Integrating Basic Sciences into Global Health by Implementing the Translational Research

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Abstract

An emphasize on herbal medicine in cancer therapy is also included as an example of translational research implementation. A translational research in Faculty of Medicine, Universitas Padjajaran, has been conducted to develop a novel genomic approach (herbal genomic) on herbal crude extracts. This study focuses on the effects of the extracts on specific gene expressions. In this aspect, the concept of molecular targets is slightly different from pharmaceutical approaches that aim to find compounds that interact with a specific molecule or macromolecule with known function. In this research strategy, the herbal genomic approaches involve screening of herbal extracts that affect particular gene expression related to cell responses rather than a single proteins. The determination of herbal concentration is based on differential gene expression before and after treatment which is analyzed by real time PCR. The results are being compared to the existing small molecule (active molecule) on the gene expressions. All these academic activities require biomedical research workforce to implement the translational research which, in the Faculty of Medicine, Universitas Padjadjaran, is fulfilled by involving the postgraduate students. New crude extract formulation plus specific gene expression profile is a concept required for developing chemotherapeutic agent in Indonesia. Hopefully, this review can support increased cooperation between hospital and academic institutions in implementing translational research in Indonesia.

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Introduction

The global health program is very popular in the millennium development era because it proposes efforts to improve the health of people in many countries, including for diseases typically associated with advanced economics. Varmus and Timble have analyzed that the program is directed towards diseases-related problems in developing countries including those related to infectious diseases and nutritional deficiencies.[1] The increased number of cancer deaths in developing countries has also drawn the attention of the health community in the world. We are interested in the epidemiological data shown by Vermus and Timble that 25% of life threatening cancers in the developing world are caused by infections.[1] Despite the fact that successful effective prevention efforts for some infectious diseases and therapy for cancer have been implemented, they are not adequate yet to satisfy the community needs, especially in Indonesia. This situation affords an opportunity to create innovations in our strategy to develop translational research in order to strengthen the vision of "from bench to bedside" which focuses on oncology and infection.

From the perspective of the government policy to develop and increase the utilization of generic drugs in Indonesia, the use of natural resources that takes in the form of traditional medicine is strongly recommended. Still, clinical trials to provide strong evidence supporting this national commodity in medicine should be conducted. With this policy, it is expected that the needs for affordable medicine among people of Indonesia can be met and domestic medical industries will grow.

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This review describes studies that are based on current gene expression science in herbal chemotherapeutic development. The focus of this review is herbal medicines that can be tested and applied in clinical trials through translational research.

Cancer or neoplasm is a group of diseases with multifactorial etiologies that causes abnormal cell proliferation. Basically, cancer is caused by abnormalities in cell cycle and its regulations which are organized by specific proteins coded by specific genes. The development of natural products for cancer therapy in Indonesia has not shown any progress in terms of clinical trials, which leads to a situation where almost all cancer therapies depend on imported products. The barriers in developing cancer therapy in Indonesia are due to rigid strategy of using the bioactive form of the natural products where the modern medicine is only based on the active molecule. This approach is time consuming and needs high budget to obtain optimal results. In addition, the cell death and survival pathways have not yet completely elucidated when the avoidance of some specific types of cell death in cancer is very important to prevent injury in normal cells.[2,3]

Some cancers are drug resistant and others tend to relaps. This indicates that the cell deaths associated to the cell survival pathway do not involve a single pathway only, which leads to difficulties in killing cancer cells. Therefore, the cancer treatment cannot rely on a single active compound and should be based on a combination therapy to eliminate cancer cells.

Enthusiasm on developing natural products as therapeutic agents in cancer has grown in Indonesia, especially for natural sources that are already known as having anticancer activities. However, the scientific aspect of it has not been tested yet. This problem is not easy to solve and a multi-discipline cooperation is needed, both from basic and applied sciences. This will be an opportunity to innovate by integrating translational research into the ongoing studies.

The Global Concept of Herbals Development in Medicine

Herbal medicine is made of natural substances containing small molecules, macromolecules, and complex molecules/crude extracts. It has been noted that 60% of the approved regimens used for treating cancer are derived from natural sources.[4,5] Traditional Indonesian medicine is a well-known herbal decoctions and consumed by many people in Indonesia as a supplement for maintaining their health. Unfortunately, information on their mechanism and potential drug ability is limited making it difficult to develop herbal medicine. Herbal decoctions can nourish the body holistically and support various organ systems.[6] The general concept of this phenomenon is based on natural products and tissue/organ interaction (Fig. 1) which can be studied from the gene expression perspective, resulting in opportunities for future research and

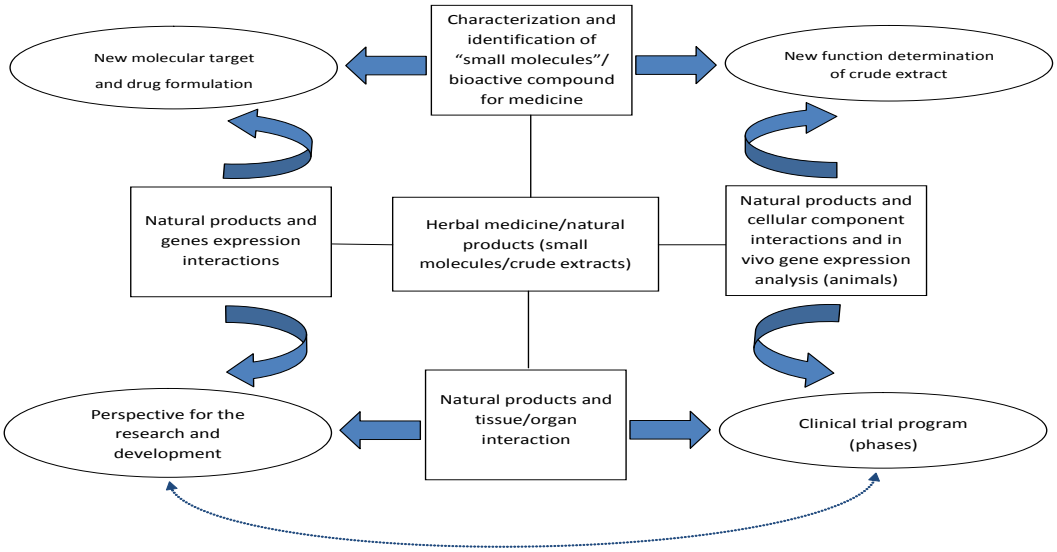

Fig. 1 The Global Concept of Herbal Development in Medicine

development. Furthermore, the scheme shows that natural products and cellular component interactions and in vivo gene expression analysis perspective can be continued into a clinical trial program. On the other hand, after the in vivo experiment is conducted, the herbal medicine can be developed based on the new functions found in the crude extracts. A research program that includes characterization and identification of natural products supported by gene expression interaction to promote new molecular target and herbal formulations is also available. Jain used natural products for treating cancer and they listed name of herbs associated with method and use for cancer treatment including *Phyllanthus niruri* and *Vitis vinifera*.[7] Jang published the natural product derived from grape's resveratrol having chemo-preventive activity.[8] Both *Phyllanthus niruri* and *Vitis vinifera* are investigated in our research program as a single agent and combination to treat cancer cells.

In recent years, it has been reported that many natural substances have been used for prevention and treatment of various degenerative diseases, such as diabetes, hypertension, obesity, cancer, and other similar diseases.[9-12] Colic and Pavelic reported their research about natural compounds with multifunctional activity and promoted both cytostatic and cytotoxic activities towards cancer cells.[13] Historically, human choose non-toxic vegetable or plants. It means in human intestine or gastrointestinal tract, the plant will be digested into small molecules, macromolecules and/or still in complex molecules that meet body requirements (Fig. 2). These molecules enter blood circulation and interact with target cell by binding cell surface proteins or enter the cytoplasma to bind with specific proteins. These scientific facts show that although there are many molecules surrounding the outer part of the cell target, only few are able to enter the cell and interact with specific receptors or proteins. These interactions trigger the corresponding pathways and cellular responses. In cancer cell, many possible cellular responses will appear, such as cell death, cell silence, cell resistance, cell migration, cell competition, cell survival, and cell senescence. Each cellular response will impact related organs/tissues. Therefore, it is possible to expand global health from gene expressions to personalized health care.

This finding is particularly interesting in terms that the functional assay was used to evaluate inhibitory effect of this herbal crude extract on cell proliferation compared to the same effect of chemotherapeutic agents (doxorubicin and cisplatin).

The Scientific Aspects of Herbal Genomic

It has been identified by the scientific community that important issues related to herbal medicine should be addressed to retain the best of the current academical research strategy including

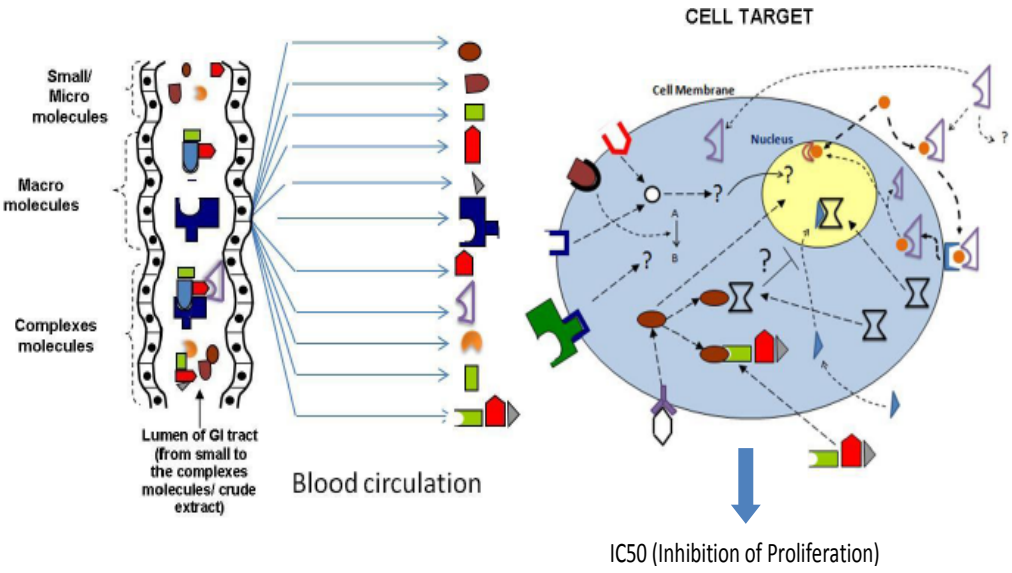

Fig. 2 Molecular Interactions of Crude Extract and Target Cell

avoiding stagnant basic theories and supporting the need of clinical trials. It is noted by Nilsen and Bierer that the translational medical research is an important, legitimate, and necessary effort for scientists in universities and research hospitals.[14] Interestingly, a central goal of academic medical institutions is to ensure that their innovation ultimately benefit patients. A tentative design that combines both traditional and modern medicine including its pharmaceutical approach in equal share is shown (Fig. 3). An overlapped area of both circles containing herbal genomics is seen. This herbal genomics cover the scientific issues starting from genome to the cellular responses. The herbal genomics are embedded into both traditional and modern medicines.

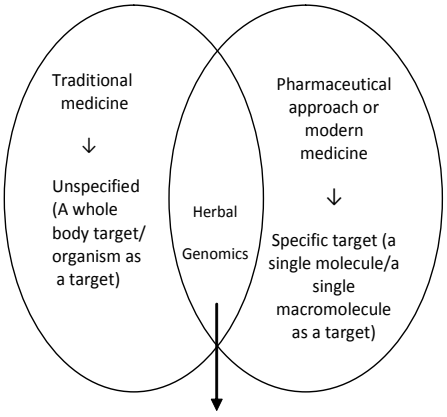

Fig. 3 Herbal Genomics as a Mediator between Traditional and Modern Medicine Strategy

The profile of gene expressions is used as an indicator of the effective dose of related herbal extract to inhibit cell proliferation or increase cell death. This molecular level interaction has been implemented to determine effective dose of herbal crude extract.[15]

The characterization and identification of the natural products may involve various molecule types including small molecules, macromolecules and complex molecules (Fig. 1). These substances are going to be analyzed and developed by pharmaceutical approaches such as clinical trials that are targetted to a single protein or a single molecule. Our concept uses herbal products as a crude extract formulation relying on gene expressions leading to cellular responses and not only a single protein. If this product can be tested in vivo, a crude extract as an anti-cancer can be created. Gene expressions which play a role in cell cycle and other genes associated with cell death (apoptosis, necrosis, autophagy) will be analyzed.

The scientific aspects of this approach include the use of molecular biology concept based on interactions between herbal extracts and the cellular components of cancer cell as the molecular target that affects gene expressions. These targets can only be gained by determining the concentration of each herbal component compared to the cancer drugs such as cisplatin and doxorubicin. The equality of concentration of cisplatin and doxorubicin in killing the cancer cells by using gene expressions will be used as an indicator to determine the concentration of the herbs combination. Gene expressions are going to be measured based on the quantity of RNA molecules using real time PCR. Gene expression based herbal formula is not yet generally known in Indonesia and they will be developed as an oral powder prototype. This will be an excellent innovation in the national scientific community, which should be proposed to get a patent right, to fulfill the need for cancer therapeutic agent in Indonesia.

Those innovations above are currently listed in the phase 1 of the translational research in the Faculty of Medicine, Universitas Padjadjaran. The research program is designed in three phases. The first phase is the laboratory and animal experiments based on basic theories to build a foundations for the next phases. This will be followed by the second phase, that includes in vivo experiments to determine a formula which is harmless and beneficial for human being. The third phase includes several types of clinical trials. After completing all phases, the formula will be used in health care. In this regards, an entrepreneurship strategy will also be needed. This research strategy may be slightly different from Khoury *et al*.[16] These initiatives are intended to integrate and develop a system for learning, comparative effective research, as well as quality health care and generating additional hypothesis for future investigations.

Chemical Compounds of Crude Extract and Their Actions on Selective Pathway

The use of traditional medicine in Indonesia is not an unfamiliar part of disease treatment in the community. Unfortunately, its development cannot compete with modern medical science which prioritizes on active molecule substances as a center of treatment mechanism. The author wanted to increase the utilization of natural resources of Indonesia in the form of crude

extracts. Due to limited human and financial resources, it is difficult for Indonesia to obtain the active compounds to achieve the ideal results. Historically, it has been noted that most people in daily treatment of disease use herbal medicine in the form of crude extracts and experience a positive effect on certain clinical symptoms. Indeed, we are very familiar with the superiority of the active compound in medicine where the molecular interactions can be obviously observed and the dosage can also be determined accurately. In respond to this scientific requirement, laboratory results from the studies on the effects of herbal medicine in the form of crude extracts on inhibiting cancer cell proliferation by analyzing gene expression were referred to the IC50.[15] These molecular data can explain the response of a cell and the pathway that is activated or inhibited by natural compounds. For certain disease, especially degenerative disease such as cancer, the activities of more than one type of signal transductions and pathways are always involved and it may even comprise a series of reactions that also have multiple or more than one pathway. It is debated whether a single active substance can act on so many different biochemical pathways in the cell target. It can be understood that all signs and symptoms of the disease are not pathogenically resulted from the work of a single molecule, but from tens or hundreds of molecules and even tens of biochemical pathways. Although, the modern medicine and the pharmaceutical approach have been able to determine the pathway of the biochemical reactions by targeting a specific molecule as a key molecule that effect the pathway, the cellular pathway is not a single process but always associated with other reactions or networks. Thus, the question whether a single active substance is able to inhibit the whole reactions or pathways in cancer cells. In fact, there is no single chemotherapeutic agent being able to recover completely the cancer patients. This leads to the notion that at the molecular level the body is naturally governed by many reaction mechanisms. This molecular process extends the research that can be categorized as a gene to protein level research through gene expressions. These processes aim to maintain homeostasis. Thus, even if an active substance is required, it would still be necessary to combine it with other active substances. Based on that idea, we should be able to develop herbal crude extracts with equal effect to active compounds and focus on molecular targets. If this can be implemented, the development of crude extract in medicine will have similar quality with modern medicine although it is still on the level of crude extract. This strategy is important for the development of generic drugs in Indonesia. A cell could be surrounded by various molecules contained in the crude extract (Fig. 4). The substance varies from large molecules or complex molecules to small molecules. These molecules will interact with their respective receptors on the cell membrane, cytoplasm or cell nucleus. The results from our studies on HeLa cells showed that the crude extract conferred inhibition of cell proliferation (IC50).[15–22]

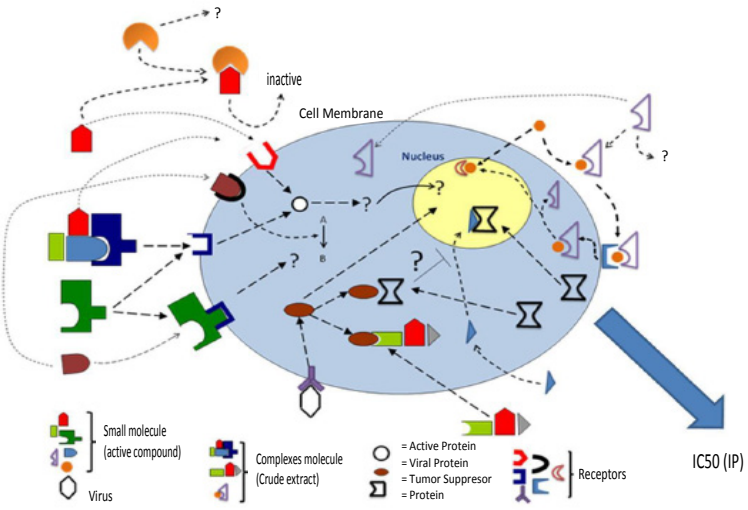

Fig. 4 Chemical Compounds of Crude Extract Affecting on Selective Biochemical Pathway in Target Cell

It is already well known that the use of the crude extract with various molecules will result in a variety of cellular responses. By setting the optimal dosage and making comparison with the existing commercial chemotherapeutic agent as a marker, a target for cancer therapy will be obtained and unwanted effects can be minimized. The implementation of this strategy to treat cancer cells can be analyzed using IC50 determination.

From Bench to Bedside

With the outcomes of the study conducted in Faculty of Medicine, Universitas Padjadjaran, that combines basic, clinical and public health sciences, some new discoveries have been made. However, moving the scientific discoveries of herbal medicine into clinical trials have always been slow, expensive, and difficult achieved.[17] It is not surprising that even in the developed countries it takes an average of 17 years for herbal medicine to enter day to day clinical practice, and that is only for 14% of all new scientific discoveries.[18] A study by Contopolous showed that only 5% of highly promising basic science findings were licensed for clinical use and only 1% were actually used for the licensed indication.[19] Therefore, there are several key questions to be asked: Is translational medicine research important in Indonesia? What should the role of the Health Department of Republic of Indonesia be in supporting clinical trial originating from university research program? In this matters, we support Meyers and Pomeroy that knowledge and technology that produce sustainable improvements in health and quality of life begin with early translational research efforts and are in need of biomedical research workforce.[20]

Sung described some barriers to translational research that range from a lack of willing participants to the lack of funding.[21] In Indonesia, little is known about translational research in medicine that transfer new understanding of disease mechanisms gained in basic laboratories into the development of new methods for diagnosis, therapy and prevention, as well as the clinical trials in hospitals.

Goldblatt and Lee mentioned in their article that primary goal of translational research is to integrate progresses in molecular biology with clinical trials, taking research from “bench to bedside”.[22] In this review on translational research, a description on the effects of herbal medicine in the form of crude extracts to inhibit cancer cell proliferation has been given and a gene expression analysis is currently performed in the Faculty of Medicine, Universitas Padjadjaran, to create a chemotherapeutic agent. The team has introduced a new terminology of herbal medicine, namely herbal genomics. This new terminology can be used in recent clinical campaigns for traditional medicine including for herbal chemotherapeutic development that addresses crude extract and genomic analysis. In this analysis, a IC50 determination of *Phyllanthus niruri* and *Vitis vinifera* that were designed for complementary therapy of cancer were performed.[23] These systematic efforts of translat ional research will increase extensive cooperation between basic researchers, clinicians and industries that integrate basic sciences into human health in Indonesia.

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