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Drug discovery and development: India



GENERAL INFORMATION

- ◆ **Implementing institution**

Central Drug Research Institute (CDRI)

- ◆ **Head**

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- ◆ **Details of institution**

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- ◆ **Implementation period**

CDRI was established in 1951 and has pursued various broad-based and long-term drug development projects over the ensuing five decades. This approach has led to the development of a pipeline of products from natural resources, including the commercialization of at least five lead compounds or products: gugulipid (hypolipidaemic), *Bacopa monniera* standardized fraction (memory enhancer),

arteether (antimalarial), Consap (spermicidal cream) and Isapent (cervical dilator). This case study will focus on the first three of these products.

◆ **Costs**

The total cost of pursuing and sustaining a multiplicity of projects in the natural product area over the last 50 years — based on 10 per cent of the total expenditure of the Institute — comes to approximately 290 million rupees, or US\$6.5 million.

SUMMARY

CDRI was established in 1951 with the mandate to provide a leading role in the development of India's science and technology capability in drug research and development, to undertake frontline research, and to provide specialized science and technology services and human resource development.

Early in its history, the Institute formulated programmes covering the whole range of activities in drug discovery and development, including

- exploration of natural products;
- synthetic chemistry for the development of new therapeutic agents;
- basic and applied studies on such medical problems as age-related, cardiovascular and metabolic disorders, fertility regulation and tropical diseases; and
- all stages of preclinical regulatory studies and Phase I clinical trials.

Over the past 20 years, and more particularly in the last decade, a new sce-

nario has emerged, spurred on by advances in molecular biology, interinstitutional collaboration, the emergence of a new international patent regime, increased global interest in herbal products, the liberalization of the Indian economy and an increase in investment in research and development by Indian pharmaceutical companies.

Each of these factors has helped to influence and mould the Institute's research and development policies. However, while the major focus is to derive novel lead molecules from medicinal plants and develop them as modern drugs, alternative approaches for developing plant products into commercially viable herbal preparations are also followed. Indeed, the CDRI drug development programme relies heavily on traditional knowledge of herbal remedies — a practice now vigorously followed by international pharmaceutical companies. Initially, at CDRI, only plants described in traditional systems of medicine such as Ayurveda and Unani were investigated. However, in the mid-1960s, the programme was widened to include other indigenous plants and to focus on the

isolation and characterization of their biologically active constituents.

In short, the main feature of the CDRI programme for developing new products from medicinal plants is its broad-based, multidisciplinary programme. Sustained efforts over 50 years have helped to develop the infrastructure, facilities and expertise required for the generation of new knowledge and the exploitation of identified lead compounds for commercialization.

BACKGROUND AND JUSTIFICATION

When India obtained its independence in 1947, traditional systems of medicine constituted the mainstay of health care service to the country's large population. Indeed, even today, 70 per cent of the population uses traditional medicine for treating various ailments and diseases.

In 1951, when CDRI was established, there was no expertise or capability in drug research in India. The basic objective of CDRI, therefore, was — and continues to be — the development of modern drugs. This is a time-consuming and expensive process and, in the early days, new drug discovery was dependent solely upon the chance finding of new lead molecules after screening a large number of potential sources. Therefore, it was decided that this search would be narrowed to plants with known therapeutic activities used in traditional remedies.

In India, three major indigenous systems of medicine are practised, namely, Ayurveda, Unani and Siddha. Among these, Ayurveda alone describes the use of over 600 plants in some 8,000 preparations — mostly crude drugs, based mainly on extracts, pastes or powders of various parts of the plants.

Before CDRI initiated this programme, there was no systematic effort in India to explore medicinal plants — or other Indian flora — for biological activity. More recently, however, the Department of Indian Systems of Medicine has been created under the Ministry of Health and Family Welfare, which is initiating programmes for the systematic study of traditional remedies.

Backed by the strength in traditional Indian systems of medicine, the CDRI programme to develop modern drugs and herbal remedies based on leads from such remedies has provided a major boost to the exploitation of traditional knowledge. In addition, the publication in 1993 of World Health Organization (WHO) research guidelines for safety and efficacy studies of herbal medicines provided a major stimulus to the development of herbal remedies wherever feasible.

Initially, the isolation of pure molecules from plants and their further development to "modern" drugs constituted the basic objective of such natural product research. This approach changed when a standardized extract of *Commiphora mukul* (gugulipid) was developed as a cholesterol-lowering drug by CDRI and approved by the Drugs Controller of

India for marketing, as described below. However, in spite of a host of guidelines and regulations issued by national and international agencies for quality assurance of herbal remedies, traditional remedies continue to be manufactured using traditional methods and are marketed without quality controls. Furthermore, there have been few organized efforts to explore plants as a source of modern medicines. The CDRI products detailed in this case study, therefore, are valuable models for the development of such herbal products.

The main issues in the development of products from medicinal plants include:

AVAILABILITY

The availability of well-identified plant material of good quality and in required quantities can be a limiting factor in developing herbal products. Many medicinal plants are threatened species and cannot be collected from the wild — a practice that is not only detrimental to both the species concerned and the wider environment but also unsustainable for commercial production. The development of appropriate agrotechnology for the cultivation of uniformly high-quality medicinal plants should, therefore, go hand in hand with their development as pharmaceutical products.

QUALITY

As the quality of the initial plant material determines the efficacy, safety and shelf life of the finished product, thorough quality control of the plant material — its

correct identification, method of collection or harvesting and storage — is essential.

SAFETY AND EFFICACY

To find a place in the global marketplace, products must undergo rigorous safety and efficacy evaluation studies that comply with guidelines prescribed by WHO.

BENEFIT SHARING

Appropriate measures should also be put in place to reward the communities that developed and preserved the knowledge of the use of medicinal plants from generation to generation and that, in many cases, have been responsible for their conservation.

DESCRIPTION

The initial task in drug research is to identify new lead compounds with desired biological activities. These can be obtained by chemically modifying known drugs or by isolating novel natural chemicals from living organisms, especially plants. Bioassay-based fractionation can be used to isolate and identify novel compounds from such botanical sources. They can then be further isolated and characterized.

This case study focuses on the commercial development of three plant-derived remedies covering the three major categories of drug preparations that can be obtained from plant sources, each containing well-characterized active ingredients:

- *Bacopa monniera* standardized fraction, developed as a herbal remedy;
- guggulipid, a standardized fraction of a plant resin developed as a modern medicine; and
- arteether, a semi-synthetic derivative of artemisinin obtained from *Artemisia annua*, marketed as a pure compound and a modern drug.

**MEMORY ENHANCER:
BACOPA MONNIERA
STANDARDIZED FRACTION**

Two standard Ayurvedic treatises, "Charak Samhita" and "Sushruta Samhita", describe brahmi (*Bacopa monniera*, family Scrophulariaceae) as being able to enhance memory and cure mental retardation. Indeed, the plant has been used for some 3,000 years as a brain tonic.

Owing to its reputation as a memory-augmenting plant, *B. monniera* has attracted the attention of Indian chemists for several decades. The first report of the chemical investigation of the leaves was published in 1944, and the first report of the chemical examination of the plant was published by CDRI scientists in 1960. Further chemical analyses of the plant constituents were published between 1963 and 1967. CDRI scientists isolated two triterpenoid glycosides from the plant, which were designated bacosides A and B. Later investigations revealed that bacoside A was a mixture of three compounds, which were designated A2, A2' and A3. Complete chemical structures of bacosides A3 and A2 were published in 1994 and 1999, respectively.

Neuropharmacological investigations of ethanol extracts of *B. monniera* have since confirmed the traditional claims. A standardized fraction, containing not less than 60 per cent bacoside A, was prepared from the plant and subsequently tested on rats using two standard laboratory techniques to assess learning, namely, the brightness discrimination reaction response and the active conditioned avoidance response. In both sets of experiments, the standardized brahmi fraction showed a significant facilitatory effect in treated animals compared with untreated controls. In addition, regulatory pharmacological studies showed that the extract did not produce any untoward effect on gross behaviour or innate and motivated responses, even at doses 25 times higher than the effective dose.

In subsequent investigations, the efficacy of the memory-enhancing effect of bacosides was tested on rats using immobilization and scopolamine-induced stress, two experimental models of amnesia. Pretreatment with bacoside attenuated these amnesias. Furthermore, at the recommended therapeutic dose level, no systemic pharmacological or toxicological effects were found to be induced by the bacosides. They were also found to be safe in subacute toxicity studies in both rodents and primates.

Preclinical neuropharmacological studies demonstrated that both brahmi extract and bacosides improved short-term and intermediate memory, thus improving long-term memory.

Based on these wide-ranging studies,

the Drugs Controller of India granted CDRI permission to conduct Phase I clinical trials in healthy human volunteers. These trials did not reveal any undesirable effects. However, owing to the time that would have been required to conduct further clinical studies on purified bacosides, the decision was taken to market the standardized fraction of the plant extract as a herbal drug.

Thus the preparation containing standardized extract of *B. monniera* was licensed to a private company that commercialized the product under the trade name *Memory Plus*. The product was formally launched in February 1996 by the then prime minister, Narsimha Rao, and was successfully marketed and exported to several countries.

In 2001, the product was licensed to another company, Lumen Marketing, Chennai, India, which commercialized the product in 2002 under the name *ProMind* (fig. 1).

Meanwhile, limited clinical trials of the herbal product have been carried out in elderly persons with age-associated memory impairment and children affected by attention deficit hyperactivity

disorder, and the preparation has been found to improve their condition without any adverse effects.

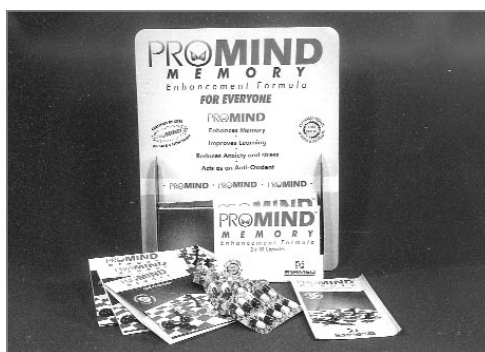
AN “ALLOVEDIC” DRUG FOR LOWERING BLOOD CHOLESTEROL: GUGULIPID

The lead for the development of guggulipid as a hypolipidaemic drug again came from the traditional system of medicine, Ayurveda, which prescribes gum guggulu — derived from the plant *Commiphora mukul* (false myrrh, family Burseraceae) — for the treatment of certain cardiovascular disorders, gout and arthritis.

The product owes its origin to the basic work on crude gum guggulu carried out at Banaras Hindu University in the 1960s. In 1970, samples of guggulu were sent to CDRI for the evaluation of their hypolipidaemic activities. Primary biological screening carried out at CDRI indicated the potential lipid-lowering capabilities of the gum and the results were first published in 1971.

Samples were also sent to a collaborator, Sukh Dev, at the National Chemical Laboratory, Pune, who successfully iden-

Figure 1 | *ProMind*, a commercially available standardized herbal fraction of *Bacopa monniera* with memory-enhancing properties.



tified the individual chemical components of the various fractions or oleoresin of gum guggulu. Meanwhile, scientists at CDRI were evaluating the biological efficacy and toxicity profile of different fractions of gum guggulu. They identified a toxic and inactive portion that was insoluble in ethyl acetate, and a safe and active portion that was soluble in ethyl acetate and contained compounds identified as E- and Z-guggulsterones (fig. 2). This ethyl acetate soluble fraction was named gugulipid. A joint patent involving Sukh Dev, then Director of Multi-Chem Research Centre, and CDRI was filed.

Clinical trials conducted by CDRI scientists showed that gugulipid reduced serum cholesterol and triglycerides by an average 24 per cent and 22 per cent,

respectively, and that some 260 of a group of 330 hyperlipidaemic patients responded to treatment. The results clearly indicated the efficacy of gugulipid and that it was tolerated better than clofibrate, the alternative available drug. Based on these results, in 1986, the Drugs Controller of India gave permission to market gugulipid as a new drug.

An agreement for licensing the product to Cipla Ltd., Bombay, was signed in January 1987, and the technology was formally released to the company by the former Prime Minister, Rajiv Gandhi.

Commercial production of gugulipid began in October 1987. It was marketed in the form of tablets and granules under the trade name *Guglip* and also exported (fig. 3).

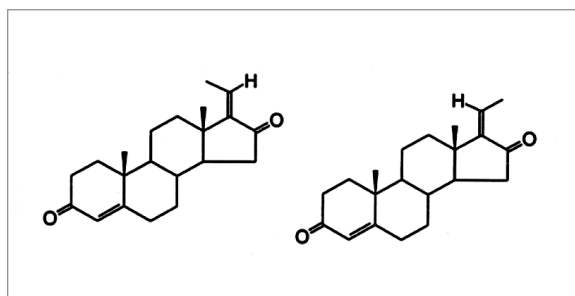


Figure 2 | The chemical structures of E- and Z-guggulsterones, the active components of gugulipid.



Figure 3 | *Guglip*, a commercial preparation containing the ethyl acetate soluble fraction of gum guggulu from *Commiphora mukul*, used to reduce blood cholesterol levels.

Since the preparation is a standardized extract of an Ayurvedic medicine and has been developed as a modern medicine, it was designated by the licensee firm as an “allovedic” drug, that is, a combination therapy incorporating concepts of modern medicine and Ayurveda. The drug was well received and demand shortly after its release showed an upward trend. Gugulipid was commercialized at 10 tonnes per annum and, from 1996 to 1997, its annual sales value was estimated at about US\$80,000. Based on the proceeds from these sales, CDRI received a good financial return in terms of royalty payments. However, owing to the unavailability of the gum guggulu raw material, demand for the drug could not be met and its production was discontinued in July 1997.

Since then, CDRI has developed a technique for manufacturing the active guggulsterones. This technology has now been licensed to a company for commercialization.

A BLOOD SCHIZONTOCIDAL ANTIMALARIAL: α - β ARTEETHER

Malaria is a major health problem in many parts of the world, particularly Africa, South America and southeast Asia. Cerebral malaria, caused by *Plasmodium falciparum*, is the most deadly form of malaria, is particularly difficult to treat and results in high mortality. Once the disease sets in, it progresses quickly. After the onset of coma, cerebral malaria patients are at high risk for 72 hours unless the disease is rapidly diagnosed

and treated with a fast-acting antimalarial drug that acts against the schizont stage of the parasite that multiplies in the blood cells. However, the available drug, chloroquine, is slow-acting, and resistance to chloroquine and other currently used antimalarial drugs is widespread and increasing.

Therefore, since the 1980s, efforts have been made to develop fast-acting blood schizontocides for the control of multi-drug-resistant malaria, and particularly cerebral malaria.

Artemisinin, derived from *Artemisia annua* (family Asteraceae, fig. 4), which is used as an antimalarial in traditional Chinese medicine, has been found effective as an antimalarial drug. Three chemical derivatives of artemisinin, namely, artemether, arteether and artesinic acid, are very effective against multi-drug-resistant malarial parasites.



Figure 4 | The *Artemisia annua* plant, source of the antimalarial compound, artemisinin.

Against this background, CDRI scientists decided to investigate the potential of developing new antimalarials belonging to the artemisinin series with different modes of action. As a result, arteether was developed in collaboration with the Central Institute of Medicinal and Aromatic Plants (CIMAP), a sister laboratory of CDRI in Lucknow. CIMAP introduced *A. annua* into India and developed efficient agrotechnology for its cultivation. Initially, it was grown in the Kashmir valley and large quantities of artemisinin were produced.

Artemisinin is sparingly soluble in water or oil and not well absorbed by the gastrointestinal tract. CDRI scientists, therefore, prepared several known derivatives of artemisinin. Among these, arteether (the ethyl ether of dihydroartemisinin) was found to be superior to the other so-called "semi-synthetic" derivatives because of its better bioavailability, lipophilicity and pharmacokinetic properties and lesser toxicity.

The conversion of artemisinin to arteether is a two-step process. First, sodium borohydride is used to reduce artemisinin to dihydroartemisinin. Then dihydroartemisinin is etherified by a Lewis acid catalysed reaction. This produces a 30:70 mixture of two chemically identical types of arteether, differing only in their structural composition: α -arteether, an oily substance, and β -arteether, which is

crystalline. Because both α - and β -arteether have been shown to be active against malaria, the activity of the latter being higher, it was decided to develop the mixture as a drug. There are three compelling reasons for following this route. First, the separation of β -arteether from the mixture would increase costs. Second, the mixture is effective and safe. Third, it has recently been shown that α -arteether has a synergistic action on the efficacy of the β form. Therefore, a mixture of α - and β -arteether was designated α/β arteether and developed as a drug jointly by CIMAP and CDRI.

After the necessary preclinical pharmacological and toxicological studies, α/β arteether was successfully used in clinical trials to treat some 500 malaria-infected patients at seven centres throughout India.

A distinguishing feature of α/β arteether is its fast-acting blood schizontocidal action. In a three-dose regimen, it is able to cure multi-drug-resistant or chloroquine-resistant *P. falciparum* malaria. Marketed under the brand name *E-mal* (fig. 5), it is a drug of choice for treating comatose cerebral malaria cases because of its quicker action. Arteether also blocks the transmission of malaria by virtue of its effect on another of the malaria parasites' life-cycle stages, the gametocytes, which are present in the blood and ingested by feeding mosquitoes.

Figure 5 |
Arteether, a three-dose semi-synthetic antimalarial drug derived from *Artemisia annua*.



PATENTING AND COMMERCIALIZATION

As described above, *Bacopa monniera* standardized fraction, guggulipid and arteether have all been patented and licensed to commercial partners. In total, 22 patents on guggulipid, arteether and *Bacopa* have been filed in India and abroad. Guggulipid was licensed to Cipla Ltd., Bombay, in January 1987 and was commercialized by the company later that year. The product was successfully marketed as tablets and granules under the name *Guglip*. By 1992, *Guglip* had reached a production value of more than US\$0.5 million at the current exchange rate (US\$1 = 45 rupees). However, since 1997, *Guglip* has not been available on the market owing to the scarcity of the raw material. During the 10 years that it was marketed, CDRI received a licensing premium plus sales royalties of about US\$70,000.

B. monniera extract was originally licensed to M/s Velvette International Pharma Products Ltd., Chennai, in 1996, and it was marketed under the trade name

Memory Plus in India and several other countries. Subsequently, the license of the company was cancelled and the product was licensed to a second licensee, Lumen Marketing Company, Chennai, which is now marketing it under the trade name *ProMind*.

The cost of developing arteether is estimated at US\$0.49 million. In 1997, it was licensed for commercial production to Themis Chemicals Ltd., Bombay. The product is marketed as *E-mal* and it has since generated almost US\$0.3 million in revenue and has been adopted in India's National Malaria Control Programme. International patents on arteether are being obtained, especially in countries where malaria is endemic. It is currently being marketed in sub-Saharan Africa and there are plans to extend its distribution to southeast Asian countries.

PARTNERSHIPS

The CDRI broad-based drug discovery and development programme involves

many partners, including:

- forest officials for help and guidance in the collection of samples from the wild;
- experts in traditional systems of medicine who help to identify plants of potential importance for drug discovery;
- the general public, national agencies, industry and non-governmental organizations for the bio-evaluation of plant samples received from them - either on a payment basis or on terms of shared benefits;
- agencies of the Government of India, including those concerned with drug regulation and traditional systems of Indian medicine, for regulatory compliance and quality control;
- foreign government agencies and international organizations for sponsorship and funding of projects of mutual interest; and
- industry, both Indian and foreign, for project sponsorship, contract research and licensing.

In particular, CDRI has received major support from the National Cancer Institute of the National Institutes of Health (NIH), United States, under which CDRI provided plant extracts for the screening of anticancer activity at NIH. This project was significant because, during its implementation, several biological test systems were reorganized to enable simultaneous screening of plant extracts for a range of biological

activities at CDRI.

As CDRI is primarily a publicly funded institution, the focus is always on those programmes relevant to national health care needs as formulated by the Ministry of Health and Family Welfare. A long-term project funded by the Indian Council for Medical Research, for example, is aimed at discovering potential drugs for diseases and disorders for which no effective therapies are available in modern medicine such as fertility regulation, filariasis, liver problems and wound healing.

Increasing emphasis on the commercialization of products and techniques, including the successful commercialization of guggulipid, bacoside fraction and arteether, have helped CDRI to develop close links with industry. In the early days, the Institute would typically license a product to industry as soon as a product had successfully completed preclinical toxicity trials. However, it is now considered appropriate to invite industrial partnership at the drug-discovery stage, thus enabling the risks and costs involved in discovery and development to be shared. Though an industrial partner may not continue as a collaborator throughout the clinical studies, perhaps owing to a change of the company's ownership or focus, CDRI retains the option to license a product to other commercial partners.

CDRI has also established links with King George's Medical College, Lucknow, and Seth G.S. Medical College, Mumbai, in order to conduct clinical studies in collaboration with physicians and involve these experts in

evaluating the clinical acceptability of products under development.

REPLICABILITY

Many developing countries are rich in traditional medicines. Their standardization will help to decide suitable dosage, control the quality and ensure their safety and efficacy. In addition, many countries are home to plant species related to known medicinal plants and these could be used as alternatives for the development of suitable products.

The CDRI drug development programme is a good model for developing countries rich in such biodiversity. However, countries lacking the appropriate facilities and expertise will find it difficult and expensive to copy the CDRI model.

The approach pursued at CDRI can be replicated by interested countries and organizations by first of all systematically documenting their medicinal plants, evaluating their biological activities, and developing protocols for quality control, standardization, safety and efficacy studies. Interested countries could outsource such evaluations to CDRI and other institutions in India.

Standardized plant extracts are therapeutically effective, devoid of side effects and toxicity, and accepted by patients. They also save on the loss of plant material used in preparing pure single-molecule drugs, use simpler technologies for commercial production and are relatively inexpensive. At least some of these bene-

fits have been demonstrated by CDRI through the research and marketing of its products, including guggulipid, *B. monniera* fraction and arteether.

POLICY IMPLICATIONS

In view of the emerging competition from global players and the increasing demand for natural products, natural resources must be protected through conservation, judicious exploitation, intellectual property protection and the sharing of benefits with local communities. Efforts in all these areas require the formulation of effective policies.

Following the new patent regime adopted by India under a World Trade Organization (WTO) agreement, new Indian patent law allows a product patent to last for 20 years, compared to the seven-year term allowed under the earlier process patent. The product patent offers better opportunities that can be exploited in several ways, including the sale of novel formulations and formulations with synergistic effects. The new legislation provides a major opportunity to research institutions such as CDRI, involved in discovery and development of new drugs from medicinal plants, to file product patents in India.

LESSONS LEARNED

To be successful, programmes for developing modern drugs from plants

and herbal remedies require multidisciplinary teams with expertise in such areas as botany, phytochemistry, pharmacology, toxicology, pharmacokinetics, pharmaceuticals and clinical studies. At CDRI, the availability of expertise in all these areas, along with the required facilities within a single institution, is a major component of the success of the Institute's programme.

Even so, the time and expense required to develop modern drugs can be prohibitive. Therefore, wherever possible, a quicker, more economical, alternative route — that of developing herbal preparations to international standards — may be followed. Such products also tend to be less expensive for the consumer.

To further reduce costs, wherever feasible, an industrial partner should be involved early in the drug/herbal preparation development process. This not only reduces the risks run by the research institution but also makes available the expertise of the industrial partner in the areas of market research, product development and commercialization.

A problem with the commercialization of herbal drugs is the requirement for a constant supply of raw plant material. Availability of plant material must be ensured by cultivation. This was achieved in the case of *A. annua*, the source of artemisinin, through collaboration with a sister institution, CIMAP, but has not been achieved in the case of gum guggul, with the result that the guggulipid supply could not be sustained.

It is the responsibility of the licensing organization, in this case CDRI, to periodically check the quality of the drug marketed by a licensee, and if manufacturing and marketing do not conform to defined standards of quality, the license may be cancelled. This also helps to maintain the reputation of the laboratory, which can be important for obtaining the acceptance of new products not only by the public but also by the regulatory agencies.

IMPACT

Herbal remedies can easily be integrated into primary health care, which requires milder medication, and thus improve the quality of life and the health of the population, reducing mortality, morbidity and man-hours lost owing to sickness, leading to overall improvement in productivity and economic activity, development and social well-being. Such preparations of required quality can be manufactured easily by small-scale units.

FUTURE PLANS

The current and future programmes of CDRI will be dictated by the urgent need for achieving global competitiveness through focused programmes and use of sophisticated high-throughput technologies and quality-assurance systems. Wherever possible, existing leads will be fully exploited to develop new products. Thus, plans for drug development will focus on:

Screening and screening tools. New *in vitro* screens and *in vivo* models will be added, including enzyme and cell-based systems and alternative animals as substitutes for conventional laboratory animals. The emphasis will be on quicker and more reliable tests for high-throughput screening.

Development of new, emerging and existing leads. Efforts to develop new leads will continue. A finite number of terrestrial plants will be collected, identified and documented annually and bioassay guided fractionation, isolation and characterization of active principles will be carried out. Active ingredients will be followed up for development as either herbal medicines or modern drugs. Several new leads that have been identified, possessing anti-diabetic and cholesterol-lowering properties, will be followed up with detailed chemical and pharmacological studies. In addition, leads at an advanced stage of development, including the liver-protecting *Picroliv* and the anti-diabetic CT-1, will be further developed for commercialization.

Networked programmes. Networking with interested institutions and industry will be established wherever feasible. Nationally coordinated projects to search for new drugs from traditional remedies and indigenous plants as well as India's marine resources will continue to be pursued. CDRI also provides opportunities for collaborative research projects with other developing countries under existing inter-governmental bilateral programmes.

New approaches. To face emerging challenges and remain competitive in the international arena, infrastructure, facilities and expertise will continue to be upgraded and strengthened.

PUBLICATIONS

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Project participants:

BACOPA MONNIERA

B.N. Dhawan and H.K. Singh: Evaluation of memory improvement activity.

Raghwendra Pal: Preparation of standardized fraction, method of quantitative estimation of bacoside A content, structure elucidation of bacoside A3.

D.K. Kulshreshtha: Preparation of the standardized fraction, detailed chemistry of bacosides.

GUGULIPID

Sukh Dev, National Chemistry Laboratory, Pune: Chemical analysis of guggul fraction.

Nitya Nand: Chemical analysis of guggul fraction.

N.K. Kapoor: Study of hypolipidaemic activity.

Ramesh Chandra: Study of hypolipidaemic activity.

Swarn Nityanand: Clinical studies.

Ram Pratap: Synthesis of active molecules, guggulsterones.

ARTEETHER

CIMAP: Supply of material for preclinical studies.

G.P. Dutta: Efficacy studies in rodents and monkeys.

Chandan Singh: Scale-up studies and collaboration with industry.

O.P. Asthana: Clinical trials.
