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Difficulties of Drug Development from Thai Herbal Medicine

Tanawan Kummalue*

Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, 10700, Thailand

Abstract

Traditional medicine has long been widely used in many countries around the world. In Thailand, over 700 species of medicinal plants have been prescribed by Thai traditional doctors whereas few scientific data on the pharmacological properties have been reported so far. For example, four Thai medicinal plants that have been investigated by our research group were *Ficus hispida* L., *Sapindus rarax* DC., *Erycibe elliptilimba* M.&C., and *Pouzolzia indica* L. with a view to be further developed as anticancer agents. Moreover, three Thai herbal remedies composed of several kinds of plants were also evaluated in this concept.

Many difficulties have been found while performing the medicinal plant research for drug development. All the processes such as collection of raw plant material, identification of medicinal plant, and extraction techniques used for investigation and clinical trial, etc, have lots of pitfalls, and hindrances. In this article, common difficulties experienced during the processes of our Thai medicinal plant research for drug development were described in detail.

Keywords: Medicinal plant research; Thai; Difficulties; Drug development

Introduction

Traditional medicine, according to the World Health Organization (WHO), refers to the health practices, knowledge, skills, and beliefs incorporating plant, animal, and mineral-based medicines, spiritual therapies, manual techniques, and exercised, applied singularly or in combination to treat, diagnose, and prevent illnesses or to maintain well-being. Moreover, if the material used is of plant origin, then it is called traditional herbal medicine. Traditional medicine has been widely used for over centuries in many countries around the world such as China, Tibet, India, and Thailand, etc. Their practices vary from country to country. Among these countries, Chinese traditional medicine is the most popular and well-known, while medicinal herbs are ones the most commonly used in practice in this field [1]. In Thailand, over 700 species of medicinal plants have been reported, used, and prescribed by Thai traditional doctors [2]. According to the previous report, only 10% of higher plants around the world have been studied so far [1].

For example, four Thai medicinal plants that have been investigated by our research group were *Ficus hispida* L., *Sapindus rarax* DC., *Erycibe elliptilimba* M.&C., and *Pouzolzia indica* L. They were all investigated for antiproliferative activites including effects on cell cycle and apoptosis with a view to be further developed as anticancer agents. In short, all of these plants showed antiproliferative activities on human cancer cell lines such as breast, lung, and leukemic cancer cell lines, etc. with significant ED_{50} values [3-7]. Interestingly, they also demonstrated the inhibitory effects via apoptotic pathway with some influence on cell cycle especially at G2/M phase. Three Thai herbal remedies were also evaluated for their antiproliferative effects [8,9]. As reported, none of them showed the growth inhibition on human cancer cell lines, whereas two of these Thai herbal remedies demonstrated the growth inhibitory effects in conjunction with chemotherapeutic agent, doxorubicin.

As mentioned earlier, very few of the higher plants, including Thai plants, have been investigated for drug development. Several difficulties in Thai medicinal plants research have influence on the success of achieving this specific goal. The following common difficulties could be found and have to be concerned when performing this kind of research.

Difficulties of Drug Development from Thai Herbal Medicine

Collection of raw plant materials

Collection of raw plant materials is the first step of performing the research and also the first difficulty to confront. It is the first important step which can lead to the wrong result at the end. This is because location and time of collection of medicinal plants have high impact on the bioassay screening results.

Location of collection refers to the cultivation area or geographical area or place of that plant species. Although most medicinal plants usually grow in the wilderness, different areas will have different nutrients which will be very special for each medicinal plant. Therefore, the chemical compositions in the plant that grows in one place or province might be different from those of the same plant when it grows in another province [10,11]. These will reflect the difference in quality of the plant extract and lead to the inconsistency of the repeated results. It is essential that we should collect the plant from a specific area if that plant shows high efficacy.

Time of collection means the appropriate climate or season when these plants are collected. For example, subterranean organs including root and rhizome of Thai herbal medicine names “Non-Tai-Yak”

***Corresponding author:** Tanawan Kummalue, Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, 10700, Thailand, Tel: 011-662-4181367; Fax: 011-662-4181367; E-mail: sitkm@mahidol.ac.th

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(*Stemona collinsae*) should be collected only at the end of the rainy season through early winter season, which is the peak of its special chemical compositions suitable for one cancer-treated Thai herbal remedy. That means the exact time of collection reflects the good properties, high quality, and the high bioactive content of components in the plant [12].

Therefore, it is difficult to prepare reproducible plant extracts or preparations because the chemical compositions in the plants are affected by many factors, including the climate and soil. Many researchers have realized these problems. Some companies or academic centers have, thus, established good agriculture practice (GAP) for plant cultivation so that high quality products can be obtained [13].

Identification of plant materials

It is important to ensure a right collection of the herbal plant before starting the entire process of study. In Thailand, one herb used in different areas may have different names but which are synonymous. For example, "*Sophora exigua*", a Thai herb which is named pan-din-yen in one province is also named as nom-rau-see, and nom-rat-cha-see in another [14]. Isonym is that which refers to different species but named with the same local names. The isonym also causes problem in identification of the correct plant for studying. For instance, *Smilax corbularia* Kunth, family Smilacaceae, and *Premna herbacea* Roxb, family Verbenaceae, both have the same name in Thai called "Khao-Yen-Nua".

Identification of plant materials usually can be processed by morphological, microscopic, physical, chemical, and genetic identification. In brief, morphological identification (or descriptive identification) is to verify the geographical information, and morphological characteristics of plants. Microscopic identification is a method using a microscope to identify plant morphology and anatomy. Physical and chemical identification are powerful tools for determination of the plants. Physical identification includes relative density, optical activity, refractive index, freezing and melting points, whereas chemical identification means color reaction, and precipitation reaction including ferric hydroxamate reaction of coumarin and lactone, Libermann-Burchard reaction of saponins, and gelatin precipitation reaction of tannin, etc. DNA molecular genetic marker as genetic identification is a newer unique and powerful technique in application in herbal medicine such as restriction fragment length polymorphisms (RFLP), DNA sequencing, and DNA chip technology [1].

Therefore, it is difficult to get the right herbs for testing in the herbal medicinal remedy, especially if the plants posses synonym and isonym phenomena [15]. It would be much better if Thai traditional doctors who always use and prescribe these medicinal plants to treat patients would help to collect the herbs in order to get the right ones for the investigation. Additionally, it is necessary that all plants collected for studying should be confirmed and identified before starting investigation.

Extraction method

Usually, the medicinal plant research should be performed on the basis of references in traditional systems. In ancient times, Thai traditional doctors often used herbal medicine in the form of mixture with several kinds of plants by boiling with water. This technique is called decoction. As we followed this traditional technique of extraction, we discovered that, unfortunately, most of the extracts we got from this method showed no activity on human cancer cell lines [8,9]. Therefore, several methods of extraction techniques are now always applied, such as methanol extraction, water:methanol extraction, and ethyl acetate extraction. These techniques of extraction may produce different bioactive compounds from the same plants than when extracted with decoction, and thus will result in different pharmacological activities from the traditional usage [16].

In our studies, most Thai herbal plants have been extracted with Soxhlet extraction. Bioassay-guided isolation have been performed with different solvents such as absolute methanol, ethyl acetate, and water:methanol to get the several groups of the extracts which we used for further study. One important difficulty found was that some extracts could not be dissolved with the cell culture medium used and this resulted in unexpected low extract concentration. Occasionally, two emulsion layers and/or undissolved droplets could be seen in the solution. In our experience, this phenomenon could be eliminated by dissolving the extracts with 100% dimethyl sulfoxide (DMSO). However, bioassay screening using cell culture technique, DMSO can kill the cells if a high percentage is used in the testing system. From our previous reports, the final percentage of DMSO in the solution without toxicity on the cells must not be over 0.5%.

The steps of clinical study are also difficult when extracting the medicinal plant with some solvents that are not safe for investigation in human beings. Nowadays, the herbal extracts have been developed into the forms that are close to the original traditional preparation by using heat dry or spray dry after boiling. In such case, the properties of the herbs should be effective, safe, and suitable for processing in therapeutic evaluation.

Standardization and quality control of the herbal formulas products

Standardization refers to the chemical analysis of components, especially bioactive and major components for identification or comparison of plants species. The most popular method nowadays is fingerprints of high-performance liquid chromatography (HPLC) [17]. Thin layer chromatogram (TLC), which is usually used by our research group, is also easy, and is a common one with low cost investment. Quality control refers to quantitative and qualitative analysis of the medicinal plants. Quantitative analysis is characterization of the main compounds from herbs, while qualitative analysis means the safety examination, involving, for example, microorganism's contamination in the herbal products, which is really the most serious problem especially for preparing the herbal drug for using in human. Not only for safety determination, qualitative analysis also included the analysis of the whole components in the herbal formulas [18].

As mentioned before, Thai traditional doctors always used the herbal remedies which are composed of several kinds of medicinal plants by boiling with water until water was reduced to about one-third level from the beginning. During this process of the preparation, the bioactive compounds in the herbal remedy will interact to each other and thus produce new complexes and later changes in the pharmacological properties [19]. The newly-formed complexes might be different from the original bioactive compounds found in each plant and difficult to analyze. Consequently, plenty of new complexes will complicate the standardization and quality control. This is the new challenge in herbal formulas studies in this period.

Therefore, standardization and quality control of the herbal remedy is very difficult to perform especially in herbal formulas with many new bioactive complexes in the mixtures. Most of all, the contamination of microorganisms in the plant extracts from both herbal formulas and single plant is one of the quality control problem that needed to be recognized. The good manufacturing practice (GMP), quality assessment (QA), and standard operating procedures (SOPs) could ensure in the quality control of medicinal plants and have already been applied in several countries.

Clinical studies of herbs

In Thailand, performing herbal research in clinical studies always needs ethical approval. One important official paper to be considered by the ethical committee is the official patients' records of Thai traditional doctors that used the herbal remedies. However, most Thai traditional doctors who treated patients have rarely recorded these kinds of paper work, unlike the doctors trained in the Western style. Regarding this issue, time is needed to complete recording and doing the patients' registration necessary for ethical permission. Also it is difficult to find volunteers to take the herbal medicine which has not yet been proven for efficacy and safety in cancer therapy.

Clinical trial design is very important for herbal drug evaluation in terms of efficacy, and safety. Although following the traditional theories, there are several points to be considered at this step such as dosage and form of herbal drug, number of patients study group, and comparison between subjects and controls, etc. Dosage of herbal drug as compared to original herbal formulas is an essential piece of information needed for a successful clinical trial. The number of subjects and controls, including details of diseases, will affect the clinical data and results, if this is not properly designed. Moreover, as herbal medicine is used in sequential doses, the course of treatment in clinical trial design is also important for final efficacy assessment.

Conclusion

In comparison with modern medicine, medicinal plants research is challenging particularly research in herbal formulas, which is very difficult both in standardization and in quality control. At present, not very many Thai medicinal plants have been yet investigated for drug development, which might be due to the many difficulties confronted during the necessary processes. Drug development from Thai herbs has still a long way to go. Strong support for this kind of research, including funding, equipment, and manpower, will certainly influence its success in the future.

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