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Why Do Medical Sciences Need Tropical Rain Forests?

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ABSTRACT

At present, one in every twelve drugs prescribed in the United States contains ingredients derived from tropical rain forest plants. Worldwide, one in three of plant-derived drugs comes from tropical rain forest plants. In view of the fact that 65% of flowering plants growing on our planet are found in the tropical belt, of which only a small fraction has been investigated for medical purposes, it is believed that further investigation of tropical rain forest plants will yield important drugs to treat diseases for which we still have no satisfactory cures. However, with the rapid process of decimation of this biome, which is currently recognized worldwide, and with the consequence of large scale species extinction, the prospect of finding new medicinal compounds from tropical rain forest plants will be slim unless serious measures are taken and sustained to conserve the tropical rain forests. Attempts should now be implemented to mount and support large scale exploration to study tropical rain forest plants for their medical potential.

INTRODUCTION

Tropical rain forests comprise the broad-leafed evergreen plant community that thrives in the tropical belt, located between the Tropic of Cancer and the Tropic of Capricorn (23° 27' north and south latitudes, respectively). The definition of the term tropical rain forest has been extensively discussed by

Richards (1952) and more recently by Myers (1984, 1986). These forests have a closed canopy at least 30 m in height, usually with several more or less distinct strata, and are rich in woody lianas and in arborescent and herbaceous epiphytes, though the woody forms predominate. They have developed in areas where the annual precipitation is at least 2,000 mm and the mean annual temperature is around 24° C and frost-free. Current estimates put the extent of this tropical biome at 9 million km^2 (about 7% of the earth's land surface), of which 5.1 million km^2 are in tropical America, 1.9-2.1 million in Asia and 1.8 million in Africa (Sommer 1976; Myers 1980, 1984).

Biotically, the tropical rain forests are the richest terrestrial biome on earth. Even though their total area is only 7% of the earth's land surface, more than 50% of the species of organisms found on our planet (estimated at between 2.5 and 30 million; Lovejoy 1980; Erwin 1983, 1988; Myers 1988; Wilson 1988) occur in these forests. For the flowering plants alone, about 50% of the estimated 250,000-500,000 species are believed to be found in the tropical rain forests (Prance 1977; Myers 1984, 1986; Schultes 1985).

Since the beginning of human existence, this tropical biome has contributed a myriad of items for the survival and well-being of man, which include basic food supplies, clothing, shelter, fuel, spices, industrial raw materials and medicines. Long before the development of modern medicine, the tropical rain forests provided many plant products that natives of various cultures used to treat various types of diseases. Examples are *Cinchona* bark to treat malaria (South America), coca leaves as a local anesthetic (South America), Indian snakeroot to treat cases of insanity (tropical Asia), castor oil as a purgative (tropical Asia/Africa) and ipecac root to treat dysentery (Taylor 1965). Several hundred years have passed since the first re-discovery of these medicinal plants by the European explorers and, lo and behold, we now have quinine to treat malaria and quinidine to treat heart tachycardia, cocaine and related synthetic analogs as local anesthetics, reserpine to treat hypertension, castor oil as a laxative and emetine as an antiamebic. Of course, it has not been without much hard work and persevering effort that these medicinally important compounds were developed for use in modern therapy. Thanks to these re-discoveries, millions of lives have been spared and much human suffering alleviated.

CURRENT IMPORTANCE OF TROPICAL RAIN FORESTS TO MODERN MEDICINE

The most important direct contribution of the tropical rain forests to medicine is to provide chemical compounds that may be used directly as pharmaceuticals in their natural or native form. Worldwide, there are 120 or so pure chemical compounds derived from approximately 102 flowering plant species, which are in use clinically (Farnsworth et al. 1985; Farnsworth 1988). Of these 120 drugs, 61 (derived from 40 flowering plant species) are currently used as drugs in the United States. Of these 61 drugs, 20 come from 16 plants

originated in and around the tropical rain forest areas. A list of all drugs used clinically worldwide that are derived from tropical forest plants is presented in Table 1.

Since 25% of all prescriptions sold in community pharmacies in the United States still contain ingredients derived from plants (Farnsworth and Morris 1976; Farnsworth and Soejarto 1985), and since 20 out of 61 drugs used clinically in the United States are derived from plants originating from the tropical rain forest areas, chances are that one in every twelve drugs sold in community pharmacies in the United States comes from a tropical rain forest plant. Although this figure seems small, the monetary value of the share is considerable. It has been estimated that in 1980 American consumers paid $8 billion for all plant-derived prescription drugs (Farnsworth and Soejarto 1985). One-third of this cost (ca. $2.7 billion) represents the share of pure compounds derived from tropical rain forest plants. This figure does not include plant products derived from more than 500 plant species sold over-the-counter, many of which are derived from plants originating from the tropical rain forest areas (Farnsworth and Soejarto 1985).

Aside from the chemicals that may be used directly as drugs, tropical rain forest plants contribute to medicine by providing chemical compounds that may be used as the starting material or precursor for synthetic modification to produce therapeutically useful drugs. A frequently cited example is the use of diosgenin, a steroidal sapogenin extracted from the tubers of tropical plants of the genus *Dioscorea*, as a starting material for the semisynthesis of steroid hormones, such as progesterone (an ingredient of female oral contraceptive pills), cortisone and hydrocortisone (antiinflammatory agents). In 1973, steroids (95% from diosgenin) represented the largest number of plant-derived compounds (225,050,000 prescriptions) sold in the United States, comprising 14.69% of the total prescriptions (1.532 billion) filled that year (Farnsworth 1977). Before the discovery of the synthetic modification of diosgenin to progesterone, the source of this hormone was animal gonads and adrenal glands, but because of its high cost, it was not practical to use the pure hormone in therapy. To quote an example, in 1934, Schering Laboratories of Berlin needed 625 kg of ovaries from 50,000 sows in order to obtain just 20 mg of pure crystalline progesterone (Tyler 1988). In 1974 alone, tropical Mexico produced about 600 tons of diosgenin which were sold at $27.70/kg (about 0.003 cents per mg) as the starting material for the manufacture of sex hormones (Oldfield 1984). Without the plant source, the cost of commercially producing large quantities of hormonal compounds would be astronomical.

Another example of a therapeutically useful drug from the tropical rain forests that has been derived through semisynthesis is the amebicide emetine (dehydroemetine is the pharmaceutically useful form). Ipecac root from Central and Northern South America (Colombia, Costa Rica, Nicaragua and Panama) contains a higher quantity of the alkaloid cephaeline than emetine. The commercial production of emetine, therefore, formerly utilized the methylation of cephaeline to produce emetine, in addition to direct extraction of this alkaloid from the plant (Tyler 1988); dehydroemetine, however, is produced synthetically at this time.

Lastly, chemical compounds produced by tropical plant species may serve as prototype molecules, "blueprints" or templates for complete synthesis of chemical analogs, the latter to be used as more efficacious and safer drugs. Some widely cited examples of completely synthesized drugs using blueprints from tropical forest plants are the various synthetic local anesthetics lidocaine, mepivacaine, benzocaine, etc. based on the molecular structure of cocaine, the tropane alkaloid isolated from the tropical South American plant *Erythroxylum coca* Lam. The number of clinically useful synthetic drugs based on prototype molecules produced by tropical rain forest plants is minimal at this moment, due to the high cost of the synthetic product. As an example, a comparison is often made between the cost of the synthetic vs. natural reserpine. In 1970's, the cost of synthetic reserpine was $1.25/g, whereas that of the naturally derived product was $0.75/g (Oldfield 1984). The higher cost of synthetic reserpine is due to the difficulty of synthesizing this compound commercially. As a result, reserpine extracted from the snakeroot plant continued to be the source of the drug.

Because of the high cost of commercially synthesized plant-derived drugs, almost all drugs derived from tropical rain forest plants are currently still extracted directly from their natural sources. Globally, only 12% of clinically useful plant-derived drugs are currently produced commercially through synthesis (based on data in Farnsworth 1988).

Another contribution of tropical rain forests to medical science is in the provision of animals used in medical research, particularly primates (Mitruka et al., 1976; Dukelow, 1983; Committee on the Use of Laboratory Animals in Biomedical and Behavioral Research, 1988). Because many primate species cannot be bred successfully in captivity, a large portion of these animals had to be collected from the wild in tropical areas. While in the past this supply of wild-bred primates has contributed in important ways to furthering medical research, it is to be hoped that the need for animal research will diminish in the future.

Based on these two contributions which the tropical rain forests have made to medicine and medical sciences, and in view of the biotic richness of this tropical biome, it is logical to ask the question "could the tropical rain forests contribute still further to modern medicine?" This question is asked for two reasons: (1) an increasing number of pathogenic organisms that cause human diseases develop resistance to the currently available drugs (Parker 1982; Webster Jr. 1985; Mandell and Sande 1985a, 1985b; Sande and Mandell 1985), (2) a number of human diseases and symptoms at present have no cures or no satisfactory cures (Brodie and Smith 1985; Tyler 1986). As we are looking ahead into the twenty-first century in the search for new drugs to replace those that have lost effectiveness against diseases for which they were developed, or to search for new drugs for the treatment of diseases or symptoms against which we have no cures or unsatisfactory cures, it is most logical that we look towards the tropical rain forests for such chemical compounds. Current data indicate that the greater proportion of the tropical rain forest plants have not been studied for medical purposes (Soejarto and Farnsworth 1989).

THE PROBLEM

In an earlier paper (Soejarto and Farnsworth 1985) the point has been made that drug discovery and development from the tropical rain forests have their particular problems. The most important of these is the problem of tropical rain forest depletion due to commercial logging, fuelwood consumption, cattle ranching and forest farming, coupled with an increasing population pressure in the area of the tropical rain forests. As a result of these forces, 8-11 million hectares of forest are depleted every year (Sommer 1976; Myers 1980, 1984, 1987).

From the drug discovery point-of-view the most important effect of forest depletion is the extinction of plant and animal species, as well as the disappearance of human cultures which have developed in and around these forests and depended on them for their existence.

Based on a conservative figure of 2.5 million species of organisms occurring in the tropical rain forests, up to 825,000 species may become extinct in a low deforestation case, and up to 1,250,000 in a high deforestation case, by the year 2000 (Lovejoy 1980). A greater proportion of the species that will become extinct comprise the insects which live on the forest canopies. As regards the flowering plants, estimates of species that will become extinct by the year 2000 vary between 10 and 25% (Raven 1988) or higher (Simberloff 1986). In fact, numerous papers have been published that deal with the extinction process (Simberloff 1986; Myers 1980b, 1986, 1988; among others), and this concern formed the basis of the National Forum on BioDiversity held in Washington, D.C., on September 21-24, 1986, under the auspices of the National Academy of Sciences and the Smithsonian Institution (Wilson 1988). Ways were discussed in this forum on how to arrest or slow down this inevitable outcome.

The result of species extinction is the loss of genetic resources which may be potentially useful to medicine and medical research. Perhaps, it is easier to to grasp the significance of this in terms of monetary value. Thus, if we put the value of one potentially useful plant species in medicine that is destined to become extinct by the year 2000 at $203 million (1980 buying power; Farnsworth and Soejarto 1985), the monetary value of flowering plant species from the tropical rain forests potentially useful to medicine that are destined to become extinct by the year 2000 is incalculable. Since the plants most likely to become extinct are the true tropical rain forest species especially those that are characteristic of or endemic to a particular forest region) of which we know nothing or very little about, not the marginal or "weedy" species of the secondary and disturbed forests, the loss of such species represents a complete loss of the genetic pools that are likely to provide us with a particular chemical compound(s) that could be useful in therapy. It took millions of years to mold a particular genetic pool; once lost, species are lost forever.

The direct consequence of the disappearance of human cultures that occupy the tropical rain forests is the loss of information on the uses of forest plants for medicine. Currently, we have information on thousands of plants that have been used, one way or another, for medicinal purposes (Anonymous 1979; Perry and Metzger 1980; Schultes 1985; Schultes and Raffauf, 1990). Yet, many

more plants that the tropical rain forest peoples know to be useful in medicine, a knowledge they acquired through millenia of trial and error, remain to be rediscovered. From the examples provided at the beginning of this paper, it is obvious that ethnomedical or folk uses represent leads for drug discovery and may shortcut the long, winding process of discovering modern therapeutic drugs. Because of the danger of the loss of such information, attempts should also be made to implement measures of effective conservation advocated by Schultes (1987). Norman Taylor's now classic book (1965) and a paper by Farnsworth et al. (1985) should provide a more convincing evidence to support this assertion.

WHAT NEEDS TO BE DONE -- URGENTLY!

Clearly, time is running short before a great number of tropical rain forest plants potentially useful to medicine and medical research are gone forever. The most urgent action that is needed in order to stem or slow down species extinction from the tropical rain forests is certainly the conservation of this tropical biome, as well as of its germplasm, either *in situ*, *ex situ* or *in vitro*. This subject has been extensively dealt with in many papers (Oldfield 1984; Anonymous 1985; among others), including those in the book Biodiversity (Wilson and Peters 1988).

More importantly, while time is still available, the immediate action needed for the discovery of plants potentially useful to medicine is the exploration of tropical rain forests in a massive and sustained manner to collect plant materials to be used for screening to detect interesting biological activities, followed by bioassay-guided chemical isolation of the active principles. Some efforts in this direction are now being taken by the scientific community. The new anticancer and anti-AIDS plant program of the United States National Cancer Institute (Booth 1987; Friend 1989) currently represents the largest effort in plant drug discovery. Similarly, many natural products scientists are carrying out field explorations and follow-up laboratory investigations of tropical rain forest plants worldwide. One can easily find confirmation of this by scanning scientific journals dedicated to publishing papers on results of research on natural products. Unfortunately, no data are available at present that can summarize numerically the extent and trends of research activities on tropical rain forest plants, especially on the flowering plants, which, by far, still represent the most important group of organisms which provides us with clinically useful therapeutic agents.

The lack of such statistics inspired us to generate our own data, albeit incomplete at this moment, which we believe will provide some information on research activities in the search for biologically active compounds from tropical rain forest plants.

We analyzed two widely read international natural product journals for the period of 1980-1988 for *research papers* on tropical rain forest plants. The results of these analyses are presented in Figures 1 and 2. If the numbers can be taken as a reflection of research activities involving plants from the tropical rain forest areas of the world, then, there is cause for concern, because a downward trend for the past three years is evident. It is to be hoped that this is not the case.

It should be noted that, in the Journal of Natural Products, the total number of articles on plants has declined from 82% to 76% in the last three years, as there has been an increasing interest in marine animal products. The percentage of plant articles concerning tropical plants was lower in 1988 (30%) than in 1986 (34%) and 1987 (35%). In Planta Medica, however, the percentage of articles concerning plants remain stable for the last three years (97-98%), but the proportion of articles on plants which concerned with tropical plants dropped from 24% in 1986 to 19% in 1988. We are extending our analyses to include other journals (both local and international) that deal primarily with medicinal plant exploration and with natural product research, in an attempt to get a better overall picture of the current trends in research on tropical rain forest plants for their potential uses in medicine.

With hard work and perseverance, our efforts should be rewarded, as shown by many recent papers on the discovery of promising biological activities from various tropical rain forest plants that may be potentially useful to medicine: antimicrobial and potential immunostimulating activity was shown by *Okoubaka aubrevillei* (Santalaceae) (Wagner et al. 1985), cardiac activity by *Dysoxylum lenticellare* (Meliaceae) (Aladesanmi and Ilesanmi 1987), and antimalarial activity by *Brucea javanica* (Simaroubaceae) (O'Neill et al. 1987). Yohimbine, potentially useful for the treatment of psychogenic impotence, has been isolated from *Pausynistalia yohimba* (Rubiaceae) (Reid et al. 1987), while castanospermine, which exhibits anti-AIDS activity, is found in *Castanospermum australe* (Leguminosae) (Duke 1989). Antisickling activity has been shown by *Carica papaya* (Caricaceae) (Thomas and Ajani 1987) and antiviral activity by *Aglaia roxburghiana* (Meliaceae) (Joshi et al. 1987). These are but a few of the recent interesting accounts of plants and plant-derived compounds with biological activities of potential medical relevance.

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TABLE 1. CLINICALLY USEFUL DRUGS FROM TROPICAL RAIN FOREST PLANTS

Compound Name	Plant Source	Therapeutic Category in Medical Sciences
Ajmalicine	Rauvolfia serpentina (L.) Benth. ex Kurz (Apocynaceae) (Indian snakeroot)	Circulatory stimulant
Andrographolide	Andrographis paniculata Nees (Acanthaceae) (Karyat)	Antibacterial
Arecoline	Areca catechu L. (Palmae) (Betel-nut palm)	Anthelmintic
Asiaticoside	Centella asiatica (L.) Urban (Umbelliferae) (Indian pennywort)	Vulnerary
*Atropine	Duboisia myoporoides R.Br. (Solanaceae) (Australian cork tree)	Anticholinergic
*Bromelain	Ananas comosus (L.) Merrill (Bromeliaceae) (Pineapple)	Antiinflammatory; proteolytic
*Camphor	Cinnamomum camphora (L.) Nees & Eberm. (Lauraceae) (Camphor tree)	Rubefacient
*Chymopapain	Carica papaya L. (Caricaceae) (Papaya)	Proteolytic; mucolytic
*Cocaine	Erythroxylum coca Lam. (Erythroxylaceae) (Coca)	Local anesthetic
Curcumin	Curcuma longa L. (Zingiberaceae) (Turmeric)	Choleretic
*Deserpidine	Rauvolfia tetraphylla L. (Apocynaceae) (Snakeroot)	Antihypertensive; tranquilizer
*L-Dopa[a]	Mucuna deeringia (Bort.) Merrill (Leguminosae) (Velvet bean)	Antiparkinsonism
*Emetine	Cephaelis ipecacuanha (Brot.) A. Richard (Rubiaceae) (Ipecac)	Amebicide; emetic
Glaucarubin	Simarouba glauca DC. (Simaroubaceae) (Paradise tree)	Amebicide
Glaziovine	Ocotea glaziovii Mez (Lauraceae) (Yellow cinnamon)	Antidepressant
Gossypol	Gossypium species (Malvaceae) (Cotton)	Male contraceptive
*Hyoscyamine	Duboisia myoporoides R.Br. (Solanaceae) (Australian cork tree)	Anticholinergic
Kawain[a]	Piper methysticum Forst.f. (Piperaceae) (Kava-kava)	Tranquilizer
Monocrotaline	Crotalaria spectabilis Roth (Leguminosae) (Rattlebox)	Antitumor agent (topical)
Neoandrographolide	Andrographis paniculata Nees (Acanthaceae) (Karyat)	Dysentery
Nicotine	Nicotiana tabacum L. (Solanaceae) (Tobacco)	Insecticide
*Ouabain	Strophanthus gratus (Hook.) Baill. (Apocynaceae) (Twisted flower)	Cardiotonic
*Papain	Carica papaya L. (Caricaceae) (Papaya)	Proteolytic; mucolytic
*Physostigmine	Physostigma venenosum Balf. (Leguminosae) (Ordeal bean)	Anticholinesterase
Picrotoxin	Anamirta cocculus (L.) Wright & Arn. (Menispermaceae) (Fish berry)	Analeptic

*Pilocarpine	Pilocarpus jaborandi Holmes (Rutaceae) (Jaborandi)	Parasympathomimetic
*Quinidine	Cinchona ledgeriana Moens ex Trimen (Rubiaceae) (Yellow cinchona)	Antiarrhythmic
*Quinine	Cinchona ledgeriana Moens ex Trimen (Rubiaceae) (Yellow cinchona)	Antimalarial; antipyretic
Quisqualic acid	Quisqualis indica L. (Combretaceae) (Rangoon creeper)	Anthelmintic
*Reserpine	Rauvolfia serpentina (L.) Benth. ex Kurz (Apocynaceae) (Indian snakeroot)	Antihypertensive; tranquilizer
*Reserpine	Rauvolfia serpentina (L.) Benth. ex Kurz (Apocynaceae) (Indian snakeroot)	Antihypertensive; tranquilizer
Rorifone	Rorippa indica (L.) Hiern (Cruciferae) (Nasturtium)	Antitussive
Rotenone	Lonchocarpus nicou (Aubl.) DC. (Leguminosae) (Cube root)	Piscicide
*Scopolamine	Datura metel L. (Solanaceae) (Recurved thornapple)	Sedative
Stevioside	Stevia rebaudiana Hemsley (Compositae) (Sweet herb; Ka'a He'e)	Sweetener
Strychnine	Strychnos nux-vomica L. (Loganiaceae) (Nux vomica)	CNS stimulant
Theobromine	Theobroma cacao L. (Sterculiaceae) (Cocoa, cacao)	Diuretic; vasodilator
*Tubocurarine	Chrondrodendron tomentosum R. & P. (Menispermaceae) (Curare)	Skeletal muscle relaxant
Vasicine (Peganine)	Adhatoda vasica Nees (Acanthaceae) (Malabar nut)	Oxytocic
*Vinblastine	Catharanthus roseus (L.) G. Don (Apocynaceae) (Madagascan periwinkle)	Antitumor agent
*Vincristine	Catharanthus roseus (L.) G. Don (Apocynaceae) (Madagascan periwinkle)	Antitumor agent
Yohimbine	Pausinystalia yohimba (K.Schum.) Pierre ex Beille (Rubiaceae)	Adrenergic blocker; aphrodisiac

Updated from: Farnsworth (1988); Soejarto and Farnsworth (1989)
*Currently used in the United States
[a]Now also synthesized commercially

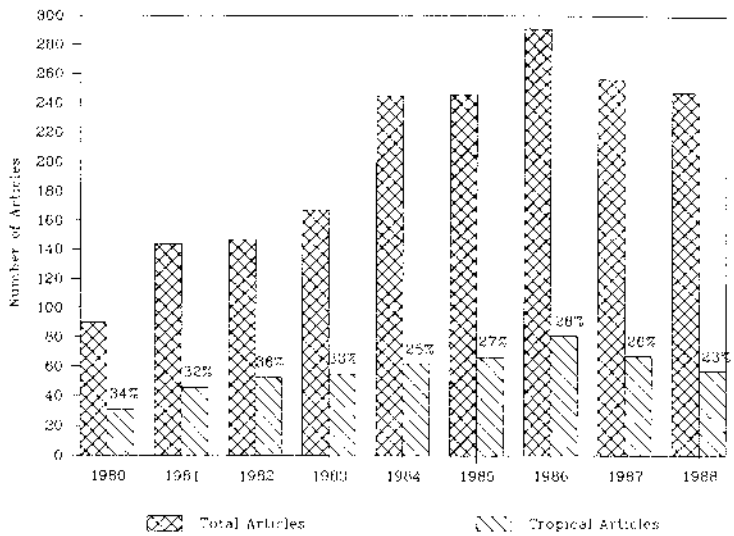

Figure 1. Trends of research activities on tropical rain forest plants, based on statistics of articles published in the **Journal of Natural Products**, 1980-1988. Tropical articles as a percentage of total articles is indicated on the graph. For further details, see text.

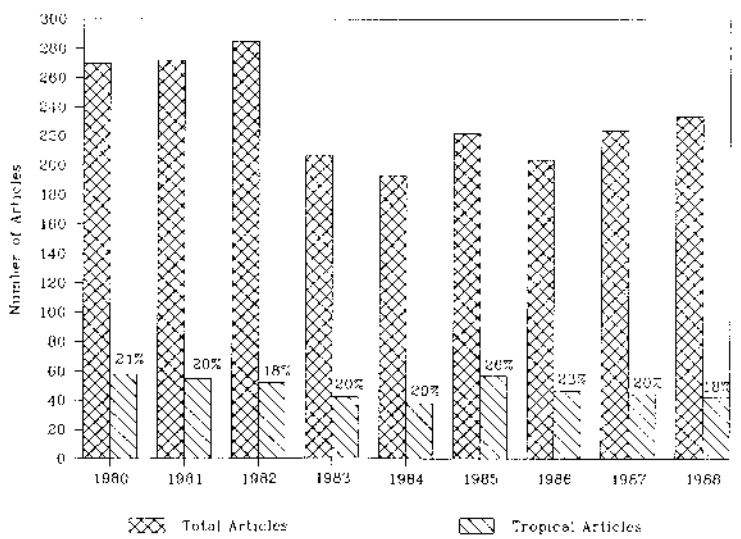

Figure 2. Trends of research activities on tropical rain forest plants, based on statistics of articles published in **Planta Medica**, 1980-1988. Tropical articles as a percentage of total articles is indicated on the graph. For further details, see text.