Discovering Our Gifts from Nature Now and in the Future.

Part I

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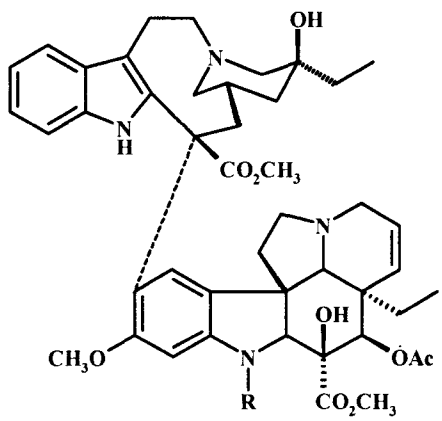
"A Miracle is a Manifestation of the Unexpected"

That splendid plant sitting in a corner of your house or apartment, or the delicate one which you tend in your garden because it has such fragrant flowers, or the giant tree which stands majestically in a nearby park and offers shade from the noonday sun, or the ones which deep in the woods or the primordial forest that you love to take your children through on a vacation day, are all gifts to the living and breathing beings of the world from an unknown force called Nature. Generations before us have both consciously and unconsciously accepted these «gifts» with a greater or lesser degree of appreciation and awareness. To me, they are miraculous "gifts" which have provided shelter, building materials, food, clothes, heat, writing materials, furniture, weapons of war, transportation, systems of communication, and healing. Making the transition from decorative plant to utilitarian use has continuously challenged human and animal ingenuity and persistence. Birds and many mammals make their homes using a diversity of plant sources, and various species of ape have found value in plants for their antibiotic uses to heal wounds[1]. When these discoveries were made is unclear, but one presumes that it occurred long before human societies in Europe and Asia developed from the cradle of civilization in Iraq approximately 12,000 years ago.

Do you realize that plants, in the form of prescription products, over-the-counter products, and traditional medicine, are a cornerstone of primary health care in every part of every community in the world to a greater or lesser extent? Isn't it a minor miracle that so many drugs that are at the core of the physician's armamentarium are derived from natural sources, such as plants, fungi, or bacteria? In 2001, Fabricant and Farnsworth[2] that there were 122 compounds from 94 plants which were approved as single entity medicinal agents world-wide. Of these, no less than 80% came from examining the plant based on an ethnomedical use.

In the health professions, as well as in the lay public, there is a serious lack of acknowledgment and appreciation that such important, life-saving drugs continue to come from natural sources. Consequently, when a physician prescribes an antibiotic, I don't believe that there is very much awareness that a fungus or a bacteria, probably associated with some decaying plant material, was the original source of that compound. We see a particular plant, such as "isabelita" (*Catharanthus roseus*), in a garden or growing wild, and we either don't realize or have forgotten that this pretty, but undramatic, plant is the source of two natural (vinblastine and vincristine, Figure 1) and two semisynthetic drugs for the treatment of various forms of cancer. Some of the other prominent plant-derived drugs and their derivatives which have been brought to the market recently include artemisin from *Artemisia annua* for the treatment of malaria, taxol from the European yew *Taxus brevifolia* for the treatment of cancer, and irinotecan and topotecan, derivatives of camptothecin from *Camptotheca acuminata*, also for the treatment of cancer.



Vinblastine R = CH_3

Vincristine R = CHO

Figure 1. Structures of Vinblastine and Vincristine

Awareness of this exquisitely intimate relationship between humankind and plants is being lost. As a result, we see that it is an easy moral step for people to slash and burn vast tracts of land for short-lived gain, unaware of either the potential to yield new medicinal agents, or that it will be many human generations before that land can be restored[3].

Perhaps in Peru, especially in Peru, no-one forgets that the last-resort antimalarial drug quinine was brought to Europe from Peru in the middle-16th century. Fortunately, the ethics and laws governing access to, and the exportation and exploitation of, bioresources are quite different now[4]. In this series of three articles, we will look at several different aspects and issues regarding the past, current, and future use of plants by humankind for their medicinal and health beneficient properties. Here we will discuss very briefly the extraordinary history of some of the pharmaceutical agents derived from plants dating back thousands of years. In the next article we will look at the role of plant-based traditional medicine in health care and what steps are necessary to rationalize the health and safety issues associated with them. Finally we will look at what will be required from plants for an effective global health care system in the middle of the 21st century, and what steps we need to be taking now.

"God hath created medicines out of the earth, and let not a discerning man reject them" (Ecclesiasticus 38:4).

In the Shanidar Cave in the Zagros Mountains in Northern Iraq, 50,000 years ago, a Neanderthal man was buried surrounded by a variety of flowers and herbs[5]. The Neolithic lake dwellers of Switzerland cultivated or gathered over 200 species of plant, some of which were medicinal. And in southwest France, 14,000 years ago, cave dwellers painted the image of a medicine man. In Mesopotamia, in the region between the Tigris and Euphrates, humankind began, in Sumerian times (2100 B.C.), to document the preparation and use of plant materials as medicinal agents. As the number of medicinal plants expanded, it became more difficult to retain and transfer knowledge through the oral tradition, and thus documented compilations of medicinal plants were assembled. In the great library of 32,000 tablets at Nineveh, collected by the Assyrian king Assurbanipal, approximately 250 drugs of plant origin are mentioned. The Ebers Papyrus, dating from 1500 BC, and found in Thebes in 1872, mentions over 700 drugs. And healing plants were also being codified elsewhere in the world. In China, for example, probably beginning around 25 AD, many *pen-t'sao* were published over the centuries. These were compilations of the plants, minerals, and animal organs being used in medicine. The most famous of these documents is the *Shen-nung pen t'sao* published in 1596, a series of 52 volumes based on the travels of Shen-nung throughout the country over 30 years. Over 1,000 plants are described in the 11,000 prescriptions. In India, the Vedic age began in about 1500 BC, but written evidence of the materials used is both scant and poorly dated. Charaka (500 BC) compiled a text which incorporated the uses of more than 2,000 plants and described their properties, their action, and the recommended dosages[6].

In the Hellenic world, a Minoan clay figurine of a goddess found on the island of Crete and dating to the 14th century BC caricatures the opium capsule (see the cover of the *Journal of Ethnopharmacology*). The major work though, for hundreds of years, was "*De Materia Medica*", the great compilation of Pedanius Dioscorides which appeared around 65 AD, and listed about 600 plants in use in the region of the Eastern Mediterranean. The work set the standard for future listings as it presented the plant habitat, a botanical description, its properties and type of action, the use and side effects, the dosages, harvesting and storage instructions, and location. The classification was by their medicinal purpose[6].

Persian physicians also set medicinal plants in a new direction. Baghdad under Caliph al-Mansur (754-775 AD) was the center of regional culture and trade which fostered the interchange of ideas about medicinal plants. To facilitate this process, in the ninth century, first the work of Galen was translated by Hunain, then those of Dioscorides, Oribasus, and Paul of Aegina. These compilations were subsequently then consolidated and re-assembled in an orderly manner as the first formularies. Shortly thereafter, Rhazes (ca. 854-935), a Persian physician, assembled all of the knowledge of medicinals written in Arabic, Roman, and Greek into fourteen volumes. He was succeeded by ibn-Sina, also known as Avicenna, whose 11th century *Canon medicinae* laid the ground work for the next six centuries, being translated into Latin, and distributed all over Europe. Because of their trading patterns, this brought into awareness and commerce medicinal plants from the Near and Far East and from Africa, thereby enhancing the storehouse of accumulated knowledge, promoting more widespread use, and enhancing health care[6].

Paracelsus (Philip Theophrastus Aureolus Bombastus von Hohenheim) working in Austria in 1524 was the first to

consider that the plant material itself was not the healing agent, but that there was some principle contained therein which was responsible. In his «Archidoxa» he wrote, "It does not matter that rhubarb is a purgative. The question is: What purges? ...Names do not have virtues, substances do..." [7,8]. He called this active material in a plant the "arcanum". It was a beginning of the concept of medicinal plant drug discovery.

When the Spanish started to sail the Atlantic in the 16th century, Philip II of Spain ordered the collection of "...an account of all medical herbs, trees, plants and seeds". Thus, in his seven years of travel in the Americas (New Spain) the physician Fernando Hernández described over 3,000 medicinal plants. These travels led over the next century to the introduction of guaicum, jalap, mechoacan, cinchona, balsam, winterian, and sassafras into the European marketplace[6]. The oldest of the New World codices of medicinal plant lore is the *Badianus Manuscript* created by an Aztec artist, Martinus de la Cruz and written by Juannes Badiano in 1552 for Charles I of Spain[9]. It describes the mostly mixed herbals used for about 100 health conditions.

However, it was not until the middle of the 18th century, when Gerhard van Swieten became Vienna's leading medical official, that clinical studies on medicinal plants began. Of those doing this work, probably Anton Störck was the most important. He conducted studies on many plants that were regarded as poisonous, including aconite, colchicum, conium, hyoscyamus, and stramonium, which he showed could be medicinally useful at doses lower than the toxic dose[6]. Thus began the important principle of a dose response. On the other hand, the English physician and botanist William Withering in 1776, studied a folk remedy for dropsy and concluded that among the many herbs of which it was comprised, one, *Digitalis purpurea,* was the most active[10]. It is used today for congestive heart failure and atrial tachycardia.

As chemistry evolved from pharmacy with the isolation of various purified chemical elements in the 18th century, the Swedish chemist Scheele, whose isolation work on elements was extraordinary, was also the first to isolate a number of the important organic acids from plants. This was a prelude to the more serious studies of medicinal plants which were about to begin in Europe in the early part of the 19th century[6]. Thus it was that in 1804 (published widely in 1817) that the German pharmacist Sertürner (working in Hannover) isolated morphine as the active principle of opium. It was the first of the plant alkaloids (named as such by Meissner in 1819) to be isolated. In Paris, Pierre Joseph Pelletier working with a series of assistants isolated emetine from ipecac and narcotine from opium. His leading assistant was Joseph Caventou, and together they were responsible for the isolation of strychnine, brucine, veratrine, cinchonine, quinine, and caffeine in the period 1818-1821[11]. Here for the first time was the clear relationship between medicinal plant, compound, and activity. Here was Paracelsus' arcanum, the seed of biological activity in a medicinal plant. And even though these isolations were achieved long before a molecule could be described in atomic terms, these studies laid the foundation for all of the discovery of the active principles from natural sources that was to follow in the next 182 years. In addition, the discoveries of these alkaloids, particularly atropine and morphine (Figure 2), became the molecular foundation for numerous synthetic and semisynthetic drugs on the market today.

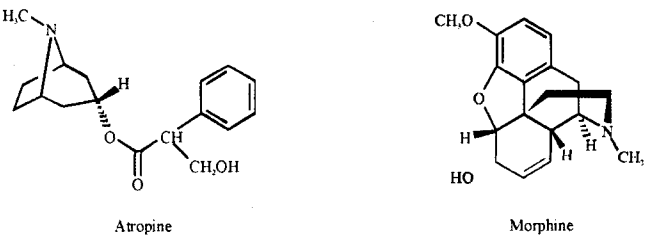


Figure 2. Structures of Atropine and Morphine

Modifications to natural products, with a view to enhancing activity or selectivity and reducing side effects or toxicity, developed as organic chemistry grew in the late 19th century[12]. The acetyl derivative of salicylic acid, itself a derivative of the glycoside salicin isolated from *Spirea ulmaria,* was named Aspirin, and was an early example of a chemically-modified (i.e. semi-synthetic) natural product drug, and recently celebrated 100 years as a commercial entity[13]. Now, such simple modifications to natural products to yield drugs are rare, (natural taxol and semisynthetic taxotere may be an exception), and often the relationship to the parent natural product is barely discernible. Yet, half of the best-selling pharmaceuticals in 1991 were actually based on natural products[14], and an analysis of drugs approved by the Food and Drug Administration in the United States in a twelve-year period (1983-1994) found that 157 of 520 drugs (30%) approved were natural products or their derivatives[15]. When a concerted long-term effort to find natural products for clinical use, such as that of the National Cancer Institute, is made, the success level doubles. Thus, in the same period,

61% of anticancer agents approved were natural products or their derivatives. Where there were no specific programs involving natural products (e.g. for analgesics, antidepressants, antihistamines, anxiolytics, cardiotonics, or antifungals), there was no successful drug developed[15].

The Drug Discovery Process

Drug discovery is likened to finding a needle in a haystack[16]. How does this process of drug discovery function and what sources are used to provide the materials for evaluation? The initial steps in the drug discovery process require that many samples are evaluated against a biological test system (assay) or a panel of assays (a screen). Those samples which exceed a particular level of activity are moved to the next phase of evaluation[17]. Because the process of drug discovery to market approval takes such a long time (often 10-15 years), the successful pharmaceutical company 15 years from now will be defined by the choices that are made today for the sources of supply of the materials evaluated and for the bioassay systems used.

Drug discovery, for the major pharmaceutical companies, requires the potentiation of the number and the diversity of the chemical entities which are evaluated against a particular biological screen in the minimum time. The collection of «compounds» to be evaluated against each screen as it becomes available is called a "library". Companies spend enormous amounts of time, money, and effort deciding how to establish, enhance, or optimize these libraries for certain types of biological screens[14]. These libraries can also be regarded as «bank deposits» since they function as a core future asset of the company, and, particularly in the case of natural products and their extracts, may well increase substantially in value as global biodiversity continues to decline. This profound symbiotic link between biodiversity and drug discovery is substantially unappreciated in pharmaceutical industry[18].

The acquisition of chemical entities for this library is an interesting and challenging activity, for the only sources of compounds for evaluation are natural, synthetic, semi-synthetic, genetic engineering, and combinatorial chemistry. From a discovery point of view, it is crucial to develop a library which maximizes the chemical, or, more succinctly, the pharma-cophoric diversity presented to the biological screen. Therefore, using these potential sources creatively to put together appropriately diverse sample libraries is an art form in itself. The number of samples that a company may assemble for testing in a particular screen is upwards of a million.

Once this library of samples is constructed, evaluation usually involves a receptor-, enzyme-, or cell-based assay. Samples are usually contained in 384-well plates, and all aspects of the process are fully automated. After the sample library has been screened, automated data analysis provides a prioritized list of samples for further consideration as an "active". These «actives» are frequently further examined in a secondary bioassay system in order to discern from among the many actives, those which are "hits".

A "hit" compound therefore has activity, has an established structure, has the possibility to develop some novelty (for patent purposes), and most importantly in many respects, is available. The latter is a very important aspect, because material will be needed in reasonable quantity for additional chemical and biological studies. It is from these studies on selected compounds that are regarded as "hits" that compounds of even higher priority, a «lead», may evolve[19]. A "lead" then is a compound which has well-defined purity, possesses genuine structure-activity relationships for the target assay(s), has a well-defined minimum structure for activity, has selective activity, and is potent, in order to maximize the desired activity and minimize toxicity and side effects.

The overall process of taking a compound from the stage of a "lead" through the successive levels of evaluation to a marketable product has been described on a number of occasions[12,17]. The various facets of the scientific work are dominated by the requirements for the evaluation of a drug candidate developed by the U.S. Food and Drug Administration[20,21]. Typically, lead development involves a series of pharmacology and toxicity studies in several species of animal, bioavailability and pharmacokinetic studies, and formulation studies depending on the proposed route(s) of administration. Trials in humans then follow, and are categorized as Phase I, Phase II, and Phase III clinical studies. Phase I studies focus on safety, Phase II studies are conducted in a small group of patients and evaluate clinical effectiveness, and Phase III studies represent larger clinical trials. In each case, there is careful monitoring of any unexpected side-effects or complications. At their successful completion, application for approval as a new drug entity is made to the FDA. If approval is granted and the drug is

marketed, post-marketing surveillance studies are required examining efficacy and side-effects on a long-term basis[17].

Usually, a pharmaceutical company conducts drug discovery programs in a number of therapeutic areas to which it is committed for product development. The choice of the therapeutic target areas to be pursued is made at the highest corporate levels, and typically involves market economists, advertizing executives, patent attorneys, clinicians, etc. The diseases which are chosen for the development of new therapeutic agents are frequently those for which the market is already established or is projected to be very large, or for which the company already has a reputation for effective products[22]. Quite clearly, the limited number of therapeutic areas is due to the very high costs ($500-600 million) of bringing a new drug to the marketplace and the need to recover those costs expeditiously, in order to fund current research programs[17]. Some of the diseases which are common therapeutic targets are cancer, heart disease, lung diseases, pain and inflammation, anti-infective agents, anti-HIV agents, diseases of aging, and diabetes.

Although a number of these diseases and conditions are also important globally, other diseases, including malaria, schistosomiasis, filariasis, diarrhea, and intestinal parasites are responsible for substantially more deaths world-wide on an annual basis[23]. Diarrhea is, for example, responsible for about 5 million deaths in infants (0-4 years) annually. Regrettably, little drug discovery in these areas is being conducted by the major pharmaceutical corporations at the present time[15]. The most frequently offered reason is that there will an inadequate return on the research investment.

As we have seen from the earlier discussion, the most significant and very dramatic change in drug discovery in the past ten years is the rate at which primary screening is being conducted as a result of biological and technological innovation[24]. In a major pharmaceutical company, the activities of four groups blend together for the purposes of the primary screening of sample libraries. One is a group devoted to sample generation and acquisition, another group is responsible for the development of bioassays, and a third is responsible for the technological aspects of automation. Finally, there is the group which is responsible for the data collection and analysis[25].

Sample generation for the library of materials to be screened may take several different forms, including, purchasing samples from commercial chemical catalogues, from academic laboratories, or from small companies dedicated to providing samples. In-house synthetic chemistry programs typically provide a large array of compounds from previous discovery programs, although these are often of quite limited structural diversity. Many companies are also generating large numbers of samples for primary screening through various combinatorial chemistry approaches[26,27], which are under constant development and evaluation[27,28]. Some companies use combinatorial chemistry to produce samples for primary screening, whereas others only use such strategies for taking "hit" molecules and optimizing their activity for the selection of "leads". Finally, there are the natural product samples, which might be purified compounds, or crude or semi-purified extracts of plants, microbes (fungi, bacteria), and animals from either terrestrial or marine sources. Each of these areas requires specialized acquisition and sample handling and processing. These samples are usually stored in 96-well plates ("master" plates) which can then be accessed automatically to generate the plates of samples for evaluation in a particular bioassay[24].

With the possible exception of antidiabetic drug discovery, animals, or even animal organ preparations, are now rarely used in primary or even secondary screening[14]. As indicated previously, all of the initial biological evaluation is conducted with cell, enzyme, or receptor-based assays. Substantial innovation has been exercised in developing genetically engineered assays and in developing new ways to indicate, often qualitatively, a biological response[29]. The need to have biological assays which are fully automated, targeted towards new enzyme and receptor targets, and which can offer an unequivocal response for a particular sample, has led to compromises with respect to the relevance of the primary assay systems to a therapeutic end-point. In addition, the biological novelty of the assay may mean that there is no positive control compound available with which to compare any "hits". Consequently, potency and selectivity may be difficult or impossible to establish at an early stage in the drug discovery process.

Automated sample preparation, automated assay preparation, and automated data collection are conducted by a single robot operating 24 hours a day. One million or more assays per robot may be conducted per library sample over a period of 1-2 months before other assays are brought on-line[17,24]. Rarely, is consideration given to any prior knowledge about the biological activity of the samples being examined.

From a natural products perspective, there is now an important question to be asked.

Where and how do natural products and natural product extracts fit into this fast-paced and highly competitive, drug discovery process? The simple answer is not very well. If we consider the requirements for participation in the early stages of the discovery process, one of the major factors is time. If a pure natural compound is used in the library and becomes a «hit», then it will be needed in reasonable quantity for structure activity relationship studies. Appropriate amounts of the compound may not be available and it may take some time to reacquire the resource (plant, fungus, or marine organism) for isolation on a sufficient scale. By this time, other synthetic products may have advanced through one or more decision stages in the discovery pipe-line. For a biologically active extract of a plant material, there are greater barriers to overcome, because it may be necessary to recollect the plant material in order to conduct a bioactivity-directed fractionation for the separation of the active principle, using the assay in which the extract showed activity, if it is still available. Having isolated the active compound and determined its structure, if the compound is known, it may be important to do some preliminary structure activity relationship work to determine if a novel entity (for patent purposes) can be generated which has the same or improved activity. If this work is successful, large quantities of plant material will be needed in order to isolate adequate active compound for the studies which would transform the "hit" to a "lead". Permission to collect, acquisition of the plant material and isolation of the compound may take time, possibly a year or more. This places the natural product, biologically effective and mechanistically and structurally interesting though it may be, at a very substantial disadvantage compared with in-house chemical entities. Thus, it is appropriate to indicate that **the major pharmaceutical companies are no longer interested in the large scale screening of natural products for the purposes of drug discovery**[18]. At this point in time, they simply do not see the short term or long term value in this investment. For those in the natural product science community who see a very different world emerging in the next twenty to thirty years, these strategies of drug discovery for global health care are simply not acceptable. This topic, and what can be envisioned as a role for natural products, will be the focus of the discussion in the third of these articles. To conclude this article, let us recognize the technology that is presently available in order to assist natural product drug discovery programs, leaving some strategic issues for the subsequent discussion.

One of the issues raised in opposition to the inclusion of natural product extracts in drug discovery programs is that once an extract is determined to be active it may take months to isolate and characterize the active principle(s). This is true. And, at the same time, that offers the opportunity to establish techniques to begin to overcome those impediments, and also advance the science for other purposes. Although tremendous advances in the chemical separation sciences have occurred in the recent past, this topic will not be discussed, rather, we will briefly mention the spectroscopic improvements and their impact, and what can be done to move closer towards the goal of identifying an active compound in a complex biological matrix, without doing the complete isolation and characterization process.

Information management with respect to plants and their constituents has a major impact in two separate areas of the discovery process. For dedicated natural product drug discovery programs, prior knowledge about the indigenous use of the plants, of the established biological activities of the various plant extracts, and an awareness of the compounds which have been isolated from them, is critical[30]. Such information may be used initially to provide direction for the collection program, or at the stage when the samples from a plant extract library to be presented for particular primary screening are being assembled. In other words, using prior knowledge on a plant possessing anti-inflammatory activity when evaluating extracts for their activity as inhibitors of the COX-2 enzyme. Another important opportunity for the use of prior information on a plant is at the stage of prioritization for fractionation after «actives» have been determined. This process is called «dereplication», and has been an established strategy in antibiotic drug discovery programs for over forty years. Initially, such studies were based on paper chromatographic and UV comparisons[31], but these studies could not distinguish a novel from a known active compound. Similarly, techniques of bioautography, whether they were TLC or HPLC-based, could not indicate the nature of the active compound, only its chromatographic parameters. An alternative approach used computer-generated biological fingerprinting, which permitted some inferences to be made about mechanisms of action of extracts or isolated compounds, but nothing about their structural characteristics[32]. More recently, we devised and implemented a dereplication program[33,34] which brings

together high performance liquid chromatography, UV spectro-photometry, electrospray mass spectrometry, a bioassay system, and the NAPRALERT database[35] on natural products. The focus of the technique is to identify those active extracts which have a high probability to afford a novel active metabolite.

In this approach, an active extract is separated by HPLC under standard conditions and the effluent, after passage through a diode array detector, is separated into two streams. One (98%) goes to a fraction collector for 96-well plates and the effluent is evaporated and the residue biologically evaluated, while the minor stream goes through an electrospray mass spectrometer. Data on the UV spectrum, mass, and biological activity are therefore collected on a unit time basis and can be directly correlated. In other words, information on the mass of the compound(s) in the area of biological activity must be correlated with those compounds that are known of that mass, whether isolated previously from the genus or not, and those compounds of that mass which are known to have that biological activity (Figure 3). If a zone in the HPLC chromatogram correlates with activity and a probable known compound, that extract is given a low priority. If, on the other hand the mass and the UV spectrum of the active metabolite does not correspond to a known active, then the priority of that extract is raised for further detailed fractionation, with the knowledge of the chromatographic location and the mass of the compound(s) in hand.

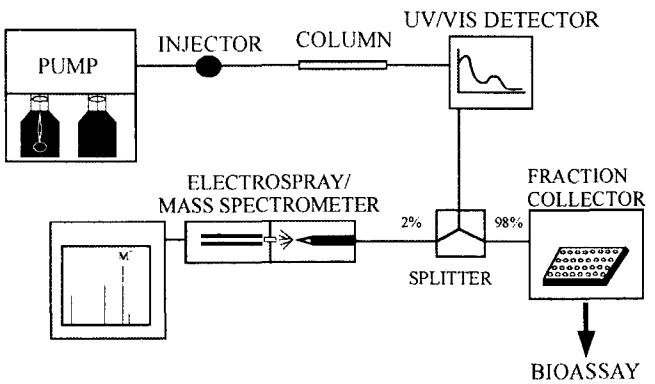


Figure 3. HPLC/ESMS-Bioassay System for the Dereplication of Biologically Active Extracts.

During the past decade or so there have been dramatic advances made to facilitate the complete structure elucidation of natural products[36-38]. Advances in NMR probe design have allowed for smaller samples to be analyzed for both proton and carbon spectra, and advances in software control systems have permitted dramatic improvements in the range of spectra that can be obtained. Many kinds of two-dimensional spectra are now available at increasingly high field (400, 500, 600, and 750 MHz) to augment the information from the one-domain spectra, and these routine spectra typically yield substantial information regarding the short and long-range proton-proton correlations and proton-carbon correlations, and proton-proton distances[36]. As a result, it is now quite routine to derive unambiguous proton and carbon assignments for almost all of the classes of isolated natural products using these techniques. Though there is a popular misconception that structure elucidation is now quite routine, the fact remains that being able to interpret spectral information, and to design experiments which can definitively answer particular structural issues remains an important aspect of natural product chemistry.

The combination of high performance liquid chromatography and $^{1}H/^{13}C$ NMR spectroscopy has also been used to help in the identification of compounds present in active extracts[39,40]. This technique is very powerful in the stop-flow mode, but has some drawbacks for new compounds and because it uses solvent systems that are not conventional for NMR, unpredictable solvent shifts may occur. At the present time, there is also no direct correlation with the biological assay. One can anticipate though that future developments in the interfacing of techniques will undoubtedly address some of these issues.

Once the structure of an active metabolite has been determined, structure modification is required in order to establish some fundamental parameters regarding those functional groups in the molecule which are needed for the demonstration of activity[17,19]. In some instances, this may be followed by the application of combinatorial chemistry to produce a more diverse set of modified compounds. Such chemical transformations may be on the whole molecule, if that is necessary for activity, or with the particular portion of the molecule which has been found to be essential for biological activity, the so-called pharmacophoric unit[19,27]. Depending on the bioassay, and knowledge of the substrate-enzyme interaction, and whether the enzyme crystal structure or that of a complex has been isolated and characterized, it may be possible to use computer-aided design to seek alternative groups or conformations of the molecule, and thereby offer an improved enzyme inhibition at the active site[41].

CONCLUSION

In spite of a long history of the use of medicinal plants in primary health care, the substantial use of isolated natural products and their derivatives in current drugs, and the available technology, the major pharmaceutical companies are no longer interested in exploring nature for the development of new drug candidates in a dedicated manner.

In the next article we will examine some aspects of traditional medicine, and the legal issues around natural product acquisition. Finally, in the third article, we will try to bring all of these issues together and present a rational approach to what needs to occur in the immediate future in order to have a coherent use of natural products for global primary health care 20-30 years from now.

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