Published in final edited form as:
Russ J Plant Physiol. 2008 July ; 55(4): 564–567. doi:10.1134/S1021443708040201.

New Strategy for the Search of Natural Biologically Active Substances

V. Dushenkov and **I. Raskin**
Rutgers, the State University of New Jersey, New Brunswick, New Jersey, United States

Abstract

The modern pharmaceutics actively screens an immense diversity of substances occurring in plants and other natural resources in the search for new effective medicinal agents. The Global Institute for Bioexploration (GIBEX) established by joint efforts of Rutgers University and the University of Illinois (United States) represents the organizational core of international scientific community whose activity is directed towards the search and development of new medicinal preparations from natural raw materials. The basis of GIBEX activity is the transfer of modern screening technologies to countries and geographical regions characterized by remarkable biodiversity. The GIBEX goals are to encourage the search for new natural biologically active substances, to maintain biodiversity, and to monitor the natural resources conservation.

USE OF NATURAL RESOURCES FOR DEVELOPMENT OF MEDICINAL AGENTS AND BIOLOGICALLY ACTIVE ADDITIVES

From immemorial time the plants have been used not only for food but also as a source of biologically active substances. The use of plants for medicinal purposes was documented in Sumerian manuscripts more than 5000 years ago. The substances of plant origin were for long the only source of medicinal drugs [1]. However, even presently these substances are extensively used in the health care practice. The discovery and exploration of alkaloids opened way to obtaining chemically uniform monomolecular medicines of natural origin [2]. Even in the era of combinatory chemistry, more than 25% of new medicinal agents are related in some way to substances of plant origin [3]. The rapidly growing application of preparations from sweet worm-wood (*Artemisia annua* L.) in the struggle against malaria [4] is a demonstrative example of effectiveness of herbal medicines.

Among 847 low-molecular-weight medicines introduced into the practice since 1981, 43 agents belong to natural compounds, and 232 agents are derivatives of natural substances. Furthermore, in the rest group of 572 preparations, the original link to natural compounds is traced for 262 preparations [5]. According to our estimates, more than 200000 of various low-molecular-weight substances were obtained from plant materials.

The plants evolved as chemical factories capturing energy from the Sun for the production of a large variety of compounds that are needed not only for the construction and functioning of the plant organism but also for plant protection against adverse environmental factors and for strengthening the competitiveness of a given species in the plant community [6]. The chemical defense is almost the only effective instrument in the struggle of plants against pathogenic organisms and multiple herbivorous animals. For the effective defense against pathogens, plants have developed a complicated system comprising the elements with different mechanisms of action. Recently, scientists from Boston (United States) have shown that *Berberis fremontii* Torrey possesses at least two complementary mechanisms defending the plant against microorganism attacks [7]. The antibacterial activity of alkaloids is supplemented

and reinforced by the operation of specific inhibitors of the bacterial transporter responsible for the resistance to antibiotics.

Owing to these complementary effects, multi-componential plant extracts might be highly effective as therapeutic agents. Interactions of chemical components in the extracts play an important role in effectiveness of plant preparations. For example, an alkaloid triptolide from *Tripterygium wilfordii* Hook F., effective for therapy of rheumatoid arthritis, is highly toxic for humans in purified form, although the toxicity of nonpurified triptolide in plant extracts is significantly reduced. Because of its high toxicity, the purified triptolide has never been allowed for therapeutic usage, whereas the medicine based on *T. wilfordii* extracts is currently at the final stage of development [8]. The effectiveness of non-purified plant preparations, as compared to that of purified ingredients, might involve other mechanisms such as protection of active substance from the attack of “foreign” enzymes, a faster transfer of the active substance across membranes, and circumvention of drug resistance of human organisms. Presently, there is a growing interest in mechanisms underlying the action of plant-derived substances on gene activities involved in disease development or vital functions of the organism [9].

According to estimates of the World Health Organization (WHO), about 80% of the population in the developing countries relies on plant preparations in therapy of diseases [10]. Traditionally, plant preparations are widely used in pharmacopeias of Japan, Germany, and other European countries. In the United States, medicinal plant preparations were allowed for registration not long ago; however, the majority of such preparations are widely used in the United States as dietary supplements. In many countries of the world, bioactive preparations of natural origin are also widely applied as biologically active dietary supplements (nutraceutics).

According to data of the Food and Agriculture Organization (FAO), more than 50000 plant species are used in the traditional folk medicine throughout the world [11]. The highest percentage of native flora species used for medication is observed in countries of Southeast Asia, such as India (20%) and China (19%). In the United States and Russia, slightly more than 10% of plant species are used for therapeutic purposes.

The chemical diversity of the plant kingdom remains largely unexplored. Even less is known about biological activity of chemical substances obtained from plants. The diverse and unique flora of our planet is an enormous source of future prospects for biotherapy and improvement of public health care. However, the boosted research and implementation of methods for obtaining medicinal agents from natural raw materials is directly related to the problem of biodiversity conservation [12]. Unfortunately, natural resources are being rapidly exhausted because of sweeping urbanization, destruction of natural communities, and pollution of the environment. Disappearance of any biological species deprives the humankind forever of the access to thousands of biologically active substances that might potentially be a useful source of medicinal or other chemical compounds. The conference of the United Nations held in Rio de Janeiro in 1992 stated that biodiversity, including genetic and chemical diversity of natural resources, is an indispensible component of the national heritage [13]. The adopted Declaration of the conference proclaimed that “activities within the jurisdiction or control” of sovereign States “should not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction.” In the contemporary dynamic community, with its progressively increasing population and rapid industrial development, the conservation of natural resources is inseparable from rational usage of these resources.

GLOBAL INSTITUTE FOR BIOEXPLORATION (GIBEX)

The intensive search for medicinal substances from natural resources reached its peak in the period from the 1960s to the 1980s [3]. Presently, the interest reappears to medicinal preparations obtained from natural raw materials [14]. The international "Biotherapeutic initiative for the research and development of natural biologically active substances" originated in the very beginning of the 21st century at Rutgers University (New Jersey, United States) and provided the basis for Global Institute for Bioexploration (GIBEX). Later on GIBEX was established by joint efforts of Rutgers University and the University of Illinois at Urbana-Champaign (United States).

GIBEX is an organizational core of the virtual international scientific community whose activity is aimed at the research of new medications from natural resources. GIBEX coordinates the work of more than two dozens of national and regional divisions and affiliated organizations. The GIBEX activity is aimed at the inventory of biological effects of natural compounds. The objective of these efforts is similar to aspirations of the academician N.I. Vavilov who managed to collect unique genetic material in many remote places around the world in the first half of the 20th century.

The goals of GIBEX include the encouraging of new initiatives in research and development of natural biologically active substances, the maintenance of biodiversity, and conservation of natural resources. An important integral part includes permanent efforts to retain the cultural and natural heritage of member countries, including the historical experience of folk medicine. The basic principle of GIBEX activity is the transfer of modern technologies in research and development of medicinal agents to member countries within the framework of comprehensive collaboration. The GIBEX activities in world regions should promote the detection, exploration, development, and marketing of new therapeutic agents based on natural products of herbal, fungal, and bacterial origin that are prospective for distribution in the form of medicines, dietary supplements, and health-promoting food ingredients.

Until recently, there was a sustained trend to collect natural materials in remote regions of developing countries and transport raw materials to the developed countries for pharmacological screening and creation of new medicinal agents. This practice has raised numerous political, social, and juristic problems. The intention of GIBEX is to radically redirect the processes of bioresource detection and assessment. Within the framework of new international "Biotherapeutic initiative," the portable field equipment and field-oriented methods for pharmacological screening are being transferred directly to bioresource-possessing countries. This is an entirely new and highly ethical approach to the obtaining of natural biologically active substances from natural raw materials.

The majority of developing regions do not participate on an equal basis in pre-clinical and clinical research and development of medicinal agents from local flora and fauna. In turn, GIBEX considers its own duty to provide scientific information and organizational basis for such investigations, relying mostly on local personnel and resources. Thus, in full conformity with general principles of equitable access to genetic resources sharing benefits from exploitation of these resources, the maximal value and profit is ensured to countries bound by the license agreement concerning new medications from local bioresources.

Scientific personnel from the developing regions are usually trained in large research centers. This approach is expensive and not always effective, because it often leads to "brain drain" exerting detrimental influence on regional economies. The international "Biotherapeutic initiative" encourages scientists from the leading world-known laboratories to work in the countries involved in the bio-exploration program. This would help regional specialists to master technologies for selecting and detecting promising sources of medications and for

conducting indispensable pharmacological studies. The educational component of these programs includes laboratory studies, practical field training, lectures, seminars, scientific conferences, and public relation activities. The trainees can obtain respective certificates from educational organizations involved in the program.

Being adhered to the principle of research development in the areas of natural resources, GIBEX sends to these regions highly qualified professionals with the purpose of teaching local personnel and conducting joint research in the copartner laboratories. Portable instruments for biological screening, which are transferred to regional or national GIBEX branches, provide for the field screening of biologically active substances and accelerate the identification of promising therapeutic agents, while guaranteeing the intellectual property rights for regional scientists.

Specific research goals of GIBEX and its national branches set the new principle of conducting the screening in the areas of potential sources of biologically active substances. The implementation of this principle would preclude the export of biological materials for primary screening and would ensure full compliance with international agreements. Presently, 16 portable mobile and reliable tests are being used under field conditions. These tests are aimed at the detection of antibacterial, fungicidal, and antihelminthic activities. An important aim of the screening is to reveal characteristics closely related to the potential use of herbal extracts for the prevention and cure of diseases. Such characteristics include the inhibition of proteinase, glucosidase, and lipase, as well as evaluation of total content of phenol derivatives, anthocyanins, and antioxidants.

In addition, the GIBEX activity includes the invention of new technologies for preclinical and clinical tests, improvement of their infrastructure, optimization of medicinal plant growing, and standardization and production of medications from natural raw materials. A particular significance is devoted to devising and accomplishing the strategy for protection and documentation of biodiversity and to completing the inventory of natural bioresources and source organisms. GIBEX is motivated to reinforce protection of intellectual property rights and to fulfill obligations according to the Biodiversity Convention and regulations of the World Trade Organization concerning the intellectual property rights. While possessing the intellectual property rights, the member country can provide commercial licenses on the conditions acceptable for the country.

The exploration of new natural biologically active substances at Rutgers University is mainly performed at the School of Environmental and Biological Sciences. The faculty of this school are involved in numerous international programs dealing with biodiversity in many countries of Asia, Africa, Europe, Australia, North and South America, and also in the World Ocean. The financial support of these programs, coming largely from the United States Government, equals to four million dollars per year. For example, the program of International Cooperative Biodiversity Groups (ICBG), established by the governmental structures of the United States, is being implemented in Kazakhstan, Kyrgyzstan, Tajikistan, and Uzbekistan with participation of six research groups from Rutgers University and at least 60 scientists from Central Asia. A widely known program of New Use Agriculture and the Natural Plant Product (NUANPP) is actively implemented in four African countries. The teachers from Rutgers University keep executive position in three out of five Centers for Botanical Studies financed by National Institutes of Health of the United States.

The activity of the Fairbrothers Plant Resources Center is an important initiative directed at the maintenance and enlargement of the herbarium, mycological museum, and the collection of plant extracts gathered at Rutgers University. This activity also serves to the use of these collections for conducting international botanical investigations and educational programs.

GIBEX extensively uses abundant collections of Entomological Museum and the Center of Deepwater Ecology. The scientists from the Cook College engaged in the search of new biotherapeutics, cooperate with pharmaceutical, food-producing, and chemical companies in the United States and other countries. More than 50 specialists from Rutgers University are associated with to GIBEX.

The leading partner of Rutgers University in GIBEX is the University of Illinois at Urbana-Champaign (United States). Both universities cooperate closely in large collaborative projects concerning the search for new biotherapeutic substances in Central Asia. Based on profound international experience and extensive facilities for investigation of natural products, the University of Illinois keeps close contacts with many countries such as Egypt, Jordan, Mexico, New Zealand, Honduras, France, and China, which provides additional possibilities of using resources of these countries.

The global goals of GIBEX necessitate a global approach. The international cooperation within the framework of GIBEX has already expanded to all continents and comprises such countries as Brazil, Ghana, Israel, Kazakhstan, Kyrgyzstan, Nigeria, New Zealand, Senegal, United States, Tanzania, Tajikistan, Uzbekistan, Ukraine, Chile, Switzerland, Ecuador, and Republic of South Africa.

The coordinated activities within the framework of a new world consortium, GIBEX has already brought first positive outcomes. In spring of 2007 a research team from Rutgers University successfully transferred their technological designs for field quantification of bioactivity of plant extracts and trained a group of specialists from the University of Dar es Salaam (Tanzania). More than two thousand extracts were tested for bioactivity under standard conditions. The first promising preparations were selected for the development of anti-inflammatory agents and medications for the fight against cancer and diabetes. Presently, active negotiations are conducted with several biotechnological and pharmaceutical companies concerning the licensing of test results obtained within the framework of GIBEX. Eleven preparations have been already licensed by the American biotechnological company for further development.

The international Biotherapeutic Initiative for Exploration and Development of Natural Biologically Active Substances launched by GIBEX expands rapidly, thus acquiring a number of new supporters and participants in various regions of the World.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health, United States (project NIH 1U01TW006674).

REFERENCES

1. Raskin I, Ripoll C. Can an Apple a Day Keep the Doctor Away? Curr. Pharmac. Design 2004;vol. 10:3419–3429.
2. Mashkovskii, MD. Lekarstva XX veka (Medicines of XX Century). Moscow: Novaya Volna; 1998.
3. Newman DJ, Cragg GM, Snader KM. Natural Products as Sources of New Drugs over the Period 1981–2002. J. Nat. Prod 2003;vol. 66:1022–1037. [PubMed: 12880330]
4. Abdin MZ, Izrar M, U RR, Jain SK. Artemisinin, a Novel Antimalarial Drug: Biochemical and Molecular Approaches for Enhanced Production. Planta Med 2003;vol. 69:289–299. [PubMed: 12709893]
5. Newman DJ, Cragg G. Natural Products as Sources of New Drugs over the Last 25 Years. J. Nat. Prod 2007;vol. 70:461–477. [PubMed: 17309302]

6. Raskin I, Ribnicky DM, Komarnytsky S, Ilic N, Poulev A, Borisjuk N, Brinker A, Moreno DA, Ripoll C, Yakoby N, O'Neal JM, Cornwell T, Pastor I, Fridlender B. Plants and Human Health in the Twenty-First Century. Trends Biotechnol 2002;vol. 20:522–531. [PubMed: 12443874]

7. Stermitz FR, Lorenz P, Tawara JN, Zenewicz LA, Lewis K. Synergy in a Medicinal Plant: Antimicrobial Action of Berberine Potentiated by 5'-Methoxyhydrocarpin, a Multidrug Pump Inhibitor. Proc. Natl. Acad. Sci. USA 2000;vol. 97:1433–1437. [PubMed: 10677479]

8. Ma J, Dey M, Yang H, Poulev A, Pouleva R, Dorn R, Lipsky PE, Kennelly EJ, Raskin I. Anti-Inflammatory and Immunosuppressive Compounds from *Tripterygium wilfordii*. Phytochemistry 2007;vol. 68:1172–1178. [PubMed: 17399748]

9. Evans DA, Hirsch JB, Dushenkov S. Phenolics, Inflammation, and Nutrigenomics. J. Sci. Food Agric 2006;vol. 86:2503–2509.

10. Who, O. Traditional Medicine. Fact Sheet. 2007. no. 134, Revised May 2003 http://www.who.int/media-centre/factsheets/fs134/en/.

11. Schippmann, U.; Leaman, DJ.; Cunningham, AB. Biodiversity and the Ecosystem Approach in Agriculture, Forestry and Fisheries. Satellite Event on the Occasion of the 9th Regular Session of the Commission on Genetic Resources for Food and Agriculture, Inter-Departmental Working Group on Biological Diversity for Food and Agriculture (October 12–13, 2002). Rome: 2002. Impact of Cultivation and Gathering of Medicinal Plants on Biodiversity: Global Trends and Issues; p. 1-21.

12. Gurib-Fakim A. Medicinal Plants: Traditions of Yesterday and Drugs of Tomorrow. Mol. Asp. Med 2006;vol. 27:1–93.

13. UNO, Rep. Conf. United Nations Organization. "Environment and Development" (June 3–14, 1992, Rio de Janeiro), Resolutions. Vol. vol. 1. New York: UNO; 1992. p. 1

14. Fowler MW. Plants, Medicines and Man. J. Sci. Food Agric 2006;vol. 86:1797–1804.