# Computer Services for Research on Plants for Fertility Regulation\*

Norman R. Farnsworth, William D. Loub, Doel D. Soejarto, Geoffrey A. Cordell, Mary Louise Quinn and Karen Mulholland

Department of Pharmacognosy and Pharmacology, College of Pharmacy University of Illinois at the Medical Center, Chicago, Illinois, U.S.A.

#### Introduction

NAPRALERT, an acronym for NAtural, PRoducts ALERT, is a specialized data retrieval system for natural product chemistry and pharmacology. The program, in its present computerized form, grew out of an attempt to document manually on paper the world literature with regard to the chemistry and pharmacology of natural products, primarily associated with plants. This was started in the department of Pharmacognosy at the University of Pittsburgh in the early 1960's. Ten years later, it took on a simple computerized form through a collaboration with Schering A.G. of Berlin, West Germany. Following an end to this collaborative effort in 1975, the program, now at the University of Illinois at the Medical Center in Chicago, was expanded to include a more comprehensive data base file covering marine, micr obial and animal sources as well.

The new data base design utilizes four distinct record types, i.e. demographic, taxonomic, chemical and pharmacologic, to assemble under sixty-five field names or categories, data from a variety of literature sources. Thus, a comprehensive computerized data file has been established which is able to store information in detail and provide retrieval through a series of specialized formats. This article discusses in some detail the utilization of the NAPRALERT data base within the Special Programme of Research, Development and Research Training in Human Reproduction of the World Health Organization (W.H.O.) program to identify indigenous plants exhibiting fertility regulating properties. Earlier papers describing various aspects of NAPRAL-ERT have been published<sup>1,2)</sup>.

#### **Program Organization**

In order to implement this new concept of a detailed computerized surveillance of the natural product literature, the program was organized into four major areas of management, i.e. literature collection, coding, verification of the accurate transfer of information prior to and following its entry into the data base and finally data entry procedures, including the generation of a permanent file of collected literature. A scheme of this organization is presented in Figure 1 and its application is further described in the following paragraphs.

<sup>\*</sup> Presented 26 February 1981 at the Seminar on Research on Plants and Plant Derived Products for Fertility Regulation, Seoul, Korea. The Seminar was sponsored by the Natural Products Research Institute, Institute of Reproductive Medicine and Population, Seoul National University, the Korean Society of Pharmacognosy and World Health Organization.

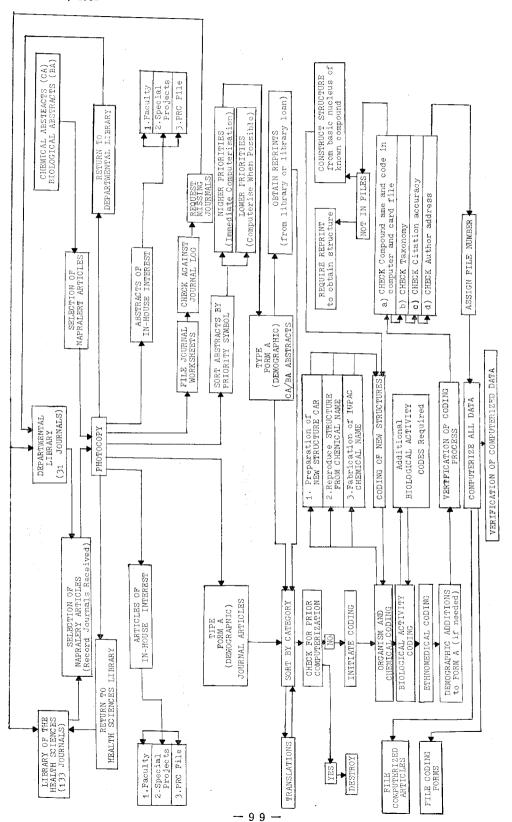


Fig. 1. NAPRALERT program organization

A first step in the organization of NAPRAL-ERT was the development of an adequate source and a reliable acquisition program for the world natural product literature. The Library of the Health Sciences on the Medical Center campus, as well as other nearby Chicago library collections provide a particularly rich source of such information. This is further supplemented through the regular acquisition of more obscure journals, dealing almost exclusively in natural product research publications, which are kindly provided through a number of individuals and institutions interested in the program.

Coverage of the literature from these various sources has included a thorough page by page search of *Chemical Abstracts* and *Biological Abstracts*. *Chemical Abstracts* alone provides the opportunity to review more than 400,000 documents each year, collected from over 14,000 individually published journals (1,2). In addition to these secondary sources, doctoral level scientists directly review the more than 160

journals obtained from the Library's periodical department, interested contributors or departmental subscriptions. These primary literature sources, given direct review, were chosen for their relevancy to natural product literature citations and it has been estimated that approximately seventyfive per cent of all new research papers devoted to natural product data appear in these journals.

Coding the variety of reseach parameters encountered under the NAPRALERT collection process has necessitated the implementation of a series of alphanumeric codes to represent many of the scientific terms computerized. Such a procedure not only reduces dramatically the number of spelling errors during data entry, but also makes storage of the information more cost efficient. The types of information which are coded and the field names used to enter and maintain this information in the NAPRALERT data base are listed in Table 1.

Although financial constraints have not allowed

Table I. Field names and types of information computerized by NAPRALERT

| Field name              | Description  |
|-------------------------|--|
| Record type-Demographic |  |
| Citation number         | File number assigned sequentially at time of data entry. |
| Citation title          | Accommodates first 765 characters of the title.          |
| Author                  | Lists all author names associated with the article.      |
| Journal                 | Stores journal name or appropriate alphanumeric code.    |
| Volume number           | Volume designation of the above journal entry.           |
| Issue number            | Accommodates issue number when needed.                   |
| Page number             | Number of first page on the article.                     |
| Last page               | Number of the last page of the article.                  |
| Year                    | Year of publication.                                     |
| Language                | Language used in the article, i.e. German, English, etc. |
| Article type            | Designates type of article, i.e. research, review, etc.  |
| Abstract                | Lists title of secondary reference source, i.e. C.A.     |
| Reference volume number | Secondary source volume number.                          |
| Abstract number         | Secondary reference abstract number.                     |
| Paragraph number        | Secondary reference paragraph number.                    |
| Address code            | Alphanumeric address code if one has been assigned.      |
| Department code         | Departmental address for senior author, if any.          |

| Table I. (Continued)            |   |  |  |
|---------------------------------|---|--|--|
| Field name                      | Description   |  |  |
| College address                 | School, college or institute name in senior author address.   |  |  |
| University address              | University, institute or company name in address.   |  |  |
| City                            | City for senior author's address.   |  |  |
| State                           | State, district or province for address.  |  |  |
| Zip code                        | ⊿ip code, if given.   |  |  |
| Country                         | Country of residence for senior author.   |  |  |
| Grant agency                    | Agency supporting reported research.  |  |  |
| Grant number                    | Granting agency identifying number.   |  |  |
| Record type-Organism            |   |  |  |
| Organism                        | Code identifying organism class, i.e. angiosperm, gymnosperm, dicot, monocot, etc.                              |  |  |
| Family                          | Botanical family name of the organism studied.  |  |  |
| Genus                           | Botanical genus name of the organism studied.   |  |  |
| Species                         | Botanical species name.   |  |  |
| Species citation                | Species authority citation.   |  |  |
| Subspecies                      | Subspecies name, if any.  |  |  |
| Subspecies citation             | Subspecies authority citation, if any.  |  |  |
| Common name                     | Accommodates common names of the organism.  |  |  |
| Taxon synonym                   | Synonym for the taxon and its authority.  |  |  |
| Organism part                   | Lists organism part studied.  |  |  |
| Part condition                  | States condition of organism part studied, i.e. dried, fresh, etc.  |  |  |
| Amount utilized                 | Quantity of organism used in the study.   |  |  |
| Record type- Compound           |   |  |  |
| Compound isolated               | Amount of compound isolated, if any.  |  |  |
| Organism country                | Geographic source of organism studied.  |  |  |
| Compound name                   | Compound name, vernacular name where possible.  |  |  |
| Compound code                   | A binary numeric code for the chemical class, i.e. indole alkaloid flavone, steroid, proteid, etc.              |  |  |
| Sub-structure code              | Stores a three digit numeric code for the carbon skeleton.  |  |  |
| Functional group code           | Stores two character codes for functional groups present.   |  |  |
| Record type-Pharmacology        |   |  |  |
| Worktype                        | Alphanumeric sorting code to designate type of work performed i.e. in vitro, in vivo, in situ and/or in humans. |  |  |
| Major phararmacologic activity  | Binary code for 16 different pharmacological classes of study, i.e. CNS, chemotherapeutic, antifertility, etc.  |  |  |
| Specific pharmacologic activity | Three digit code for specific pharmacological activity studied. 1,000 codes available, to date.                 |  |  |
| Director codes                  | Enters "PDC" code (see Table 4).  |  |  |
| Weighting codes                 | Enters weighting point designator (see Table 2).  |  |  |
| Alert codes                     | Enters "Alert Data" codes for sorting, efficiency.  |  |  |
| Experimntal modifications       | Stores miscellaneous statements describing a special disease conditoir or test parameter.                       |  |  |
| Extract                         | Binary code used to identify type extract studied.  |  |  |
| Mode of administration          | Binary code used to identify mode of administration.  |  |  |
| Test species<br>Sex             | Binary code describing type of animal used, if any.  Sex of above animal, if appropriate                        |  |  |

Table I. (Continued)

| the control of the co |   |
|--|---|
| Field name   | Description   |
| Dose expression  | Identifies type and numeric amount of dose, i.e. LD50 1.0, MLD        |
|  | 2.5 or concentration, i.e. MIC 25.0                                   |
| Dose unit  | Dose unit of above dose or concentration, i.e. mg, mcg, etc.          |
| Per unit weight  | Per unit weigt of above dose or concentration, i.e. kg, per plate,    |
|  | gm, person, etc.  |
| Qualitative result   | Qualitative expression of result, i.e. active, inactive, equivocal.   |
| Quantitative result  | Numerical expression of result data.                                  |
| Expression   | Type of quantitative result, i.e. increased life span (ILS).          |
| Pathological system  | Alphanumeric code for disease test organism substrate or tissue used. |
|  |   |

computer entry of all of the natural product data collected on an absolute basis, the following general guidelines apply to the types of information that have been covered and are currently computerized. First, all literature reporting chemical compounds present in or isolated from natural sources are given immediate priority for data entry. These data include the taxonomic source in detail, the organism part from which the compound was derived, its geographic source and percentage yields, where this has been stated or can be calculated from the data presented. Primary interest has been with "secondary" chemical constituents, and articles reporting predictable occurrences ubiquitous simple sugars, amino acids, fatty acids and the like are not usually computerized.

Secondly, all literature describing biological effects of extracts prepared from plants, animal, microbes and marine organisms, or for chemical compounds of natural origin, are also given immediate priority for computerization. In most cases, biological effects for well established natural products such as atropine, digitoxin, reserpine, tubocurarine, the penicillins, etc., are not considered unless they represent unique types of activity or unusual toxic effects.

In addition to maintaining current literature coverage on the subject matter indicated above, a large number of retrospect searches, reaching

back into the early 1900 or late 1800 literature have been carried out and the data computerized. NAPRALERT, with regard to cytotoxic and/or antitumor effects of natural products, as well as natural products affecting mammalian reproduction, is perhaps the most extensive and complete data base in existence today. Presently, more than 35,000 individual citations have been computerzed in the form of more than one-half million individual records. In addition to the wide variety of biological activities stored in these records, more than 50,000 different chemical compounds of natural origin are also described. Folklore (ethnomedical) information contained in the data base has been accumulated where mentioned in a scientific article or following a partial or complete computerization of more than 400 books on the subject, the latter representing virtually every country in the world.

Negative as well as positive data, whether dealing with biological effects or the analysis of chemical constituents, are computerized into the NAPRALERT data base file. Important to the WHO Task Force on Indigenous Plant for Fertility Regulation has been the assignment of various alert codes and numerical weighting values for purposes of applying a predictive analysis to the data contained in the NAPRALERT file. Tables 2 and 3 list some of the criteria used to assign these values.

Table II. Positive and negative weighting values used to rank-order experimental and/or ethnomedical data computerized

| Type of data assessed   | Type of weighting |
|---|-------------------|
| Statistical data given in the report.   | +                 |
| Data reported by author are adequate to support conclusion.                               | +                 |
| Well designed and executed study with believable positive results reported.               | 4-                |
| Superb study: Data support conclusions of the author in all respects.                     | +                 |
| Poor experimental design. Data lacking to support conclusions of the author.              | -                 |
| Control animals not used in the study.  |                   |
| Data reported in article are insufficient to support the conclusions of the author(s).    | _                 |
| Experimental details are inadequate to evaluate the data.                                 | _                 |
| Details of ethnomedical use are too vague to evaluate.                                    |                   |
| Ethnomedical use may be associated with "Doctrine of Signatures".                         |                   |
| Confusing data are reported making it difficult to assess the results. See notes attached | to                |
| original manuscript in file.  | _                 |
| Control animals did not receive the solvent or suspending agent used for test material.   | _                 |
| Doses employed do not make sense. See comments attached to original article for expla     | nation. —         |
| This plant is predictably hepatotoxic and/or carcinogenic                                 | _                 |
| Reported positive results may be due to a nutritional deficiency in the test animal.      | _                 |
| Data not statisticaly analyzed.   | _                 |
| Correct identification of the plant highly questionable.                                  |                   |
| Data not believable. See comments attached to original article for explanation.           | _                 |
| Positive data reported are of questionable significance to fertility regulation.          |                   |
| Dose-response relationship invalid.   |                   |
| Reported effect diminishes on repeated dosing.  | _                 |
| Ethnomedical use most likely based on magic, ritual or superstition.                      | <b>,</b>          |
| Data reported are inconsistent. See remarks attached to original article for explanation. | _                 |
| Data reported are adequate to support conclusions of the author.                          | +                 |

Table III. Approximate weighting values assigned to ethnomedical data

| Computer points assigned | Criteria   |  |  |
|--------------------------|--|--|--|
| 150~200                  | Reference has details concerning dosage regimen and has been reported as part of an anthropological and/or ethnomedical study.   |  |  |
| 100~150                  | Field notes by scientific investigators, i.e. notes on herbarium voucher specimens, etc.   |  |  |
| 100~125                  | Same as above, but specific details are lacking.   |  |  |
| 100~125                  | Plant is claimed to be used in an organized system of medicine, i.e. Traditional Chinese Medicine, Ayurvedic Medicine, etc., and details of dosing with the preparation are given. |  |  |
| 50~ 75                   | Same as above, but details are lacking.  |  |  |
| 50 <b>∼</b> 75           | Ethnographic data only are given.  |  |  |
| 50 <b>∼</b> 75           | Incidental mention of use in a scientific paper as an introduction, without details.   |  |  |

### The Predictive Analysis Program

When the new NAPRALERT data base was conceived in 1975, a prime consideration in its construction was the development of a capability to evaluate the world literature on natural products for the purpose of identifying new sources of clinical drugs. Thus, when the WHO Special Programme of Research Development and Research Training in Human Reproduction established a Task Force on Indigenous Plants for Fertility Regulation, the first opportunity to utilize NAPRALERT as a predictive tool to identify leads was challenged.

A review of the NAPRALERT data base for plant sources having biological, chemical or folkloric data indicating a possible involvement in fertility regulation produced a list of more than 1,300 plant species. A series of retrospective searches of the literature, directed toward this same type information, provided a list of more than 3,200 additional species having related properties. It therefore became prudent to develop a means to rank order the more than 4,500 plant species in such a manner that the

most promising 300 or so could be identified for evaluation in experimental protocols, since random selection from a list of plants this size could not be considered a feasible approach to the problem.

Using a multidisciplinary approach, e.g. the input of pharmacologists, reproductive physiologists, chemists and botanists prime consideration was given to the identification of those biolog ical activities which result in some form of fertility regulation. These were further identified with one or more appropriate modes of administration, designated by nine "Priority Designator Codes" (PDC). Table 4 presents a description of these codes. A second consideration was the identification of those fertility regulating activities of priority interest to the WHO Task Force namely interference with the implantation process in the female and those which may interefere with spermatogenesis and/ or sperm maturation in the male.

A program was then developed whereby the computer could apply these considerations to the list of plants in question by assessing the collective values of positive and negative weights assigned according to the subjective codes

Table IV. Priority designator codes (PDC)

| PDC | Fertility regulation application  |
|-----|---|
| A   | Used once per month by the female, just prior to expected menstruation.   |
| В   | Male antifertility agent (Used by the male).  |
| С   | Used by the female after one missed menses.   |
| D   | Post mid-cycle (post-ovulatory) coital (interceptive, anti-implantation) use by the female.   |
| E   | Continuous administration by the female (could be postcoital), that was not used only post-ovulatory.   |
| F   | Unable to calssify more specifically (human and/or animal data, ethnomedical and/or experimental), but only designated as "contraceptive", etc. |
| G   | Male antifertility agent, used in the female (could also be continuous administration, but definitely not "D" above).                           |
| H   | Used by the female after more than one missed menses.   |
| I   | Used by the female just after menstruation.   |

presented in Table 2 and 3. These values, used to rank-order the list of plants, were further modified by criteria established under combinations of the PDC process to identify the biological attributes of interest to the Task Force Programme. For three successive years, 1978~1980, this predictive computer program has been applied to the most current data available in the NAPRALERT data base and a rank ordered list of plants prepared.

The Task Force on Indigenous Plants for Fertility Regulation, in addition to being multidisciplinary, supports a collaborative multicentered program involving research groups in Hong Kong, the Republic of Korea, Sri Lanka and the United States. Plants identified through the above process as most promising were then assigned to these centres primarily on the basis of their indigenous character. Modifications in the predictive program, arrived at by experimenta tion, were applied to the computer analysis and the resulting changes in the rank ordering of plants on the list were reflected in changes of assigned plants to each of the Centres.

To date, approximately fifty plants from the top 300 on the list have been tested and several of these appear to have reproducible anti-implantation activity in two different animal models. The real practical value of these plants and this novel approach to drug development must await further studies, but it would appear that NAP-RALERT has performed a very important service with regard to the aims of this WHO program.

## Future Computer Services Available to the WHO Special Programme

Up to the present, the NAPRALERT system has served to provide the Task Force on Indigenous Plants for Fertility Regulation with the

global literature concerned with alleged and/or experimental data on plants as they relate to any aspect of fertility regulation. It has also provided a unique system for analyzing all of the data in these literature reports in order to identify promising candidate plants for experimental studies. Initial test results seem to indicate that the number of plants required to uncover anti-implantation activities is far less than if a random selection process was used. It will only be considered as a valid procedure after active compounds of known structure are isolated from the plants being studied.

Our literature surveillance activities continue in the future, although at this time there does not appear to be a need for periodic evaluation of data to identify further plants that should be included in the activities of the Task Force. At some future date, however, such an analysis can be performed if required. If the progress of this program can draw on the experience of conventional drugdevelopment programs, one can anticipate that many of the active leads will not culminate in agents useful in humans. Some of the active principles will prove to be too toxic, some will be unstable, and others will be obtainable in only trace quantities and may have structures that are not amenable to commerical synthesis. Thus a continuous infusion of new leads into the program will be necessary.

Based on a systematic surveillance of the literature concerned with fertility regulating plants over the past three years, it is obvious that the number of publications is markedly increasing. Apparently the activities of the Special Programme have attracted sufficient attention as to stimulate other investigators in the field of natural products to initiate research on fertility regulating plants. Thus, in order to provide all scientists involved in the activities

of the Task Force on Indigenous Plants for Fertility Regulation with current literature in this field, the Special Programme has set forth the following areas in which NAPRALERT will continue to provide service.

- 1. To provide bimonthly reports on current literature containing information pertinent to the biological effects (ethnomedical and experimental) of plants relating to fertility regulation. These bimonthly reports will provide full citations of each article, but will not provide the details in each report.
- 2. Biannual updates on all computerized data for each plant being actively studied in each of the centres will be provided. These will be extensions of the quarterly update reports that have been provided in the past and will consist of expanded computer output of (a) ethnomedical, (b) in vitro, (c) in situ and/or in vivo, and (d) human effects of plants that have been assigned to each Centre. In addition, updated information on chemical compounds reported present in these plants will be provided.
- 3. Since many of the articles from which data have been computerized may not be available in some of the centres, copies of the articles will be provided to investigators.
- 4. As chemical work accelerates in each of the centres, there are elements of the NAPRA-LERT data base that can prove useful to speed up the identification and/or structure-elucidation of isolated active compounds.

A recent example can be cited as to how NAPRALERT can be used to identify compounds.

We isolated a crystalline compound form Amyris pinnata and obtained all of the usual spectral data, e.g. UV, IR, PMR, CMR, MS and specific rotation. Analysis of the data indicated that our isolate was a lignan having the skeletal type I, which contains at least one meth-

oxyl group, at least one methylenedioxy group, a lactone that was not  $\alpha, \beta$ -unsaturated: phenolic hydroxy groups were absent.

A query of the NAPRALERT data base for a list of compounds having these characteristics indicated that 153 linans of skeletal type I were available. However, the print-out indicated that only six contained the skeleton and functional groups previously indicated.

These were found to be austrobailignan 1 (II), austrobailignan 2, bursehernin, morelensin, deoxypodophyllotoxin. An inspection of physical data for all of these compounds revealed that austrobailignan I, (II) was identical in all respects with our isolate.

Another application of the data base was to identify all naturally occurring compounds having the same general molecular features as embelin (III), a benzoquinone of interest to the Task Force. Prenyl side chains, characteristic of the ubiquitous ubiquinone and related compounds were to be excluded, as were compounds having methoxy substituents. It was found that only five compounds could be identified in the

data base, e.g. embelin (III), maesaquinone

(IV), polygonaquinone(V), rapanone(VI) and

bhogatin (VII). It can be anticipated that all of

$$R_1$$
  $O$   $O$   $R$ 

Vol. 12, No. 2, 1981

| Compound name   |     | R                                     | $R_1$             |
|-----------------|-----|---------------------------------------|-------------------|
| Embelin         | П   | -n-C <sub>11</sub> H <sub>23</sub>    | H-                |
| Maesaquinone    | N   | $-CH_2(CH_2)_{12}-CH=CH(CH_2)_3-CH_8$ | CH <sub>3</sub> - |
| Polygonaquinone | V   | $-n-C_{21}H_{43}$                     | CH <sub>3</sub> - |
| Rapanone        | VI  | $-n-C_{13}H_{27}$                     | H-                |
| Bhogatin        | VII | $-n-C_9H_{19}$                        | CH <sub>3</sub> - |

these compounds would have similar biological effects, but perhaps one or more could be more active and less toxic than the parent embelin.

5. On request we will be able to provide chemical and/or biological activity profiles on all species of a genus being investigated for fertility-regulating activity. Quite often information on related species of the same genus can aid the investigator in designing schemes for the rapid and efficient isolation of active principles.

In the past, we have had problems in photocopying computer output, since reduction of normal computer sheets, coupled with the often mediocre clarity of print, has produced difficulties in reading the data provided to investigators. We are now utilizing a Xerox 9700 printer, coupled with computer output, to generate much clearer copy. An example of the new format is presented in Exhibit 1, in which representative data from profiles on *Plumbago rosea* L. have been printed.

In conclusion, NAPRALERT represents a unique data base of information concerned with the chemistry and pharmacology of natural products. It is the largest known collection of data on plants with fertility-regulating potential available today. We are confident that there are

many different applications of the data base that will enhance the productivity and efficienty of scientific studies being carried out on fertility regulating plants and encourage all of those affiliated with the WHO Task Force on Indigenous Plants for Fertility Regulation to take advantage of its availability. We are anxious to provide any service to colleagues, and welcome inquiries at to the applicability of the data base to solve problems related to their research.

Acknowledgements: The NAPRALERT data base has been supported, in part, by funds from the World Health Organization, Special Programme of Research, Development and Research Training in Human Reproduction (Project 78135) and from the National Cancer Institute (U.S.A) (Contract CM-97259).

#### Literature Cited

- Soejarto, D.D., A.S. Bingel, M. Slaytor and N.R. Farnsworth: Fertility regulating agents from plants. Bull. WHO 56, 343-352 (1978).
- Farnsworth, N.R.: World Health Organizati on Program on Indigenous Plants for Fertility Regulation. Proc. IUPAC 11th Internat. Symp. Chem. Nat. Prod., Golden Sands, Bulgaria 4(2), 475-489 (1978).

#### Exhibit I. A Computerized profile of ethnomedical, biological and chemical data for Plumbago rosea

```
ETHNOMEDICAL INFORMATION ON PLUMBAGO ROSEA
```

(NO ADDRESS GIVEN)

```
(THIS PLANT IS COMMONLY KNOWN AS BINASA : CHERAKA MERAH : CHERAKA MERAH (MALAY) : CHET TAMUM PLONGDENG : CHITRA : FIRE PLANT
LAL CHITRA : LAL CHITRA (HINDUSTANT) : LAL CHITRAK : LAL-CHITA : LALCHITRA : LAUREL : LEADWORT,OFFICINAL : LFOWORT,ROSY-FLOWERED
OFFICINAL LEADWORT : PLANT,FIRE : ROKTA-CHITA : ROSY-FLOWERED LEADWORT : SETAKA : SHITURRIUE : SITAKA : TURRAKA MERAH : )
                             (SYMONOMOUS LATIN BINOMIALS FOR THIS SPECIES ARE CLAIMED TO BE PLUMBAGO COCCINEA.: PLUMBAGO INDICA : )
PLUMBAGO ROSFA . CLUMBAGINACEAE BARK PHILIPPINES

USED AS AN ECBDLIC

HOT HOD CAT-OPAL-HUMAN(PREGNANT) - A4508(47.1)

PLUMBAGO ROSEA . PLUMBAGINACEAE PART NOT SPECIFIED INDONESTA

USED AS AN ARDRITFACIENT

TYPE EXT NOT STATED-ROUTE NOT GIVEN-HUMAN(PREGNANT) - A6682(48.1)

PLUMBAGO ROSEA . PLUMBAGINACEAE PART NOT SPECIFIED PARTSTAN

USED TO PROCURE ABBRITON

TYPE EXT NOT STATED-ROUTE NOT GIVEN-HUMAN(PREGNANT) - A1908(28.1)

USED SOR POST-PARTUM HEMBREHAGE

TYPE EXT NOT STATED-ROUTE NOT GIVEN-HUMAN (PREGNANT) - A1908(28.1)

USED SOR POST-PARTUM HEMBREHAGE

FULUMBAGO ROSEA . PLUMBAGINACEAE ROOT EAST INDIES

USED AGAINST INTERMITIENT FEVER

HOT HOD EXT-OPAL-HUMAN ADULT - A4712(7.7)

USED AGAINST SCABLES

HOT HOD EXT-ORAL-HUMAN ADULT - A4712(7.4)

USED AGAINST CANCEROUS DISEASES

HOT HOD EXT-ORAL-HUMAN ADULT - A4712(7.5)

USED AS A BIURETIC

HOT HOD EXT-ORAL-HUMAN ADULT - A4712(7.5)

USED AS A BIURETIC

HOT HOD EXT-ORAL-HUMAN ADULT - A4712(7.2)

USED AS A BIURETIC

HOT HOD EXT-ORAL-HUMAN ADULT - A4712(7.2)

USED AS AN ABBRITFACIENT

TYPE EXT NOT STATED-GRANT) - A4712(7.1)

PLUMBAGO ROSEA . PLUMBAGINACEAE ROOT INDIA

USED AS AN ABBRITFACIENT

TYPE EXT NOT STATED-GRANTHUMAN PREGNANT) - A4712(7.1)

USED AS AN ABBRITFACIENT

TYPE EXT NOT STATED-GRANTHUMAN PREGNANT) - A4712(7.1)

USED TO EXPEL THE FETUS FROM THE WOMEN WHETHER DEAD OR ALLYE

CHEW THE ROOTS FOR 7 DAYS, MORNING AND EVENTING, ALONG WITH HETEL NUT AND ABBRITON RESULTS

PLANT-ORAL-HUMAN(PREGNANT) - A6590(122.1)

INTRODUCE ROOT INTO VAGINAT TO HUMCE ABORTION

ROOT-VAGINAL-HUMAN(PREGNANT) - A6590(122.2)

USED AS AN ABBRITFACIENT

TYPE EXT NOT STATED-GRANTHUM AND PREGNANT - A6590(122.2)

USED AS AN ABBRITFACIENT

TO THE OWN HUMCE ROOTION AND ABBRITFACIENT

TO THE AND ABBRITFACIENT

TO THE ABBRITFACIENT LINK BOUGED THAT THE VAGINA AND APPLIED DIRECTLY TO THE NECK OF UTERUS ROOTI-VAGINAL-HUMAN(PREGNANT) - A6590(122.2)

USED AS AN ABBRITFACIENT

LUSD AS AN ABBRITFACIENT LINKBOUGED THAT THE VAGINA AND APPLIED DIRECTLY TO THE NECK OF UTERUS ROOTI-VAGINAL HUMAN(PREGNAN
   USED AS AN ARBORTIFACIENT: INTRODUCED INTO THE VAGINA AND APPLIED DIRECTLY TO THE NECK O GOOT-VAGINAL-HUMAN(PREGNANT)** AO115(190.1)

USED AS AN ABORTIFACIENT
HOT HZO EXT-ORAL-HUMAN(PREGNANT)** WOOQZ(G.1)

PLUMBAGO ROSEA PLUMBAGINACCAE ROOT INDOMESIA
SAID TO CAUSE DEATH WHEN POULTICE IS APPLIED VAGINALLY
HZO EXT-VAGINAL-HUMAN ADULT** A4162(21.2)

*USED AS AN ABORTIFACIENT
POULTICE APPLIED LOCALLY
HZO EXT-VAGINAL-HUMAN(PREGNANT)** A4462(21.1)

PLUMBAGO ROSEA PLUMBAGINACCAE ROOT MALAYA
USED AS AN ABORTIFACIENT
MIXED WITH LAWSONIA ALEA, GARDENIA GRIFFITHII, CANANGA DORRATA, GONIOTHALAMUS TAPIS
HIGH HZO EXTIVAGINAL-HUMAN(PREGNANT)** A4462(21.1)

PLANT MIXTURE USED, ACTIVITY COULD BE DUE TO OTHER THAN THIS ONE
PLUMBAGO ROSEA PLUMBAGINACCAE ROOT MALAYSIA
INSERTED IN THE OS UILPI AS AN ABORTION STICK OR USED GRALLY IN FORM OF A DECOCTION
PLANT-MAGINAL-HUMAN(PREGNANT)** A4587(26.1)
MENTIONED BY SANSKRIT WRITERS AS AN ABORTIFACIENT
DRIED ROOTS CLAIMED LESS ACTIVE THAN FEESH ROOTS
PLANT-ORAL-HUMAN(PREGNANT)** A4589(121.1)
INTRODUCE ROOT IN VAGINA TO INDUCE ABORTION
ROOT-VAGINAL-HUMAN(PREGNANT)** A5590(121.1)

DECOCTION WITH CROTION CAUDATUM GIVEN TO PRODUCE ABORTION
HOT HZO EXT-ORAL-HUMAN(PREGNANT)** A5590(121.2)

PLANT MIXTURE USED, ACTIVITY COULD BE DUE TO OTHER THAN THIS ONE
PLUMBAGO ROSEA PLUMBAGINACEAE ROOT PHILIPPINES

TAKEN INTERNALLY OR APPLIED LOCALLY TO THE GENITAL ORGANS IT ACTS AS AN ABORTIFACIENT
ROOT-VAGINAL-HUMAN(PREGNANT)** A0599(121.2)

TAKEN INTERNALLY OR APPLIED LOCALLY TO THE GENITAL ORGANS IT ACTS AS AN ABORTIFACIENT
ROOT-VAGINAL-HUMAN(PREGNANT)** A0115(109.2)

PLUMBAGO ROSEA PLUMBAGINACEAE ROOT THAILAND.

USED TO PROCURE ABORTION

JYPE EXT HOT STATED-ROUTE NOT GIVEN-HUMAN(PREGNANT)** A05590(120.1)
                                                                                                                                                                                                                                                                  LITERATURE OF LED
                                                                                                                                                                                                                                                    AD115 MEDICINAL PLANTS OF THE PHILIPPINES.
                                             MEDICIPAL FILE.

OUTSIMETING, E:
1ECH BULL 16, REP PHILIPPINES, DEPT AGR NAT RESOURCES, MANILLA 1951
(NO ADDRESS GIVEN)
                                                                                                                                                                                                                                                                                                                                                                                                       1- 1951 ENGLISH
                                             COMPILATION OF HERBS, PLANTS, CROPS SUPPOSED TO BE EFFECTIVE IN VARIOUS COMPLAINTS AND ILLNESSES.
                                                                                                                      1- 1952 ENGLISH
                                              (NO ADDRESS GIVEN)
                                             A NOTE ON THE PLANTS OF MEDICINAL VALUE FOUND IN PAKISTAN, GOVERNMENT OF PAKISTAN PRESS, KARACHI.
                                              A NOTE OF THE STATE OF T
                                             MALAY POISONS AND CHARM CURES. U & A CHURCHILL, LONDON, 3RD EDITION, 1929.
        A3602
                                              MALAY POLICE
GIMLETTE, JD:
1929 ENGLISH
```

#### Vol. 12, No. 2, 1981

#### Exhibit I. (Continued)

```
#44132 EGBOLIC PROPERTIES OF INDIAN MEDICINAL PLANIS. PART 1.
SAHA, JO: SAVINI, EC: KASINATHAN, S:
INDIAN J MED RES 49 130- 1361 ENGLISH
(DEPT BIOL PHARMACOL • MED COLL • PONDICHERRY • • INDIA )
 44162 SELECT INDONESIAN MEDICINAL PLANTS.
          SELECT INDURESTANT MEDICATION - STEEMIS - KRUSEMAN JAN:
ORGANIZ SCI RES INDONESIA BULL 18 1- 1953
( - FLORA MALESIANA FOUNDATION - KEBUN RAYA INDONESIA - BOGOR + JAVA + - INDONESIA )
 .A4508 DESCRIPTION OF THE PHILIPPINES, PART I., BUREAU OF PUBLIC PRINTING, MANILA.
          ANON: - .1903 ENGLISH
          BOOK
          (NO ADDRESS GIVEN)
.44587 A DICTIONARY OF MALAYAN MEDICINE, OXFORD UNIV. PRESS., NEW YORK, USA.
          A DICTIONAR: U
GIMLETTE, JD: 1939 ENGLISH
          (NO ADDRESS GIVEN)
 44712 ON THE PHARMACOLOGICAL ACTION OF PLUMBAGIN.
          VAP J MED'SCI PHARMACOL 6 259- 1933 ENGLISH
          INC ADDRESS GIVEN)
A.65889 A DICTIONARY OF THE ECONOMIC PRODUCTS OF THE MALAY PENINSULA, MINISTRY OF AGRICULTURE AND COOPERATIVES, KUALA LUMPUR MALAYSIA.

BURKILL, IH:
BOOK 1 1- 1966 ENGLISH
          (NO ADDRESS GIVEN)
 .46590 DICTIONARY OF THE ECONOMIC PRODUCTS OF THE MALAY PENINSULA, MINISTRY OF AGRICULTURE AND COOPERATIVES, KUALA LUMPUR,
          MALAYSIA,
BURKILL, IH:
BOOK II
                               1966 ENGLISH
          INO ADDRESS GIVEN)
         POISONDUS PLANTS OF INDIA, MANAGER OF PUBLICATIONS, GOVERNMENT OF INDIA PRESS, CALCUTT. VOLUME 1. CHOPRA, RR: BADHWAR, RR: GHOSH, S: BOOK - 1949 ENGLISH ( * • DRUG RES LAB • JAMMU-TAWI • • • INDIA )
#BIOLOGICAL ACTIVITIES FOR EXTRACTS OF PLUMBAGO POSEA
LITERATURE CITED
A2318 A PRELIMINARY PHARMACOLOGICAL SCREENING OF PLUMBAGO ROSEA
         A PRELIMINARY PHARMACOLOGICAL SCREENING OF PLUMBAGU RUSEA.
MISRA.MB: TEWARI.JP: BAPAI.SK:
LABDEV 4 55- 1966
[DEPT PHARMACOL PHYSIOL • • GSVM MED COLL • KANPUR • • • INDIA }
A2426 ANTIFERTILITY SCREENING OF PLANTS. PART III. EFFECT OF SIX INDIGENOUS PLANTS ON EARLY PREGNANCY IN ALBINO RATS.

VOHDRA, SB: GARG, SK: CHAUDHURY, RR:

INDIAN J MED RES 57 893- 1969

(DEPT PHARMACOL * • POSTGRAD INST MED ED RES • CHANDIGARH • • • INDIA )
44219 ACTION OF SOME INDIGENOUS DRUGS ON UTERUS. A PRELIMINARY HOLE.
         ACTION OF SOME INDIGENOUS DROGS ON DIEROS. A PRELIMINARY WIFE.
KAPUR RCI.
INDIAN J MED RES 36 47- 1948
(DEPT PHARMACOL * * KG MEDICAL COLLEGE * LUCKNOW * * * INDIA )
```

#### Exhibit I. (Continued)

```
A5104 A SURVEY OF NATURAL PRODUCTS FROM HAWAII AND OTHER AREAS OF THE PACIFIC FOR AN ANTIFERILLITY EFFECT IN MICE.

MATSUL, ADS: HOSKIN,S: KASHIWAGI,M: AGUDA, 8W: ZEBART, BE: NORTON, IR; CUTTING, WC:

INI Z KLIN PHARMAKOL THER JOXIKOL 5 65- 1971

(PHARMACOL DEPT + MED SCH + UNIV HAWAII + HONOLULU + HAWAII + 9G816 + USA )
          W1362 SCREENING OF INDIAN PLANTS FOR ANTIFERTILITY ACTIVITY.
                                  SCREENING OF INDIAN PLANTS FUR ANTIFERTILLITY ACTIVITY.
PRAKASH, AD: MATHUR R:
INDIAN J EXP BIOL 14 623-626 1976 ENGLISH
( • SCH STUDIES ZOOLOGY • JIWAJI UNIV • GWALIOR • • 474 002 • INDIA )
    A. i
                                                                                                                                                                              LITERATURE CLIED
       AO480 PHARMACOGNOSY OF THE ROOT OF PLUMBAGO ZEYLANICA.

IYENGAR MA: PENDSE GS:

INDIAN J PHARMACY 24 290- 1962

CA 59 903 H

( * * INDIAN DRUG RES ASS LAB * POONA * * * INDIA )
       A0481 CHEMICAL EXAMINATION OF THE ROOT BARK OF PLUMBAGO ROSEA.
TUMMIN KATTI, MC: PATWARDHAN, VN:
J INDIAN INST SCI SER A 15 9-15 1932 ENGLISH
(DEPT BIOCHEMISTRY • 1 INDIAN INST SCI • BANGALORE • • • INDIA)
       A0532 PHYTOCHEMICAL INVESTIGATION OF DOMESTIC PLANTS AND AN ASSORTMENT OF GATERSLEBEN SPECIES. 11.
AURICH.O: DANERT,S: PUFAHL,K: ROMEIKE,A: RONSCH,H: SCHREIBER,K: SEMBONER,G:
KULTURPFLANZEN 14 447- 1966
(NO ADDRESS GIVEN)
                              TOXICOLOGICAL CHEMISTRY OF PLUMBAGO ROSEA.
ROY,AK:
U PROC INST CHEM(CALCUTTA) 32 1 17-21 1960 ENGLISH
(NO ADDRESS GIVEN)
        40662
                               PLANT POLYPHENOLS, V. OCCURENCE OF AZALEIN AND RELATED PIGMENTS IN FLOWERS OF PLUMBAGO AND RHODODENDRON SPECIES.
                                HARBORNE, UB:
ARCH BIOCHEM BIOPHYS 96 171- 1962 ENGLISH
( * * JOHN INNES INST * BAYFOROBURY * HERTFORD * * ENGLAND )
       W0823 PLANT POLYPHENOLS, 5. OCCURRENCE OF AZALEIN AND RELATED PIGMENTS IN FLOWERS OF PLUMBAGO AND RHODDDENDRON SPECIE
                                HARBORNE, JB:

ARCH BIOCHEM BIOPHYS 96 171- 1962

( * * JOHN INNES INST * HERTFORD * * * ENGLAND )
       CUMPOUNDS ISOLATED FROM OR IDENTIFIED IN PLUMBAGO ROSEA
   PLUMBAGO ROSEA . PLUMBAGINACEAE ROOT INDIA
IDENTIFICATION OF
PLUMBAGIN 2300234
GLUCOSE 17001E1E7
FRUCTOSE 17001E1E7
PLUMBAGO ROSEA . PLUMBAGINACEAE ROOTBARK INDIA
ISOLATED FROM
PLUMBAGIN 2300234
ISOLATION FROM AFTER SAPDNIFICATION
SITOSTEROL,BETA: 45027E786
OLEIC ACID 1600211
LIGNOCERIC ACID 1600211
LIGNOCERIC ACID 1600211
LIGNOCERIC ACID 17001E17
IDENTIFICATION OF
GLUCOSE 17001E17
PLUMBAGO ROSEA . PLUMBAGINACEAE ROOT INDIA
IDENTIFICATION OF
NAPHTHOOUTNOW, ALPHA: 23002
NAPHTHYLAMINE, ALPHA: 2002
NAPHTHYLAMINE, ALPHA: 500327788
BENZENE, META-DINITRO: 2400125
LUMBAGO ROSEA . PLUMBAGINACEAE FLOWERS
ISOLATED FROM
PELARGONIDIN-3-0-ALPHA-HYDROXY: 2300234
PLUMBAGO ROSEA . PLUMBAGINACEAE FLOWERS
ISOLATED FROM
PELARGONIDIN-3-0-ALPHA-L-RHAMNOSIDE 200090134
CYANIDIN-3-0-ALPHA-L-RHAMNOSIDE 200090134
AFZELIN 200020134
PLUMBAGO ROSEA . PLUMBAGINACEAE FLOWERS
ISOLATED FROM
PELARGONIDIN-3-0-ALPHA-L-RHAMNOSIDE 200090134
AFZELIN 200020134
CYANIDIN-3-0-ALPHA-L-RHAMNOSIDE 200090134
CPHINDIN-3-0-ALPHA-L-RHAMNOSIDE 200090134
CYANIDIN-3-0-ALPHA-L-RHAMNOSIDE 200090134
                                                                                                                                                                                                                                                                                                                                                         A0480(1 1)
                                                                                                                                                                                                                                                                                                                                                         A0481(2 1)
                                                                                                                                                                                                                                                                                                                                                        40481(2.2)
                                                                                                                                                                                                                                                                                                                                                        A0662(1 1)
                                                                                                                                                                                                                                                                                                                                                        A7203(2.1)
                                                                                                                                                                                                                                                                                                                                                        W0823(2.1)
       PHYTOCHEMICAL SCREENING FOR PLUMBAGO ROSEA
PLUMBAGO ROSEA . PLUMBAGINACEAE ROOT INDIA
PHYTOCHEMICAL SCREENING SHOWS ALKALOIDS ABSENT
PHYTOCHEMICAL SCREENING SHOWS GLYCOSIDES ABSENT
PHYTOCHEMICAL SCREENING SHOWS SAPONINS ABSENT
PHYTOCHEMICAL SCREENING SHOWS ALKALOIDS ABSENT
PHYTOCHEMICAL SCREENING SHOWS ALKALOIDS ABSENT
PHYTOCHEMICAL SCREENING SHOWS ALKALOIDS PRESENT
PHYTOCHEMICAL SCREENING SHOWS APONINS PRESENT
PHYTOCHEMICAL SCREENING SHOWS SAPONINS PRESENT
PHYTOCHEMICAL SCREENING SHOWS STEROLS AND/OR TRITTERPENES PRESENT
                                                                                                                                                                                                                                                                                                                                                         A0480(1,2)
                                                                                                                                                                                                                                                                                                                                                          A048011.21
                                                                                                                                                                                                                                                                                                                                                         A0480(1.2
                                                                                                                                                                                                                                                                                                                                                        A0532(1,1)
A0532(1,1)
A0532(1,1)
```