reproducibility and constancy of its quality. Its efficacy and safety are validated by etnopharmacological studies on traditional use, technical and scientific documentation, or in phase 3 clinical trials. Medicines that include in their compositions any isolated substance of any origin cannot be considered herbal medicines (Anvisa, 2004).
Herbal drug	Any purified substance isolated from raw vegetal material with a particular chemical structure and pharmacological activity. They are used as an active principle in medicines. Isolated compounds that underwent any semisynthesis or chemical modification step cannot be considered herbal drugs (Anvisa, 2010b).
Medicinal plant	Any vegetal species, whether cultivated or not, used for therapeutic purposes (Anvisa, 2010b).
Marker	Any compound of class of compounds (e.g. alkaloids, flavonoids, fatty acids) found in raw vegetal materials, that preferably are correlated with the therapeutic effect, which is used as a reference in quality control of the raw material and the herbal medicine (Anvisa, 2010b).
Phytocomplex	Any group of compounds originated from the plant's primary and/or secondary metabolism that are responsible, in conjunction, for the biological effects of a medicinal plant or its derivatives (Anvisa, 2010b).

Complexity of drug discovery

The use of natural products as a complex brings a challenge to their development as drugs. Indeed, important medicines such as ivermectin were developed and marketed in the past as complexes because it was not possible to purify the individual components at a sufficient scale (Koehn & Carter, 2005). The current method of drug discovery, HTS, is not easily adaptable to extracts produced from natural sources. This is mainly due to the high cost per sample, complexity of resupply, difficulty in isolation and characterization of actives compounds, lack of reproducibility, and interference from compounds in complex mixtures (Schmidt et al., 2008). In fact, the reductionist approach of modern pharmacology is not designed to study complex mixtures of substances (Lila & Raskin, 2005). Clearly, many technologies required for the successful discovery, development and production of herbal medicines are not yet in place, and efforts required for their emergence need to be substantial (Raskin & Ripoll, 2004). Nevertheless, while new technology is not in place, ethnopharmacology still is more efficient to discover new drugs from plants.

Lack of evidence

In a recent survey of roughly 1000 herbal medicines, only for 156 of them had clinical trials supporting specific pharmacological activities and therapeutic applications. Moreover, clinical trials actually failed to demonstrate activity for one-third of the studied medicines. In the same survey, the use of about 500 herbal medicines was supported only by *in vitro* and *in vivo* studies. In 200 of the 1000 herbal medicines, only phytochemical studies were found. Also, among the medicines currently available in the Western market, 12% of them did not have substantial studies published. Surprisingly, in this study, there was strong evidence that 1 in 200 medicines were toxic or allergenic, so their use should be discouraged or forbidden (Cravotto et al., 2010).

In another recent study, only 35 studies (1.4%) from approximately 2500 citations on herbal medicines for arthritis met the criteria for inclusion in the review, and only six adequately met all six validity criteria and were at minimal risk of bias (Cameron et al., 2009). The main reason for excluding studies from this review were: a formal diagnosis was not established at baseline, the diagnostic criteria were inconsistent, heterogeneity of diagnostics, absence of control groups, randomization, or full study details, impossibility to identify the herbal components of the intervention, and inadequate statistical analysis (Cameron et al., 2009).

Interestingly, there are many treatments with unknown efficacy. From around 3000 treatments currently used in modern medicine, it is estimated that a surprising proportion of 51% has unverified effectiveness, including many psychological, surgical, and medical interventions, such as cognitive behavioral therapy for depression in children, thermal balloon ablation for fibroids, and corticosteroids for wheezing in infants (Clinical Evidence, 2011). There are some situations in which, although we know that a treatment was never proven to be effective, its wide use makes placebo-controlled studies on these interventions to be considered unethical (Als-Nielsen et al., 2004).

It's also said that many studies on herbal medicines, although well designed, are probably

underpowered and the observed lack of effect may be due to type II errors (Cameron et al., 2009). A type II statistical error refers to the situation where the study failed to reject the null hypothesis when it is actually false; in other words, it failed to detect an effect that actually exists. According to Descartes (Descartes, 2011): "it is better to repudiate a dozen truths than to admit a single error, a false theory." However, the amount of human and financial resources that are spent on these inconclusive studies could be better used. On the other hand, larger sample sizes may have the power to detect small "statistically significant" effects that are not necessarily translated into clinical benefit.

These findings show the need for future studies that comply with the current best scientific methods. Many efforts have been made in this direction, such as the Consolidated Standards of Reporting Trials (CONSORT) statement, which tries to help authors and editors to improve reporting of randomized controlled trials, including the herbal interventions ones (Gagnier et al., 2006). Some authors have suggested the creation of a database of clinical trials to improve the quality of study design. Clinicaltrials.gov is a good example of such initiative (National Institutes of Health, 2011).

Standardization

Other contributing factors to the negative results of some trials are the functional and structural diversity of compounds in herbal medicines, variable content in different batches of plant materials, and inconsistent use of extraction methods and formulations (Raskin & Ripoll, 2004). Indeed, the complexity of plant extracts makes the development of an evidence-based herbal medicine a difficult task that requires a huge analytical effort and manufacturing skills to produce well-defined, standardized herbal preparations (Cravotto et al., 2010). There is also a need for the development of new methods for pharmacological studies and clinical trials evaluating the effects produced by complex mixtures of compounds (Lila & Raskin, 2005).

Besides all that, there may be variation on the chemical composition of plants according to the climate, soil type, and interactions with the environment. We believe that urbanized, contaminated, or artificially fertilized areas are not adequate for production of medicinal plants. They should be cultivated in environments that mimic the wild as much as possible. This would provide an ecologically well-balanced medium with all the biotic and abiotic interactions that stimulate the metabolic routes. These routes produce the secondary metabolites that are responsible for the therapeutic effects. It is possible that, in the future, we will have specific areas for the production of certain medicinal plants, in the same fashion we have today with selected areas where different varieties of grapes are grown, resulting in wines with a particular flavor and bouquet. This scenario can contribute for a standardization that should start in the field throughout the post-harvest processes for the production of herbal medicines.

Education

Ethical prescription of herbal medicines certainly depends on the application of methods of standardization that can assure a consistent chemical profile, the absence of contaminants and, consequently, desirable and reproducible therapeutic effects. It has become vital to educate health care professionals and show that there are some features which are unique to herbal medicines and which contribute both to efficacy and safety (Williamson, 2001; Raskin & Ripoll, 2004). In recent surveys among American and German physicians and medical students, the self-evaluated knowledge about complementary and alternative medicine was poor (Abbott et al., 2011; Munstedt et al., 2011). Interestingly, both groups believed that it should be included in medical education; however, they believed that it demanded more investigation and should be taught criteriously (Munstedt et al., 2011). This would include choosing specific contents based on evidence, demographics and medical conditions, providing students with the skills that are necessary for future learning (Abbott et al., 2011; Munstedt et al., 2011). This task can be more easily accomplished with the involvement of multidisciplinary teams, supported by medical schools and associations that have real interest in developing studies with strong scientific methodology, free of prejudice.

Conclusion

Herbal medicines are widely used all over the world. However, there is still a huge gap between "best scientific evidence" and what people actually use to treat a disease. The lack of acceptance of herbal medicines by medical community is based both on false and true premises. It is important that the study of Herbal Medicine is offered to all health care professionals. Both research groups and the pharmaceutical industry should put their efforts on high-quality studies on herbal medicines, pursuing an "evidence-based herbal medicine," making people's health care better and safer. Maybe then we'll see "health for all" as reality

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