

Review

Current phytotherapy - A perspective on the science and regulation of herbal medicine

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Phytotherapy is the use of plant materials to prevent and treat ill health or promote wellness. The practice dates to antiquity, yet remains current. It began in Mesopotamia, and subsequently spread to the rest of the Old World. The primacy of herbalism in medicine is evident from the large number of modern drugs that owe their origin to ethnobotanical remedies. This review traces the origins, the science and breakthroughs, and the effort of the World Health Organization to regulate herbal medicine. It notes three instruments as decisive in that effort: the Alma-ata Declaration of 1978; the manual on quality control of medicinal plant materials of 1998; and the general guidelines for methodologies on research and evaluation of Traditional Medicine of 2000. This review notes that while plants synthesize a large variety of secondary metabolites for various ecophysiological causes, most of such metabolites originate from a relatively few biosynthetic pathways. The pathways include those for alkaloids; terpenes/ terpenoid/ steroids; shikimic acid/ aromatics; and polyketides. These secondary metabolites, better called phytochemicals, affect man in ways that require that their production, quality, distribution and use be regulated. The review comments on the impact of World Health Organization on the regulation of herbal medicine.

Key words: Phytotherapy, world health organization (WHO), traditional medicine, Alma-ata declaration, ecophysiological causes, biosynthetic pathway, phytochemical, quality control, regulation.

INTRODUCTION

Three decisive events connected with the current popularity of herbal medicine include: the Alma-ata Declaration (WHO, 1978); the manual on quality control methods for medicinal plant materials (WHO, 1998); and the general guidelines for methodologies on research and evaluation of Traditional Medicine (WHO, 2000). Currently, medicinal plant research is one of the fastest growing areas of biomedical research. This is illustrated by the following observation: The number of citations in PubMed from 1990 - 2007 containing the word "phytotherapy" was less than 100 in 1990, but rose to over 1, 000 in 1998, then to 12, 000 in 2005, and to over 15, 000 in 2007 (Wikipedia-phytotherapy, 2008). In 1999, the world

market for herbal remedies was US\$19.4 billion, with Europe in the lead (US\$6.7 billion), followed by Asia (US\$5.1 billion), North America (US\$4.0 billion), Japan (US\$2.2 billion) and the rest of the world (US\$1.4 billion). As at 2003 over 50, 000 plants were in use for medicinal purposes worldwide (Mapdb.com, 2003). This trend or outlook for phytotherapy is assumed to result partly from the failure of chemical agents to fully realize the hope it raised when Paul Ehrlich introduced Salvarsan in 1909. Ehrlich had coined the term "chemotherapy" to refer to the use of chemical agents (pharmaceutical medicines) to treat illnesses. The prevailing conception of chemotherapy had led biomedical scientists to imagine that someday there will be for every disease a magic bullet (Albert, 1981).

However, owing to the supposed failure of pharmaceutical medicine, phytotherapy, which had begun to gain more ground after the Alma-ata Declaration in 1978,

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entered a new phase of rapid growth in the early 1990's.

Aim of the review

Three decades after the Alma-ata Declaration of 1978, the time has come to take stock of the historical development of phytotherapy. This review will attempt to do this by examining issues or queries such as:

- (1) Why has phytotherapy become so popular today?
- (2) How have the advances in the science of medicinal plants facilitated the rise and popularity of phytotherapy?
- (3) What are phytochemicals and why do plants produce them in the first place?

Why did the WHO take the bold step of regulating the use of phytochemicals in health and disease?

- (4) This review aims to draw the attention of scholars to the vast literature on this subject, with a view to sharpening the focus of research in medical herbalism.

HERBALISM AS AN ANCIENT PRACTICE

It is generally agreed that herbalism is an ancient practice worldwide. Lietava (1992) provided evidence that Neanderthals, living thousands of years ago in present-day Iraq, used plants for medicinal purposes, similar to those described some 3,000 years ago in 2 Chronicles 16:13 - 14: "Asadied in the one and fortieth year of his reign. And they buried him in his own sepulchres, which he had made for himself in the city of David, and laid him in the bed which was filled with sweet odours and divers kinds of spices prepared by the apothecaries' art". It is notable that the word "apothecary" or "apothecaries", meaning pharmacist, occurs six times in the Scofield Study Bible (1996), indicating that pharmacy is as old as religion.

It is also generally agreed that from time immemorial, people practiced herbal medicine as an integral part of religious art, and that from such origins, the systems of herbalism developed in the Middle East (Green, 2006), Africa (Elujoba, 2005), Asia (Ninivaggi, 2001) and Europe (herbplace.com, 2009). Among the earliest reports of herbalism is that of Emperor Shen Nung of China (3000 - 2700 BC) who had a pharmacopoeia that included chaulmoogra oil for treating leprosy (Sofowora, 1982). Other reports include: Ebers papyrus, dated 1550 BC, describing plants used in Egypt; a classification of medicinal plants by Theophrastus (370 - 285 BC); *De Materia Medica* (77 AD), listing over 600 remedies, mostly of plants; list of over 1400 drugs and medicinal plants in *Corpus of Simples* (people.vcu.edu, 2009a).

In the New World, especially North America, herbal medicine became a blend of two separate traditions: European herbalism, brought by Europeans; and the herbal traditions of Native Americans. During the 1800s

the most effective American healers combined European and Native American herbalism. By the 1850s the influx of Chinese immigrants added Chinese herbal traditions to the mix. However, this triple heritage began to decline after the American Civil War, partly because conventional medicine improved during that war, and because of the highly influential *Flexner Report* of 1910, which favoured conventional medicine, but was critical of herbal medicine and other alternative approaches (Pelletier, 2008) In South and Central America, where Native American and European herbal traditions had been in vogue, there came a third factor - Yoruba herbalism (Grotte, 2008), made possible by the Atlantic Slave Trade.

BIOCHEMISTRY OF HERBAL DRUGS

Herbal drugs are the secondary metabolites of plants. They are better called phytochemicals, to differentiate them from primary metabolites because they are needed for growth and maintenance. By contrast, phytochemicals are required only indirectly, to enable plants survive and reproduce in a given competitive ecosystem. Medicinally useful phytochemicals fall into a relatively few broad groups, but perform several functions. Some are toxins, used to deter predation; some are pheromones, used to attract insects for pollination; others are phytoalexins, which protect against microbial infections; and yet others are allelochemicals, which inhibit rival plants competing for soil and light (Lai, 2004; Tapsell, 2006; Taiz and Zeiger, 2006). Thus, although plants synthesize a large variety of phytochemicals, most are derivatives of a relatively few biosynthetic pathways (people.vcu.edu, 2009a). These are briefly outlined.

Biosynthesis of alkaloids from amino acids

In nature, alkaloids represent a diverse group of compounds that are related only by the occurrence of one or more atoms of nitrogen in a heterocyclic ring. Plants produce about 12,000 alkaloids that are organized into groups according to their carbon skeleton (Ziegler and Facchini, 2008). The nitrogen makes the compounds basic, so that they exist as salts in the plant. Plant alkaloids are often toxic to animals; have a complex structure; and are widely distributed in plants. The structures of some are given in Figure 1.

Among the most famous alkaloids are: the cinchonines, of which quinine is an example; the tropane alkaloids, of which hyoscyamine and cocaine are examples. Others include: the ergot alkaloids, of which the most famous is lysergic acid diethylamide (LSD) - a synthetic derivative of the ergot alkaloid, ergine. Others include opium alkaloids, of which morphine is an example. The well known drug of addiction, heroine, is a synthetic derivative of morphine obtained by acetylation. The structures of the four examples are shown in Figure 2).

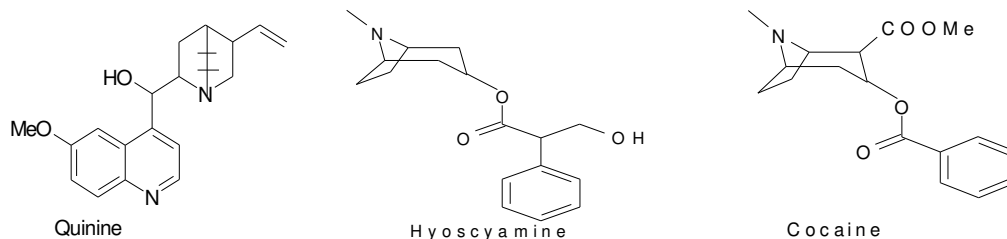


Figure 1: Plants produce 12, 000 alkaloids representing a diverse group related only by the occurrence of 1 or 2 atoms of nitrogen in a heterocyclic ring as shown in the 3 examples above.

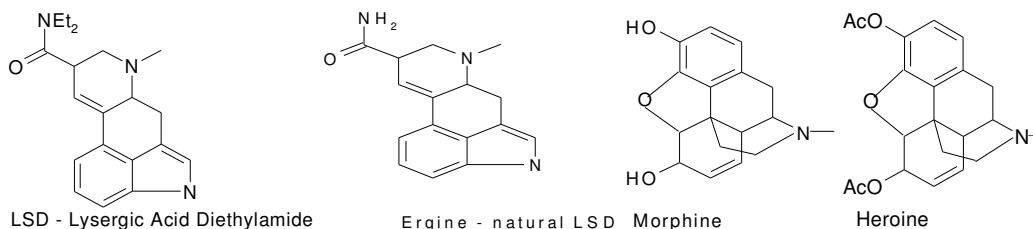


Figure 2: Above are examples of drugs of addictions, lysergic acid diethylamide (LSD) – an ergot alkaloid derived from ergine; and heroin – an opium alkaloid derived from morphine.

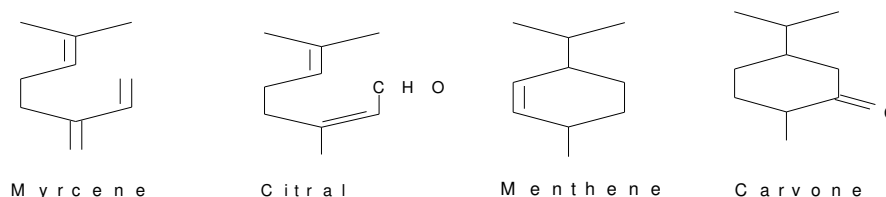


Figure 3: Above are examples of acyclic monoterpenes - myrcene and citral; and of cyclic monoterpenes – menthene and carvone.

Some alkaloids are not so easily classified, however. An example is vincristine - an extremely complex alkaloid isolated from *Catharanthus roseus*, along with vinblastine, a homologue in which the N-methyl group is oxidized to an aldehyde.

The precursors of most alkaloids are L-amino acids. For example cocaine and coniine are derived from ornithine and lysine respectively, while noradrenalin and mescaline are derived from phenylalanine and tyrosine respectively. Strychnine and LSD are derived from tryptophan, while morphine is from tyrosine (Ziegler and Facchini, 2008).

Biosynthesis of terpenes, terpenoids and steroids from isoprene

Terpenes are a large and varied class of hydrocarbons, produced by a wide variety of plants. Each terpene ($C_{10}H_{16}$) consists of a pair of isoprenes (C_5H_8). The names monoterpenes ($C_{10}H_{16}$), sesquiterpenes ($C_{15}H_{24}$), diterpenes ($C_{20}H_{32}$) and triterpenes ($C_{30}H_{48}$) are based on the number of isoprene units. The mono- and sesqui-

terpenes are the so called essential oils, and have been utilized in perfumery since ancient times (people.vcu.edu, 2009c).

A few examples of essential oils are indicated in the structures in Figure 3. Myrcene and Citral are examples of acyclic monoterpenes, while menthene and carvone are cyclic monoterpenes.

The name "terpene" is derived from "turpentine". Terpenes, as biosynthetic precursors, are found in all living things. For example, steroids are derivatives of the triterpene, squalene. Terpenes and their oxidation products are the main constituents of the essential oils of plants used widely as food colorants and flavorants; and as fragrances in perfumery, and as agents in aromatherapy. When terpenes are modified by oxidation with or without rearrangement of the carbon backbone, the resulting compounds are called terpenoids. Citral and carvone are examples of acyclic and cyclic monoterpenoids respectively. Some authors however, use the term terpene to include all terpenoids. Included among the terpenoids are also the carotenoids, which are the attractive colorants of tomatoes, oranges, yellow corn, pumpkin and grape. They are tetraterpenoids.

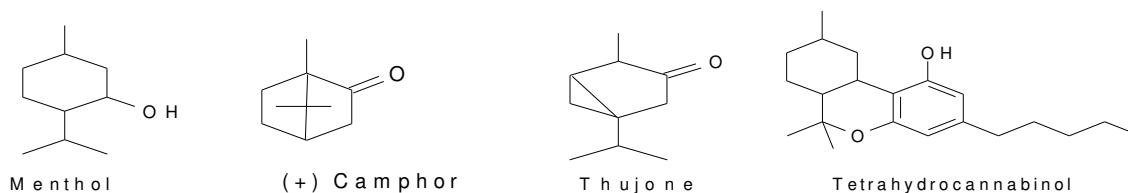


Figure 4: Menthol, camphor, thujone and the cannabinoids found in *Cannabis sativa* are typical of the terpenoids.

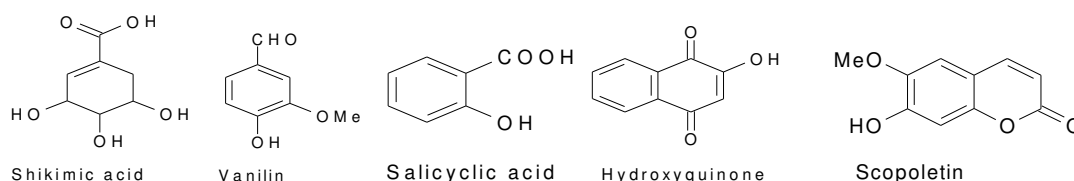


Figure 5: Aromatics derived from shikimic acid vary in complexity from the simple – vanillin, salicylic acid, hydroxyquinone and scopoletin; to the more complex – podophyllotoxin.

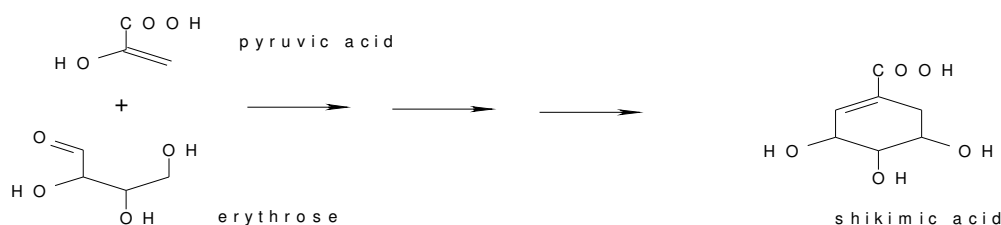


Figure 6: Shikimic acid, a precursor of many medicinal phytochemicals – secondary metabolites, is formed from two primary metabolites - pyruvic acid and erythrose.

Other important derivatives of isoprene are: vitamin A, a diterpenoid; quinones, such as vitamin K; alcohols, such as vitamin E; and sterols, such as vitamin D. Terpenoids are responsible for the aroma of eucalyptus and the flavors of cinnamon, cloves and ginger. Other well-known terpenoids include menthol, camphor, thujone and the cannabinoids found in *Cannabis sativa* (Figure 4).

Biosynthesis of aromatics and other products of shikimic acid pathway

Aromatics and other natural products derived from shikimic acid vary in complexity from the simple, such as vanillin, salicylic acid hydroxyquinone and scopoletin; and to the more complex, such as podophyllotoxin (people.vcu.edu (2009d) (Figure 5).

Shikimic acid is formed from two primary metabolites - pyruvic acid and erythrose (Figure 6).

It is an important intermediate in plants and microorganisms. The name comes from the Japanese flower “shikimi” - *Illicium anisatum*, from which it was first isolated (people.vcu.edu (2009d). The acid is a precursor of many important compounds, including:

- (1) Two key aromatic amino acids - phenylalanine and tyrosine.
- (2) Indole containing aromatic derivatives - for example, tryptophan.
- (3) Many alkaloids and other aromatic derivatives.
- (4) Tannins, flavonoids, and lignin.

Aromatics contain at least one benzene ring. Included among them are the flavones and isoflavones and their substituted products, collectively called anthocyanins - that give flowers, fruits and seeds their various colours. Quercetin is a substituted flavone, or a flavinoid. Also included are the tannins that give teas their astringency (people.vcu.edu (2009d) (Figure 7).

Tannins are mostly colorless, widespread in nature, and many are glycosides. They are non-crystalline, form colloids with water, precipitate alkaloids and proteins, and form dark blue complexes with ferric chloride - a property exploited in ink production. The name “tannins” derives only from their ability to tan leather.

There are two groups of tannins:

- (1) Hydrolysable tannins, which are esters of gallic acid (structure below) and their glycosides.
- (2) Condensed tannins, which are polymers derived from

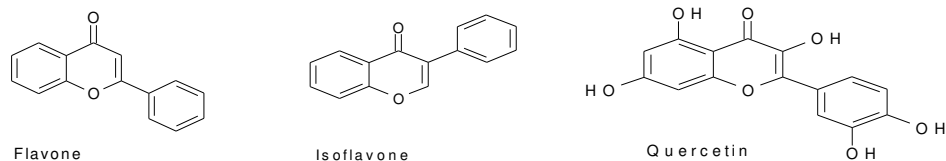


Figure 7: Aromatics contain at least one benzene ring. Included among them are the flavones and isoflavones and their substituted products, collectively called anthocyanins, such as quercetin.

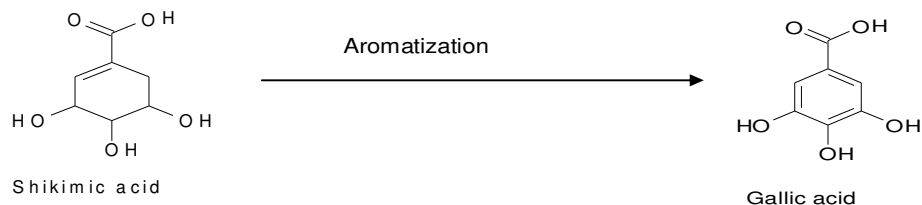


Figure 8: Gallic acid from which many medicinally important phytochemicals are derived is formed from enzymatic aromatization of shikimic acid in plant cells.

various flavonoids, such as quercetin (structure in Figure 7).

It should be noted that gallic acid results from aromatization of shikimic acid (Figure 8).

Biosynthesis of polyketides

The polyketide pathway is major biosynthetic pathway for several medicinally important products. The compounds are derived from poly- β -keto unit, formed by the coupling of acetate or substituted acetate units via a condensation reaction catalyzed by polyketide synthetase complex (people.vcu.edu, 2009d; Robinson, 1991).

As would be expected, poly- β -keto units are the building blocks for a wide range of natural products, collectively called polyketide. They include polyketide antibiotics, antifungals, cytostatics, anticholesterolemic, antiparasitics, coccidiostatics, insecticides and other economical important compounds. A few examples are given below (people.vcu.edu, 2009d).

- (1) Macrolide antibiotics - an example is erythromycin-A, produced by *Streptomyces erythreus*.
- (2) Polyene antibiotics - an example is amphotericin-B, produced by *Streptomyces nodosus*.
- (3) Tetracycline antibiotics - an example is oxytetracycline, produced by several different species of *Streptomyces*. The antitumor agent, doxorubicin, is a polyketide glycoside similar in structure to the tetracyclines.
- (4) Anticholesterolemic - an example is Lovastatin, isolated from *Aspergillus terreus*.
- (5) Other economically important polyketides include the carcinogenic mycotoxins, called aflatoxins.

Among the simplest compounds derived from the polyketide pathway are the essential fatty acids present in all living organisms. A key example is arachidonic acid - the precursor of the prostaglandins, which mediate in several physiological activities (people.vcu.edu, 2009d).

A comment on glycosides

A large number of medicinal compounds exist as glycosides - they do not constitute another class of phytochemicals, and many of the phytochemicals already mentioned exist as glycosides (Tapsell, 2006). By definition, glycosides consist of a glucose moiety or some other sugar attached to an aglycone. The aglycone is the portion of the molecule that is bioactive in its free form but inert until the glycoside bond is broken by water or enzymes. This mechanism allows the plant to defer the availability of the molecule to an appropriate time, similar to a safety lock on a gun. An example is the cyanogenic glycosides in cherry pits that release toxins only when bitten (Taiz and Zeiger, 2006). Other examples of glycosides include: andrographiside, one of the bitter principles present in *Andrographis paniculata*; rutin, one of the antimicrobial principles of *Mitracarpus scaber*; and strictosamide, one of the many alkaloid glycosides present in *Nauclea latifolia*.

Selected examples of scientific exploitation of natural molecules

It is amazing how so many of today's most patronized drugs are synthetic analogues of natural products. For instance, Farnworth (1990) showed that some 119 medicinal compounds in use today arose from about 90 plant species. The now popular antimalarial, artemisinin,

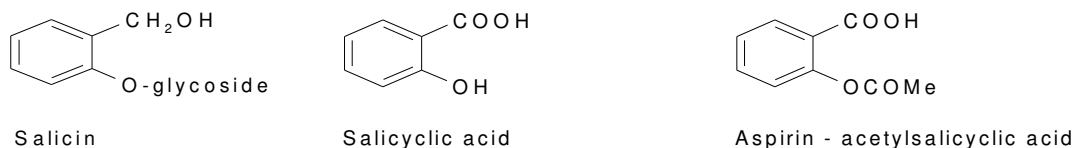


Figure 9: Introduction of sodium salicylate and aspirin to medicine in 1875 and 1899 followed the discovery of salicin - a glycoside of salicyl alcohol, found to be the analgesic agent in willow bark.

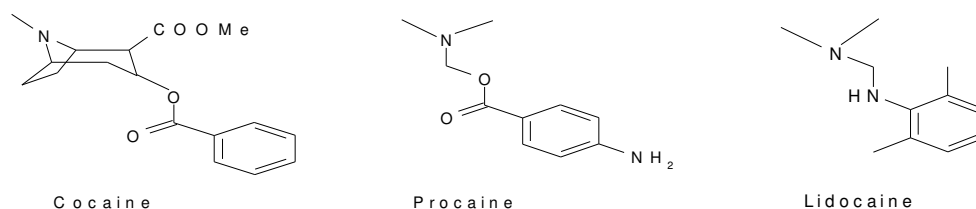


Figure 10: Attempts to synthesize compounds as beneficial as cocaine, but without its undesirable effects, led to such drugs as procaine and lignocaine.

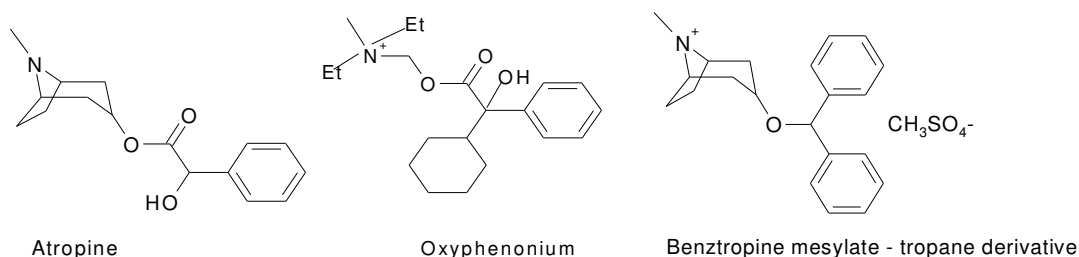


Figure 11: Attempts to modify DL-hyoscyamine, a belladonna alkaloid, led to such drugs as adephenine, oxyphenonium and benztropine mesylate.

was developed from a Chinese herbal medicine (Klayman and Bingel, 1977). Here a few examples selected from Finar (1970), Albert (1981) and Sofowora (1982) is presented with comments:

Salicin: The introduction of sodium salicylate and aspirin to human medicine in 1875 and 1899 respectively, followed the discovery that salicin, the analgesic agent in willow bark. Salicin is a glycoside of salicyl alcohol (Figure 9).

Cocaine: As soon as the structure of cocaine, an active principle from coca leaves, became known, attempts began to synthesize related compounds in the hope of finding a molecule that would be as beneficial as cocaine, but without its undesirable effects. This led to drugs such as procaine and lignocaine, which like cocaine contain tertiary nitrogen (Figure 10).

Atropine: From knowing the structure of this compound, also called DL-hyoscyamine, a belladonna alkaloid, attempts were made to modify its structure, leading to

several important synthetic drugs, such as: adephenine, oxyphenonium and benztropine mesylate (Figure 11).

Morphine: Although the structure of this opium alkaloid had been known since 1806, it was not until 1938 that pethidine was introduced as an analogue. After 1938 however, other synthetic opiates rapidly followed. Examples are: nalorphine, methadone or amidone, pentozocine, butorphanol, and etonitazine - an extremely addictive substance, which is claimed to be 1,500 times more potent than morphine. The presence of tertiary nitrogen in the following structures of morphine, pethidine and codeine are notable (Figure 12).

Cinchonine: This alkaloid, along with quinine and others, occurs in the bark of various species of cinchona. Their synthetic analogues include: Mepacrine, Quinacrine, and chloroquine. Note that both quinine and chloroquine contain the quinoline nucleus (Figure 13).

It is quite clear from the foregoing that medicinal plants, have not only been the major source, but have largely been the inspiration for many synthetic remedies.

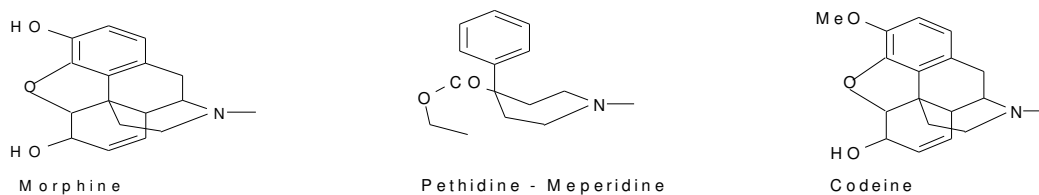


Figure 12: Morphine was known in 1806, but only in 1938 was pethidine introduced as its analogue. After 1938 however, many synthetic opiates including codeine rapidly followed.

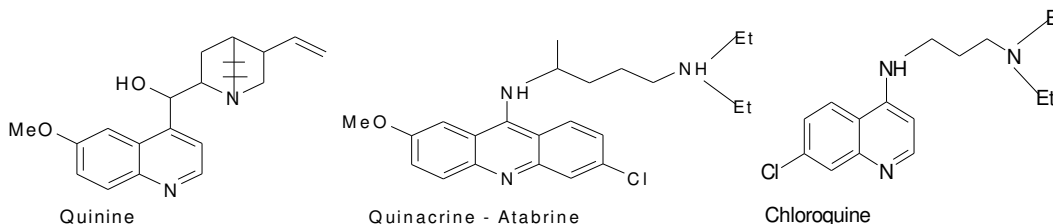


Figure 13: Cinchonine, along with quinine and others, occurs in the bark of various species of cinchona. Their synthetic analogues include: Mepacrine, Quinacrine, and chloroquine.

RISING PROFILE OF HERBAL MEDICINE – THE CORE OF TRADITIONAL MEDICINE

Spread of patronage

Up to 80% of the Third World relies on traditional medicine (WHO, 2003). In many industrialized countries, 70 - 80% of the populations have used some form of alternative or complementary medicine (WHO, 2008). The herbal aspect of the practice is the most popular form, and is highly lucrative in the international marketplace. In the EU annual revenues from herbal medicines surpassed US\$ 6 billion in 2003 (Current status of medicinal plants, 2003). In China sales of the same fetched US\$ 14 billion in 2005, while in 2007; herbal medicine boosted the Brazilian economy by US\$ 160 million (WHO, 2008). In 2006, a US-based company, Xechem Incorporated, commenced commercial production of Niprisan, an herbal medicine for sickle cell disorder developed in Nigeria (Wambebe et al., 2001).

Issues arising from the rising patronage

Globalization of practices that developed over centuries in certain communities, without a concurrent internationalization of standards for their evaluation and regulation is bound to produce challenges (WHO, 2003). Since many countries are yet to adopt national policies on traditional medicine, it is difficult to regulate such practices globally. Secondly, the means to test the safety, efficacy and quality of traditional therapies are highly limited for both raw and finished products. The suitability of products depends on the quality of their raw materials,

which often include several natural constituents. Thirdly, since medicinal plant materials are mostly collected from the wild, the expanding herbal medicine market could threaten biodiversity. Thus efforts must be made to preserve wild plants and the indigenous knowledge for their utilization in medicine. Fourthly, many erroneously believe that since herbal medicines are natural, they are safe and free of risks. This, according to WHO (2003), calls for increased public awareness of the true situation - namely, that herbal medicines do have potentials to harm, especially if used wrongly. Since the early 1980's WHO had steadily responded to these issues by promoting the integration of traditional medicine into the national health systems (WHO, 2005a; 2005b; 2007).

WHO GUIDELINES FOR ASSESSING HERBAL MEDICINES

Some key definitions and objective of the guidelines

Since the Alma-ata Declaration, WHO has been promoting traditional medicine, inclusive of herbal medicine. This has led to the upsurge in global demand, leading to many countries seeking WHO's advice in identifying safe and effective herbal remedies. In response the WHO published the requirements for clinical trials of herbal products (WHO, 2005b), which contains the following definitions:

- (1) Herbal substance - material derived from the plant(s) by extraction, mechanical manipulation or some other process.
- (2) Herbal product - the herbal material administered to

Table 1. Documentation of safety based on experience.

Condition	Action needed
No toxicological data exist	Documented experience of long-term use (at least 20-30 years) without problems should form the basis of risk assessment
Some toxicological data exist	The period during which the drug had been in use should be noted. The health disorder treated with the drug should be noted. The number of patients so treated should be noted. The location in which the treatment was carried out should be noted.
There is toxicity	Attempts must be made to establish its dose-dependency. Attempt must be made to explain (a) above
There is potential for misuse	All cases of abuse or dependence must be documented
Long-term tradition cannot be proved	Attempts must be made to conduct toxicity studies

clinical subjects.

(3) Herbal product synonyms - herbal remedy, herbal medicine, herbal drug, botanical drug.

The objective of the guidelines (WHO, 2000) is: "To define basic criteria for evaluating quality, safety and efficacy of herbal medicines; and to thereby assist national regulatory authorities, scientific organizations and manufacturers to undertake an assessment of documentations submitted in respect of such products" (WHO, 2000) . Traditional experience with a given product is a key factor in assessing such a product. As a general rule, traditional experience must take the following into consideration: Long-term experience in the use of the product; Medical indications of the product; Ethnographic background of the product; and Historical background of the product. The definition of "long-term" may vary from culture to culture, but must be at least 20-30 years. Another general rule is that: "Prolonged and apparently uneventful use of a substance usually offers testimony of its safety" (WHO, 2000).

Assessment of quality

In assessing the quality of medicinal plant materials or their preparations (WHO, 2000), the issues that foremost are: whether the item is supported by a monograph; whether the item is a crude plant material or a defined finished product; and the conditions under which the item is stable. For imported items, the regulatory status in the country of origin must be declared.

Assessment of safety

Long-term usage: The guiding principle is that: if the

product has been in use traditionally for at least 20 - 30 years, but usually more, without demonstrated harm, no specific restrictive regulatory action need be undertaken, unless new evidence demands a revision of risk-benefit assessment (WHO, 2000). A review must be made of all literature pertaining to the subject matter. This should, as much possible, include original articles and references. Available oral traditions should also be taken note of. If official monographs or review articles exist, they must be perused and assessed.

Pharmacovigilance and routine toxicological studies

Known side-effects are to be documented according to normal pharmacovigilance practices. Similarly, results of any toxicological studies carried out should feature in the assessment of safety (WHO, 2000).

Documentation of safety based on experience: The key points are shown in the Table 1.

Assessment of efficacy

The issues raised (WHO, 2000) in assessing the efficacies of an herbal medicine are:

- (1) Whether the ingredients and their pharmacological actions are known, and whether these have any relations with observed clinical results.
- (2) Whether the indications for use of the medicine are specified. Evidence that such indications are evidence-based must be rigorously sought, unless they relate to minor disorders, unspecific complaints or prophylactic use.
- (3) If long-term traditional use has not been established, it is needful to seek fresh clinical evidence.

WHO GUIDELINES FOR LABELING AND PROMOTION

Product information for the user

These refer to product labels and package inserts. They are designed to be understood literate consumers, and should contain information necessary for correct usage. The following are called for: name of the product; quantitative list of active ingredients; dosage form; and indications. Information under indications include: dosage (if appropriate, specify for children and the elderly); mode of administration; duration of usage; major adverse effects, if any; over-dosage information; contraindications, warning, precautions and major drug interactions; and use during pregnancy and lactation. Others include expiry date; lot number; and holder of marketing authorization, or manufacturer. Active ingredients are to be identified by their botanical names, in addition to the common names. Where all the above information cannot be supplied, the minimum required must be determined by the national drug regulatory authority (WHO, 2000).

Promotion

Advertisements and other promotional materials directed to health workers and the general public must be consistent with the elements of information approved for labels and inserts (WHO, 2000).

Conclusion

The World Health Organization had over time produced a large corpus of data on how medicinal plant materials and their products should be handled, starting from the collection of materials, through manufacturing, to clinical trials. These dossiers, better called guidelines, are intended to facilitate the work of regulatory authorities, scientific academies, industries and interregional agencies concerned with the regulation and trade of herbal medicines. It is intended that assessments by these agencies would reflect current scientific knowledge, and that such assessments would form the basis for classifying herbal medicines for the purpose of regulation and trade. Since effective control of herbal medicines moving in international commerce requires close liaison between national agencies, such agencies should be able to monitor the production and use of these products. Such an exercise requires common terms of reference, which the WHO guidelines represent. Familiarity of governments and businesses with these guidelines should stimulate and facilitate sponsorship of researches designed to evaluate the efficacy, acceptability, cost and relative value of herbal medicines as compared with other remedies.

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