Validating ethno- medicines with a view to developing new drugs

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Abstract

The botanical medicine industry is experiencing rapid growth world-wide. Annual growth rates are between 10-20% in most countries. Botanical medicines, as distinct from pharmaceuticals, are produced directly from whole plant material and as a result, they contain a large number of constituents working in conjunction with each other, rather than a single, isolated active compound. These botanical medicines have long histories of traditional use and which confirm efficacy. With the growing emphasis on quality control, safety has become a key factor in assessing the value of botanicals.

Key words: drug discovery, ethnomedicine, plants, traditional medicine, Mauritius.

Definition

The development of traditional medical systems incorporating plants as a means of therapy can be traced back to the Middle Paleolithic age some 60,000 years ago.

Ethnomedicine, which may be defined broadly as the use of plants by humans as medicines, is a highly diversified approach to drug discovery that involves observation, description, and experimental investigation (screening) for possible biological/medicinal properties from indigenous drugs. It is based on botany, chemistry, biochemistry, pharmacology, physiology and other disciplines such as anthropology, archaeology and history that contribute to the discovery of natural products with medicinal activity[1]. According to the World Health Organization, more than 60 % of the world's population use ethnomedicine as part of their primary health care[2].

Being given that plants have been used by humans (often hundreds or thousands of years), one could therefore expect any bioactive compounds obtained from such plants

to have low human toxicity. Therefore the goals of using plants as possible leads for therapeutic agents are four folds: a) to isolate and characterize bioactive compounds for possible use as drugs, e.g., the cardiac drug, digoxin, as well as morphine andtaxol; b) to produce bioactive compounds of novel or known structures as lead compounds for semi-synthesis to produce pharmaceuticals that may display lower toxicity and for which patents can be acquired, e.g., metformin, verapamil, and amiodarone; c) to use agents as pharmacologic tools; and d) to use the whole plant or part of it as a herbal remedy, e.g., garlic, bitter melon.

With the use of traditional plants as herbal remedies over the centuries, some of these plants obviously may be toxic within a given endemic culture that has no reporting system to document these effects. It is unlikely, however, that acute toxic effects following the use of a plant in these cultures would go unnoticed or unreported. The plant would then be used cautiously or even lose its importance in the local usage. However it is worth mentioning that in case of chronic toxic effects, the symptoms may be less likely apparent at the early onset. Should be plant(s) prove to possess such undesirable properties; its use should be immediately discontinued.

In addition, many of the plants, which are use for their medicinal properties, possess an array of chemical diversity of secondary metabolites as a result of evolution. These medicinal properties that the secondary metabolites could possess may be equal or superior to that found in synthetic combinatorial chemical libraries.

Approaches to Drug Discovery Using Plants

Plants have long been a very important source of drugs and many plant species (like microbes) have been screened to see if they contain substances with therapeutic activity.

Many plant drugs of long-standing were discovered by investigating the scientific basis of old folk remedies to determine the active ingredient in the concoction. Several reviews are available in the literature pertaining to approaches for selecting plants as candidates for drug discovery programs[3,4] .

As mentioned earlier, the discovery digoxin from foxgloves (an old discovery) used to treat heart failure is a classical example whilst a recent discovery in the form of paclitaxel (discovered in yew leaves) has shown promising anti-cancerous propertiesIn earlier times, all drugs and medicinal agents were derived from natural substances, and most of these remedies were obtained from higher plants.

Drug development is a complex process, and only companies with a consequent investment in research and development can afford to bring drugs from conception to market. Today, many new chemotherapeutic agents are obtained synthetically, based on "rational" drug design. The study of natural products has many advantages over synthetic drug design. The former leads to materials having new structural features with novel biological activity. In this context not only do plants continue to serve as possible sources for new drugs, but chemicals derived from the various parts of these plants can also be extremely useful as lead structures for synthetic modification and optimization of bioactivity. The starting materials for about one-half of the medicines we use today come from natural sources. There is no doubt that the future of plants as sources of medicinal agents for use in investigation, prevention, and treatment of diseases is very promising.

In the context of isolation and screening for chemicals that may possess medicinal properties from plants, different approaches can be used. The following is a brief

summary of the current approaches being used by scientists to isolate and characterize these agents.

Random selection followed by chemical screening. This technique is also known as phytochemical screening approaches whereby the plants are analysed for alkaloids, terpenes and flavonoids etc. This approach has been used in the past and is still being used in the developing countries. The tests are simple to perform, but false-positive and false-negative tests often render results difficult to assess[5]. More important, it is usually impossible to relate one class of phytochemicals to specific biological targets; for example, the alkaloids or flavonoids produce a vast array of biological effects that cannot be usually predicted well in advance.

Random selection followed by one or more biological assays. In the past, plant extracts were evaluated mainly in experimental animals, primarily mice and rats. The most extensive of these programs were sponsored by the National Cancer Institute (NCI) (24,31-34) in the United States and the Central Drug Research Institute (CDRI) in India (35-41). More than 35,000 species have been screened in vitro primarily. However between the period 1960-1981, the NCI has sponsored in vivo screening for biological properties emanating from these plants. Two major pharmaceutical agents namely taxol and camptothecin (42) were discovered through the program. Several other plant-derived compounds has turned out to unsuccessful in human studies. The above process has been discontinued since 1986 onwards by the NCI who has from then on embarked on to continue to collect and screen plants using a battery of 60 human tumour cell lines and also initiated

a screening of plants for anti-HIV activity in vitro. Calanolide A, has been discovered through this program and is currently in its Phase I clinical trials. (43,44).

Follow-up of biological activity reports. These reports showed that the plant extracts had interesting biologic activity, but the extracts were not studied for their active principles. The literature from the 1930s through the 1970s contains these types of reports.

Follow-up of ethnomedical (traditional medicine) uses of plants. Several types of ethnomedical information are available especially in the different cultures mainly in the Asian and African continents. It is of no denying facts that plants used in organized traditional medical systems. Ayurveda and traditional Chinese medicine have flourished as systems of medicine in use for thousands of years.

These systems which include practice and theory are still in place today because of their organizational strengths, and they focus primarily on multicomponent mixtures[2]. There are still certain beliefs in though Western medical science that still view such systems as lacking credibility and validity despite the fact that these plants are undeniably still being widely used by a wide section of the population of poorer countries on this planet. One should however recognize that adverse effects from those widely used plants are not well documented, and efficacy of these plants and plant mixtures is more difficult to assess by Western scientific methods.

The Value of Ethnomedicine

At first interest in the western countries especially the United States, was directed toward antifungal and of antiviral agents[2,3] from traditional medicinal plants. The approach was to send scientist including botanist as well as physician teams to tropical areas to assess

firsthand the use of plants by traditional healers and to collect interesting plants and assess them for validity in the Shaman laboratories. It is extremely difficult to assess the value of any approach to the use of higher plants to develop new drugs.

Several active compounds were discovered. Unfortunately many failed to live up to the promise. Many plants/extracts were either toxic or failed in the clinic. Priorities were then shifed or re-toward screening for possible antidiarrhoeal activity. A successful candidate that emerged from such programs is SP-303, an oligomeric proanthocyanidin (81). SP-303 has proven to be clinically efficacious and is currently marketed as a dietary supplement for diarrhoea. In addition, a major effort has also been directed toward discovery of novel antidiabetic agents, which resulted in the discovery of several patented compounds: cryptolepine[6-7], maprouneacin [8] .

The World Health Approach.

During the past decade, traditional systems of medicine have become a topic of global importance. Current estimates suggests that, in many developing countries just like Mauritius, a large proportion of the population relies heavily on traditional practitioners and medicinal plants to meet primary health care needs. Although modern medicine may be available in these countries, herbal medicines (phyto-medicines) have often maintained popularity for historical and cultural reasons. Concurrently, many people in developed countries have begun to turn to alternative or complementary therapies, including medicinal herbs[2].

Even with this vast array of data, few medicinal plant species have been scientifically evaluated for their possible medical application. Safety and efficacy data are available for even a few plants, their extracts and their active ingredients, and the preparations

containing them. Furthermore, in most countries the herbal medicine market is poorly regulated and herbal products are often neither registered nor controlled. Assurance of safety, quality and efficacy of medicinal plants and herbal products has now become a key issue in industrialised and in developing countries. Both the general consumer and health-care professionals need up-to-date information on the safety and efficacy of medicinal plants.

Thus it is with this background that the project on the validation of some medicinal plants of Mauritius was carried out. The plants that have been selected are widely used and are important not just for Mauritius but for the region as well.

The purpose of this work has been to provide:

- Preliminary scientific information on the safety and efficacy of the widely used medicinal plants in Mauritius. (The list of plants has been made from the survey carried out in Mauritius and Rodrigues between 1990-1994)[9].
- The preliminary validation process was based on the following assays: anti-bacterial, anti-fungal screenings as well as the toxicity tests have been effected. The antibacterial assays were complemented with an assessment of their ability to contract and relax, *in vitro*, the ileum of rats and frogs.
- Provide a model and protocols for the preliminary evaluation of other medicinal plants.
- Study from the phytochemical and pharmacological point of view some of the endemic medicinal plants of Mauritius.

In Mauritius, work on ethnopharmacology has been concentrated over the years to assess the first hand use of medicinal plants by the local population[9] From there on, laboratory

studies have been to try to evaluate the possible medicinal properties of these palnst using phytochemical analyses as well as in vitro and in vivo studies in small animals. There are advantages and disadvantages of using plants as the starting point in any drug development program. If one elects to use information suggesting that specific plants may yield useful drugs based on long-term use by humans (ethnomedicine) one can rationalize that any isolated active compounds from the plants are likely to be safer than active compounds from plants with no history of human use. Also, plants are a renewable source of starting material in many but not all cases.

The trend nowadays especially in industrialized and rich countries is to seek bioactive compounds from plants that will serve as lead compounds for synthetic or semisynthetic development, to assure patent protection. Thus, this diminishes the need to isolate novel bioactive structures from plants, since the ultimate goal is to use the active compound to produce synthetic derivatives with lower toxicity and higher efficacy.

In summary, the industrial approach most likely to be used to evaluate plants for bioactive compounds will be based on random collection followed by automated, robotized, in vitro screening. The ethnomedical approach lends itself more to being carried out in academic institutions. Since plant-derived drug discovery efforts began, the ethnomedical approach has been more successful. However, the random collection of plants, which provides the highest biodiversity, is forging ahead as the method of choice. The latter approach requires significantly more financial resources than the former.

Conclusion

The body of existing ethnomedical knowledge has led to great developments in health care. With the rapid industrialization of the planet and the loss of ethnic cultures and customs, some of this information will no doubt disappear. An abundance of ethnomedical information on plant uses can be found in the scientific literature but has not yet been compiled into a usable form. Collection of ethnomedical information especially in the poor countries or developing countries remains primarily an academic endeavour of little interest to most industrial groups.

Findings from our screening studies have provided important baseline data regarding possible biological properties of the indigenous plants. As far as we are aware, it is the tradition in Mauritius that for most ailments and symptoms, lay people still rely heavily on the use of tisanes and medicinal plants despite the fact that not much is known about the possible beneficial and side effects of the species being used.

Our findings also highlighted the risks of use or overuse or abuse of these plants. Though our work definitely showed that many indigenous plants do possess quite useful biological properties especially when it comes to the effects on the intestine (whereby the extracts could be used against diarrhoea), the properties displayed on the aorta should not be overlooked. Almost all the extracts screened did show contractile properties on the rat aorta strips to various degrees. Once again use of these plants by persons who may have coronary artery diseases should be discouraged. The reason being that though the intestinal properties are well appreciated, contraction on the aorta could lead to serious cardiac disorders such as angina.

Toxicity tests of the various extracts carried out on a small number of rats have revealed that each extract tested has led to an increase in mean weight gained as compared to the controls. At this stage one has to be cautious in interpreting the data.
No statistical analyses could be performed since tests were performed on too small a sample size. The possible mechanisms or reasons for the observed gain in weight in the animals are not clear yet.

Further work should in fact consider testing a smaller number of extracts that have caused a greater gain in body weight on a larger sample size of laboratory animals. Measurements in these proposed studies should also include determination of lipids levels by colorimetric methods using commercially available kits (to be adapted for small animals).

- Studies of the various extracts on the animals should be performed over a longer period of time.
- Effects of extracts on body weight should be also studied on other animals such as rabbits.
- Studies on the urinary excretion of metabolites could also be envisaged.

In conclusion, our data form the basis of certain stages of Phase I screening studies for potential pharmacological studies and findings at this stage should be dealt with in a very cautious manner. It would be advisable now that further studies are undertaken on these indigenous plants to establish relevant properties that could lead to their effective use by people.

N.B. This work is the first of its kind in attempting to validate the medicinal plants of Mauritius. It will need to be updated with further detailed and more rigorous testing of the plants mentioned therein. The work reported here is purely of a scientific nature.

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