BMB Reports - Manuscript Submission

Manuscript Draft

Manuscript Number: BMB-16-221

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Article Type: Mini Review

Keywords: Botanical drug; natural product; reverse pharmacology; IND; plant extract bank

Corresponding Author: Kyungseop Ahn

Authors: Kyungseop Ahn[1,*]

Institution: [1]Natural Medicine Research Center, Korea Research Institute of Bioscience and Biotechnology, Cheongju 363-883, Korea,

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Author's name: Kyungseop Ahn

Affiliation: Natural Medicine Research Center, Korea Research Institute of Bioscience and Biotechnology, Cheongju 363-883, Korea

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Corresponding Author's Information: Tel: +82-43-240-6113, Fax: +82-43-240-6129, E.mail: ksahn@kribb.re.kr

ABSTRACT

Natural product drugs, or botanical drugs, are drugs composed of natural substances which has constituent and efficacy. In Korea, government-led projects brought attention to botanical drugs invigorating domestic botanical drug industry. Foreign markets, as well, are growing bigger as the significance of botanical drugs stood out. To follow along with the tendency, Korea puts a lot of effort on developing botanical drugs suitable for global market. However, standards on approving drug sales varies by countries. And also, thorough standardization, scientification, clinical studies and data of these will be required as well as data confirming safety and effectiveness. Meanwhile, as international exchange in botanical drug market continues, importance of plant resources was emphasized, thus countries' ownership on domestic natural resources became vital. Not only establishing systematic method to secure domestic plant resources, but also cooperation with other countries on sharing natural resources is essential to effectively procure natural resources. Korea started to show visible results with botanical drugs, and asthma/COPD treatment made out of speedwell is one example. Sufficient investment and government's active support on basic infrastructure for global botanical drugs will bring Korea to much higher level of botanical drug development.

INTRODUCTION

Natural product, in a broad sense, is a generic term for plants, animals, minerals, microorganism and their metabolites from the natural world. If so, will it be possible to use the term 'natural product drug' on drugs randomly made with any kind of materials from natural world? Apparently, this vague definition is seldom used.

In Korea, the term 'natural product drug' was defined -according to the enactment of 'Natural Product Drug R&D Acceleration Law' in 2000- as drugs researched and developed using substances from natural products that contain new constituent and efficacy.

The U.S. officialized the term 'botanical drug' for natural product drugs, referring to drugs manufactured with plant substances including algal, microfungi (the term botanical drugs will be used for natural product drugs hereafter). Marketing botanical ingredients as foods and dietary ingredients in the United States is commonplace. Getting them approved as prescription drugs is a somewhat new frontier, and so far only two botanicals have achieved this goal. On 2006, the US Food and Drug Administration (FDA) approved the first botanical drug, Veregen®(sinecatechins; ointment, 15%; Medigene, Planegg/Martinsried, Germany), a proprietary extract of green tea (*Camellia sinensis* Kuntze) for treating genital and perianal warts.(1) FDA approved the second botanical New Drug Application (NDA) on 2012, for Fulyzaq™(crofelemer; 125 mg tablet; Salix Pharmaceuticals, Raleigh, North Carolina), the first oral prescription botanical drug for the novel indication of HIV-associated diarrhea. Fulyzaq is a proprietary extract of the blood-red latex of the South American croton tree (*Croton lechlerii* Müll. Arg). (2, 3)

In Europe, they use the term 'herbal medicinal product (HMP) to encompass all drugs that contain one of more kind of herbal substance of herbal preparation. Chinese developed TCM(traditional chinese medicine) a prescription in their traditional medicine, based on their

own experience of its usage, and eastern ideas.

DEVELOPMENT TRENDS OF BOTANICAL DRUGS

In 2000, 'Natural Product Drug R&D Acceleration Law' was established as a institutional support from Korean government, and based on this law, the government and various institutes initiated 5-year-plan of research and development of botanical drugs. Botanical drugs drew more interest from public when botanical drugs were selected as one of the five tasks of government-derived project. Only in the first half of 2011, 3 products including Shinbaro Capsule from Greencross, Synatura Syrup from Ahn-gook, Motilitone from Dong-A got approval for marketing, and in 2012, PMG Pharm's osteoarthritis treatment and Layla tablet, Yungjin's atopy cure Utoma was accepted as botanical drug. In 2013, according to the data from UBIST, a program aggregating statistics on drugs, Stillen tablet from Donga-ST raised more than 60million dollars, Ahn-gook raised 30million dollars with Synatura Syrup, and 18 million from Motilitone, 36.4million from Joins Tablet from SK Chemical, 6.7 million from Shinbaro Capsule, 5.2million from Layla Tablet-5.2million as prescription performance. These performances indicate a successful settlement of botanical drugs in domestic market. Encouraged by these facts, pharmaceutical companies reinforced their developing processes of botanical drugs. Currently, 24 companies are researching and developing botanical drugs, and out of 240 pipelines for newly developed medication, 23% of them are for botanical drugs. These companies mainly focus on digestive system, metabolic and central nervous system diseases.(4)

Meanwhile, the size of global market including medical supplies, functional food for health act etc. is estimated to be 1 trillion dollars, and is growing 8 to 10 percent annually. About half of the medical supplies currently on sale are botanical drugs itself, or extracts composed of single-element substance from natural products. Tamiflu(Oseltamivir) is one

typical example. Tamiflu was discovered from natural substance called star anise which is a Chinese native plant, and its sales from all over the world reached 3 billion dollars. Besides Tamiflu, Aspirin, Taxol, ginkgo biloba extract, plantain extract were developed and put on sale raising big profits. In 2004, FDA established a industrial guideline of botanical drugs(Botanical Drug Guidance), as an effort to take the initiative in botanical drug market. As a result, FDA approved 868 kinds of natural product originated semisynthetic substance since 1982 and developed 20 kinds of anticancer drug derived from natural substances until 2002(Science Times, 2010. 8). Veregen Ointment 15%(Veregen®, Phynova, warts treatment on pubic area, approved in 2006) made by Medigen, German Pharmaceutical, is one of the products FDA approved. This drug reached 4.5million dollars of sales. Fulyzaq, the second botanical drug developed, is the first oral medication developed by Salix Pharmaceuticals using proanthocyanidin polymer extracted from wild plants in Amazon river bason, and this drug was approved for sales in 2012, as an orphan drug which relieves symptoms of diarrhea fro AIDS patients. GW Pharmaceuticals, an England company, developed Sativex(Oromucosal Spray), a marijuana extract efficacious on rigidity due to multiple sclerosis. GW Pharm raised 11million dollars with Sativex. China intends to found world's biggest Chinese medication basis of natural compounds. Sales of chinese medication holds 22.7% of the entire drug market and recorded high growth at an average of 35% annually over the past 5 years and expected to grow at the same pace.(5, 6)

CHALLENGES IN DEVELOPING GLOBAL BOTANICAL DRUGS

Although global market of botanical drugs is expanding continuously, Korea's performance overseas is not quite satisfactory. Stillen, one of the representative botanical drugs in Korea, raised only 200 thousand dollars abroad after its release. Other domestically developed botanical drugs are no different when it comes to sales performance. Performances

until now is fairly contrasting with government's prediction that botanical drugs will be one of the major source of income in Korea.

Botanical Drug Approvals in US

More than 500 pre-IND meetings and IND applications have been submitted to FDA for botanical drugs; two botanical drug NDAs have been submitted to FDA and both were approved (see **Figure 1).** While it appears that many sponsors have accomplished the IND step, only two have reached the final NDA step. Why are there only two FDA-approved NDAs? Based on these authors' experience, the following represent three of the most common reasons that could explain why more botanical drug NDAs have not been submitted to FDA for review: (7, 8)

· ***Failure to show efficacy***

Failure to show clinically relevant and statistically significant efficacy is the single most common reason why most drugs ― not just botanical drugs ― fail to reach the NDA step. Although many sponsors "believe" that their product "works," the stringent criteria for US drug approval consist of documented safety and efficacy from one or more multicenter "adequate and well-controlled" clinical studies. For pivotal studies (those efficacy studies that will be used to support the NDA), it is very important that target populations be well-circumscribed by the protocol eligibility criteria, with appropriate and FDA-agreed upon outcome measures, proper controls (*e.g.*, placebo or active treatment), and be well-monitored and accurately analyzed.

· ***Unrealistic Expectations***

Inexperienced drug sponsors often have unrealistic expectations when it comes to planning and executing a drug development program. This may be due, in part, to FDA's relatively relaxed requirements during initial stages of IND development, which may give sponsors a false sense of security that the requirements for botanicals are less rigorous than those for non-botanical drugs. It also may be due to the fact that regulatory requirements for botanicals are not internationally harmonized, as they are for other drug categories, which creates confusion, because US requirements differ from those of other countries. Also, many botanical drug sponsors have never developed a drug for the US market, or come from different industries or regulatory environments. Some sponsors are unwilling to accept — or simply deny — that the United States requires submission of "raw" data (chemistry, nonclinical safety testing, clinical study databases, etc.) to support drug filings, rather than data summaries or "expert" opinion, as is commonplace in other countries.

· ***Insufficient Funding***

Lack of or insufficient funding to complete the development process is not an uncommon problem for many botanical drugs under IND. This may be due to the economic climate, lack of acceptance by the investment community, lack of patent status (although the product may enjoy other forms of intellectual property that may be superior to patents), or insufficient planning. Again, many botanical drug sponsors, particularly those whose products are in other market channels (*e.g.*, dietary supplements), or foreign markets, underestimate the level of documentation and data that FDA requires to assess that a drug does what it claims to do in its labeling.

STRATEGIES FOR DEVELOPING 'GLOBAL BOTANICAL DRUG'

Development of novel botanical drugs using traditional medicinal plant sources

Botanical drugs are, by nature, plant-derivative materials and their complexes. This makes them unfit for conventional "single-target/single-drug" development processes and thus have been largely disregarded in the field of medicine. However, it is widely understood in synthetic medicine that the single-drug "magic bullet" strategy is not adequate for treating chronic illnesses (e.g. cancers, immune disorders, mental illnesses, cardiovascular diseases, lifestyle diseases) due to their complex pathogenetic mechanisms, and that a "multi-target/multi-component" approach involving control over a number of target sites is more effective. [9-11]

Traditional herbal medicine, itself being a mixture of various components, corresponds to the "multi-target/multi-component" approach, with therapeutic effects that are clinically confirmed--albeit with no analytically defined mechanisms--through experience and knowledge accrued over a long history of treatment of chronic illnesses. The strategy for developing novel botanical drugs by the reverse-engineering of traditional herbal medicine is called reverse pharmacology. (Figure 2) Reverse pharmacology involves the study of active ingredients based on traditional herbal medicine and formulations as well as the subsequent development of drug candidates or formulations for preclinical and clinical research. This is deemed to be the most optimal strategy for the development of cures for chronic illnesses because it utilizes materials (traditional herbs) with proven safety and clinical efficacy, which allows the development process to be opposite that of the initial stages of synthetic drug development and therefore reduces the cost and duration of development compared to conventional synthetic drug development methods. [12-13] Using knowledge from traditional Korean medicine in botanical drug development is also a reverse pharmacology approach with many successes reported worldwide, which prompted the reevaluation of traditional medicinal herbs and greatly spurred the research and development of botanical drugs.

Keeping the pace with global standards of botanical drug development

For Korean botanical drugs to successfully compete in global market, there are some conditions institutes and pharmaceuticals to keep in mind. Since licensing procedure of new drugs varies by countries, it is reasonable to begin development procedure in accordance with such country's distinct regulations.

Secondly, scientification and standardization of botanical drugs, complex clinical studies, scientific data for sale approval is essential. For materials, specific origin of the medicine and securing bioequivalence is the most important and procuring bioequivalence is the most challenging part in drug development process. Equivalent production of material is also a vital portion, scientification of plants, ecological environment, record of cultivation should be conducted. If a company imports natural products as materials, they need to secure a reliable supply chain in terms of collection, cultivation, and importation for seamless supply of medicine.

The third requisite is safety and effectiveness. All countries, including the US, Europe, and China, set safety as the to priority. They accept oriental medicine texts of cases of drug usage abroad to some extent, but mainly, they request data on drug-drug interaction (DDI), mechanism of action (MOA) and pharmacokinetic (PK). (14, 15)

Meanwhile, Nagoya Protocol came into effect. There are articles related to ABS, agreement of access to genetic resources and benefit sharing, in Nagoya Protocol which consequently acknowledges each country's ownership on its domestic natural resources. Therefore, biotechnology institutes and universities, especially those that are at the beginning process of developing botanical drugs, should be well informed about ABS articles. To sensibly deal with this matter, institutes should build partnership with countries providing resources or such organizations. Also, they need to analyze regulation regarding access and benefit share in different countries, and come up with counterplan for future anticipated

problems. For counterplans, financial benefit sharing, technology transfer, co-ownership of patent and intellectual property may be possible. (16)

Promoting infrastructure on securing plant resources

Industrial value of plant resource in drug market is prominent. Traditional plant resources were not only the key material for drug development, but also a core resource in the market of botanical drug products since 85% of the world's traditional medication derive from plants. Korean, China, Japan, India, Germany, countries that have long developed traditional medicine and herbal medication, are striving to procure plant resources countrywide to develop botanical drugs using plant extract. Specific strategies among countries might differ, but the point is they all acknowledge the significance of plant resource.

Korea has constructed their own method of securing plant resources. Korean Research Institute of Bioscience & Biotechnology (KRIBB) founded South Korea's first mass-distribution system named Korea Plant Extract Bank. Extract Bank provides researchers screening samples at the beginning of food and drug development phase, assisting researchers to acquire resources regardless of season, and holds vouchers of materials to provide origin of plantation, and subsidiarily preventing overexploitation of rare species. From 2000 to 2010, extract bank gathered 1,699 species of Korean native plants, which takes up 40% of entire Korean plant species, excluding garden plants and food crops, and made extracts with 5,164 samples separated by parts then offered them to researchers (total 416,829/ 2013. 12) as a part of supporting research of domestic natural substances. Meanwhile from 2006, in terms of extending variety of resources, extract bank has launched 'International Biological Material Development Project' (2006-2016) and established 4 local centers near tropical/subtropics area (China, Indonesia, Costa Rica, Vietnam) where broad range of life exists. Each year, through formal agreement, extract bank assembles foreign resources (27,000 pieces of extract,

2015. 12) and establishes database of basal activity(anti-inflammatory, cytostoxic, antioxidation, insecticide). After that, they give out foreign resources (1,600,000 pieces 2015. 09) to researchers and provide them information based on the database. (17)

ENDEAVORS OF KOREAN PHARMACEUTICALS FOR GLOBALIZING DOMESTIC BOTANICAL DRUGS

In spite of some challenges Korea had in globalizing domestic botanical drug products, some companies are starting to show visible results throughout the US and Europe. Korean government suggested 'Global Leading Natural Pharmaceutical Project' as a project to forge developing industries to the highest level and make internationally recognized drugs. With Donga-ST in charge, 10 pharmaceutical companies participated with the support of 16 industry-academic collaboration institutes. As a result, Donga-ST's new diabetic neurotherapy treatment was approved by the US for clinical study phase Ⅰ IND in April 2013, and recently got down to clinical trial. Motilitone is on standby for FDA's approval on phase Ⅱ within the first half of 2014. COPD/asthma treatment from Yungjin Pharmaceutical completed phase Ⅰ and is in the middle of phase Ⅱ base on the approval in 2014. For pharmaceuticals aiming Europe market, Greencross HS developed anticancer supplements and is in the process of phase Ⅰ trials and SK Chemicals has set a goal of their asthma treatment to acquire authorization of Phase I trials in Europe. (18)

All of these medicine were developed is Korea and later got approval at clinical studies from institutes of Europe and the US, quantitatively/qualitatively comparable with botanical drugs made in developed countries.

KRIBB Natural Medicine Research Center developed a asthma/COPD treatment and the natural substance they used is speedwell genus (Pseudolysimachion genus) plants. Speedwell, according to Chinese medicine dictionary, is a kind of herb medicine used to treat

loosen phelegm, chronic cough, and asthma/COPD. However in Korea, there was no record of speedwells in 10 major books being utilized as herb medicine which means that the usage of speedwell was not extensively known to traditional Korean medicine world. From the beginning of research, relying on the clinical effects referred in old books, research center conducted clinical studies on animals and they discovered active materials substantially effective. Since 2006, these results were applied for patents in 12 countries. For following study, selected mountain spike speedwells which aerial part is relatively larger, and active component content is high. Then, after identifying excellency for cultivation at central inland area, they massively cultivated wild seeds proving phytoequivalence between wild type and cultivated type seeds.

Afterwards, they transferred such results along with the patent to Yungjin Pharmaceuticals in May 2010, and July of the same year, KRIBB Natural Medicine Research Center was selected as supporting organization of pharmaceuticals on 'Global Botanical Drug Development Project'. For the past 3 years, Natural Medicine Research Center conducted studies on standardization of raw material medicine/herb medicine suitable for US guideline of clinical studies, and biological researches on animal effectiveness/biomarker/MOA. Ultimately, KRIBB successfully supported Yungjin Pharmaceutical to complete phase Ⅰ trials in US.

CONCLUSION

International perspective of drug development recently has been rapidly changing. As the world's population is constantly aging, and lifestyle diseases and chronic diseases have become more prevalent, and more and more people pursue improved quality of life which focuses on preventing diseases, drug development shifted its focus towards treating aging, cancer, chronic diseases, and lifestyle related diseases. Consequently, traditional medication,

which safety and clinical effects had been confirmed over a long period of time for treating diseases mentioned earlier, and botanical drugs which stand on the basis of traditional medication are expected to grow tremendously. However, Korea relies most of its resources on foreign countries and it can be a hinderance in developing botanical drugs. To resolve this matter, externally, Korea needs to establish systematic network with countries possessing such resources and internally, needs to build up well organized infrastructure on procuring natural resources residing in Korea. Lately, global trend has been towards acknowledging country's claim on its biological resources, and in the close future, countries providing biological resources(including intellectual resources) may demand their share of profits produced by developing natural resources. This ongoing trend would be a serious limitation to Korea's development strategy with foreign resources, so Korea needs to prepare plans to resolve this matter. In addition, basic structures for legal system, analyzing and standardizing system for improving quality and GAP cultivation management of domestic natural resources should be set up, and continuously supervised. Government's active support and companies' investment based on this structure will bring forward the days that Korea moves up to higher level on developing botanical drugs.

ACKNOWLEDGMENTS

FIGURE LEGENDS

Figure 1. Botanical drug applications in US FDA during 1999-2012.

Figure 2. Reverse phamacology.

Figure 3. Construction and Use of the Plant Extract Bank.

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Figure 1

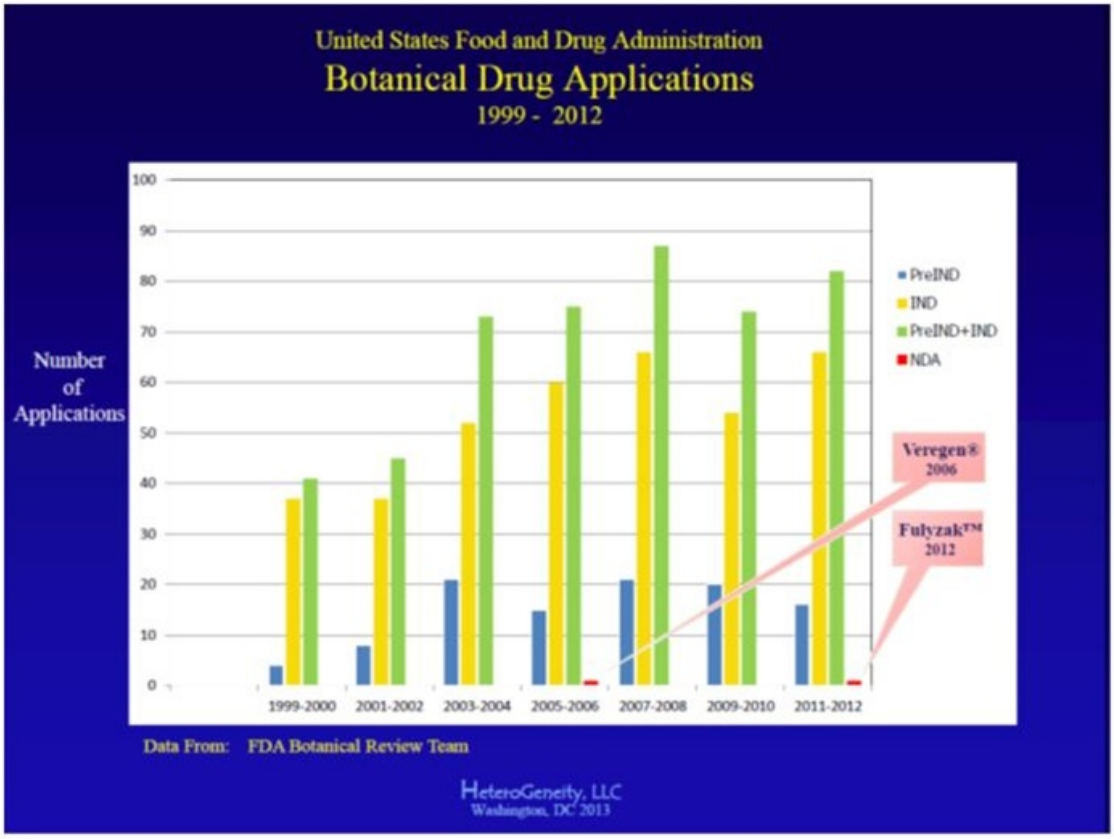

United States Food and Drug Administration
Botanical Drug Applications
1999 - 2012
Number of Applications
100
90
80
70
60
50
40
30
20
10
0
1999-2000
2001-2002
2003-2004
2005-2006
2007-2008
2009-2010
2011-2012
PreIND
IND
PreIND+IND
NDA
Veregen®
2006
Fulyzak™
2012
Data From: FDA Botanical Review Team
HeteroGeneity, LLC
Washington, DC 2013

Figure 2

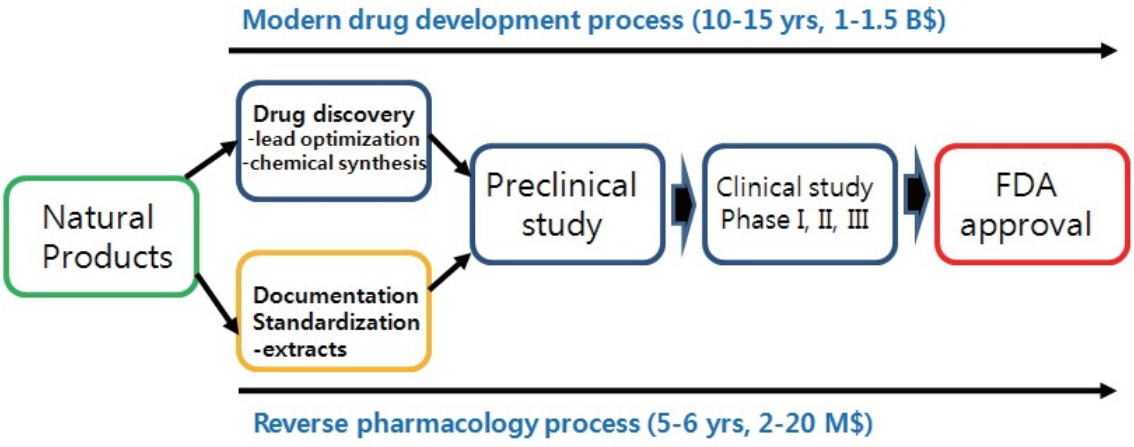
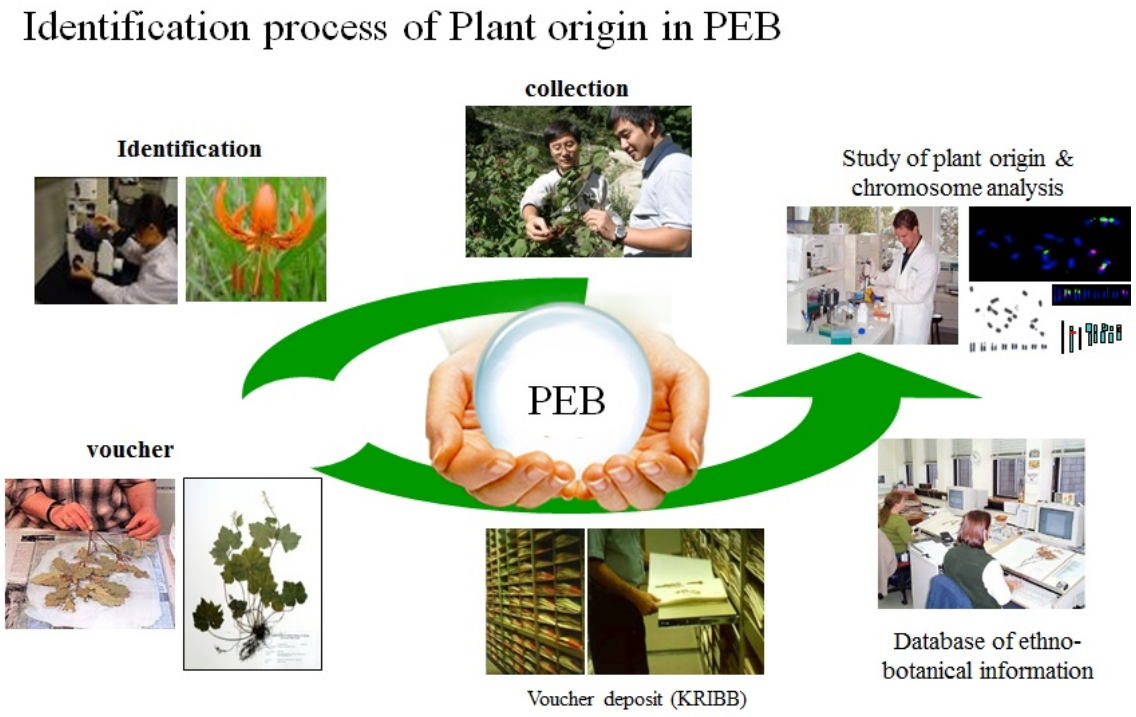

Modern drug development process (10-15 yrs, 1-1.5 B$)
Natural Products
Drug discovery
-lead optimization
-chemical synthesis
Documentation
Standardization
-extracts
Preclinical study
Clinical study
Phase I, II, III
FDA approval
Reverse pharmacology process (5-6 yrs, 2-20 M$)

Figure 3


Identification process of Plant origin in PEB
collection
Identification
Study of plant origin & chromosome analysis
PEB
voucher
Database of ethno-botanical information
Voucher deposit (KRIBB)