

Update Le point

Articles in the *Update* series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, and, over a period of years, will cover many different aspects of the biomedical sciences and public health. Most of the articles will be written, by invitation, by acknowledged experts on the subject.

Les articles de la rubrique *Le point* fournissent un bilan concis et fiable de la situation actuelle dans le domaine considéré. Des experts couvriront ainsi successivement de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés sur demande par les spécialistes les plus autorisés.

Medicinal plants in therapy*

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One of the prerequisites for the success of primary health care is the availability and use of suitable drugs. Plants have always been a common source of medicaments, either in the form of traditional preparations or as pure active principles. It is thus reasonable for decision-makers to identify locally available plants or plant extracts that could usefully be added to the national list of drugs, or that could even replace some pharmaceutical preparations that need to be purchased and imported. This update article presents a list of plant-derived drugs, with the names of the plant sources, and their actions or uses in therapy.

Since most medicinal plants occur naturally in a large number of countries, a plant of potential importance in one country may well have been studied by scientists elsewhere. Considerable time and effort could be saved if their findings could be made available to all interested people. Pooled information is especially critical when it comes to drugs, as a value judgement on the safety or efficacy of a particular drug can rarely be based on the results of a single study. In contrast, a combination of information indicating that a specific plant has been used in a local health care system for centuries, together with efficacy and toxicity data published by several groups of scientists, can help in deciding whether it should be considered acceptable for medicinal use (1).

No accurate data are available to assess the value and extent of the use of plants or of active principles derived from them in the health care systems of countries. WHO has estimated that perhaps 80% of the more than 4000 million inhabitants of the world rely

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chiefly on traditional medicines for their primary health care needs, and it can safely be presumed that a major part of traditional therapy involves the use of plant extracts or their active principles.

In the developed countries, too, plant-derived drugs may be of importance. In the USA, for example, 25% of all prescriptions dispensed from community pharmacies from 1959 to 1980 contained plant extracts or active principles prepared from higher plants. This figure did not vary by more than $\pm 1.0\%$ in any of the 22 years surveyed (2, 3), and in 1980 consumers in the USA paid more than \$8000 million for prescriptions containing active principles obtained from plants (4). Despite this, virtually no interest is shown by pharmaceutical companies in the USA in investigating plants as sources of new drugs. Industrial interest in exploiting plants for this purpose is almost exclusively found in China and Japan. Clearly, the pathway is open for scientists in developing countries to organize and implement interdisciplinary research programmes for the further utilization of these natural sources of drugs. These sources are usually available in abundance and can provide safe, stable, standardized, and effective galenical products for use in primary health care or can lead to the discovery of new biologically active plant-derived principles that may be candidates for use as drugs. However, before considering how such programmes can be implemented, we must examine whether plants are a logical starting-point for drug development programmes.

MEDICINAL PLANTS IN THERAPY

Secondary plant principles in primary health care

The drugs listed in Annex 1 have been, or are currently, obtained from plants. As many examples as possible have been included of plant-derived drugs of known chemical composition that are used in various countries in primary health care or that are recognized as valuable drugs in widespread (i.e., non-prescription) use. For this purpose we have relied primarily on recent pharmacopoeias of selected countries, on the current clinical literature, and on personal knowledge of drug use in various countries.

A few of the drugs are simple synthetic modifications of naturally obtained substances. In some cases, the natural product is now replaced by a commercially synthesized product. Annex 1 shows that there are at least 119 distinct chemical substances derived from plants that can be considered as important drugs currently in use in one or more countries. In Annex 2 these drugs are classified according to therapeutic category in order to highlight the broad range of uses for which plant principles can be employed. Altogether, about 62 therapeutic categories can be distinguished. From Annex 3 it can be seen that these drugs are primarily obtained from only about 91 species of plants. Most of these plants could be adapted for cultivation and use in almost every country. Research is nevertheless required to determine whether the useful active principle could be produced by plants cultivated in an alien habitat. The economics of cultivating such plants and obtaining their active principles has also to be carefully considered.

Correlation between the use of plants in traditional medicine and of the drugs obtained from them

One of the major approaches in developing new drugs from plants is to examine the uses claimed for a traditional preparation. Although investigators involved in the development of drugs from natural products usually argue that there is a close relationship between a traditional preparation and a drug obtained from the same plant, data supporting such claims have not been presented. However, an attempt has been made to present in Annex 1

a correlation between the traditional uses of some plants with the pharmacological action of the isolated drug for 119 substances extracted from plant sources. Although our studies are incomplete at present, we believe that the three levels of correlation indicated in Annex 1 are reasonably accurate. The correlations were established as follows:

(1) If there was positive proof of a correlation, based on a study of the ethnomedical uses of plants and a knowledge of the actions of the chemical substances extracted from them, this was designated as "yes".

(2) If there was some correlation between the use of a traditional plant preparation and the use of substances derived from it or a related plant, we considered this as a positive correlation and indicated it as "indirect". For example, *Digitalis lanata* Ehrh. has not been found to be used in traditional medicine as a diuretic or for the treatment of congestive heart failure or dropsy, uses that are related to cardiotonic activity. However, the isolation of several drugs from *D. lanata* (acetyldigoxin, deslanoside, digoxin, lanatosides A, B and C) that are currently used as cardiotonic agents was due to the known usefulness of *D. purpurea* L. as a cardiotonic agent. Chemical studies on *D. lanata* were therefore initiated with the possibility of finding cardiotonic agents, even though *D. lanata* itself was not used in this manner. Similarly, the "indirect" discovery of tubocurarine was based on a study of *Chondodendron tomentosum* R. & P. and other plants used as arrow poisons by Indians from various cultures; study of the paralysis of the skeletal muscles of birds in flight and of running animals by arrows dipped in "curare" products led to the discovery of tubocurarine. Altogether, 10 plant sources are designated in Annex 1 with an "indirect" correlation.

(3) Thirty-one plant-derived drugs were found for which no correlation could be found between their use as drugs and the traditional uses of the plants from which they were obtained (Annex 1). However, more careful study of the older literature may reveal some relationship.

Of the 119 plant-derived drugs listed in Annex 1, 88 (74%) were discovered as a result of chemical studies to isolate the active substances responsible for the use of the original plants in traditional medicine.

Approach to the study of plants used in traditional medicine

Annex 1 shows that a fairly high percentage of useful plant-derived drugs were discovered as a result of scientific follow-up of well-known plants used in traditional medicine, and it can be concluded that this is a good approach for discovering other useful drugs from plants. In contrast, other approaches, such as phytochemical screening, massive biological screening of randomly collected plants, and phytochemical examination of plants with the aim of identifying new chemical compounds have not proved to be very helpful in discovering new drugs.

However, there are two fundamental questions that must be considered before one initiates research on plants used in traditional medicine. Is it desirable to put in effort to discover pure compounds in the hope of using them as drugs *per se* or is it preferable to go on using traditional preparations and make no attempt to identify the active principles?

For the majority of developing countries, the cost of imported drugs on a large scale is almost prohibitive. On the other hand, these countries have an enormous wealth of information on medicinal plants, which are not only cheap and abundant but also culturally acceptable. Furthermore, most developing countries have neither a well-organized pharmaceutical industry nor the manufacturing capacity to isolate large quantities of active principles from plants should they be discovered. Thus, programmes for this kind of drug development in these countries have to be well planned and

coordinated (within the country), and they may be carried out in stages as illustrated in Fig. 1. This flow chart focuses on the initial need to produce safe and effective galenical products but includes the long-term objective of discovering the active principles. These programmes could eventually lead to the development of a pharmaceutical industry in the country.

Critics of the use of galenical products rather than pure active constituents should consider the following simplified example, which illustrates the value of galenical preparations. A chemically standardized tincture of *Atropa belladonna* for use in treating stomach ulcers has a therapeutic efficacy at least equivalent to that of a standard dose of atropine sulfate (the major active principle of *A. belladonna*). The plant itself can be cultivated easily in almost any country and the manufacture of a stable, standardized tincture would require little in the way of hard currency, which would be needed to import tablets of atropine sulfate. Other similar examples of efficacious galenical preparations that could be promoted in developing countries can be identified from the information presented in Annex 1. There is therefore much in favour of establishing programmes for producing standardized and safe galenical traditional preparations for potential use in primary health care, as shown in Fig. 1, with the eventual aim of discovering their active principles.

Even if the active principles have not yet been identified in some of the plants used in traditional medicine, historical evidence of the value of such plants could result in useful preparations, provided they are safe. Evaluation of safety should therefore be a prime consideration, even at the expense of establishing efficacy of the preparation.

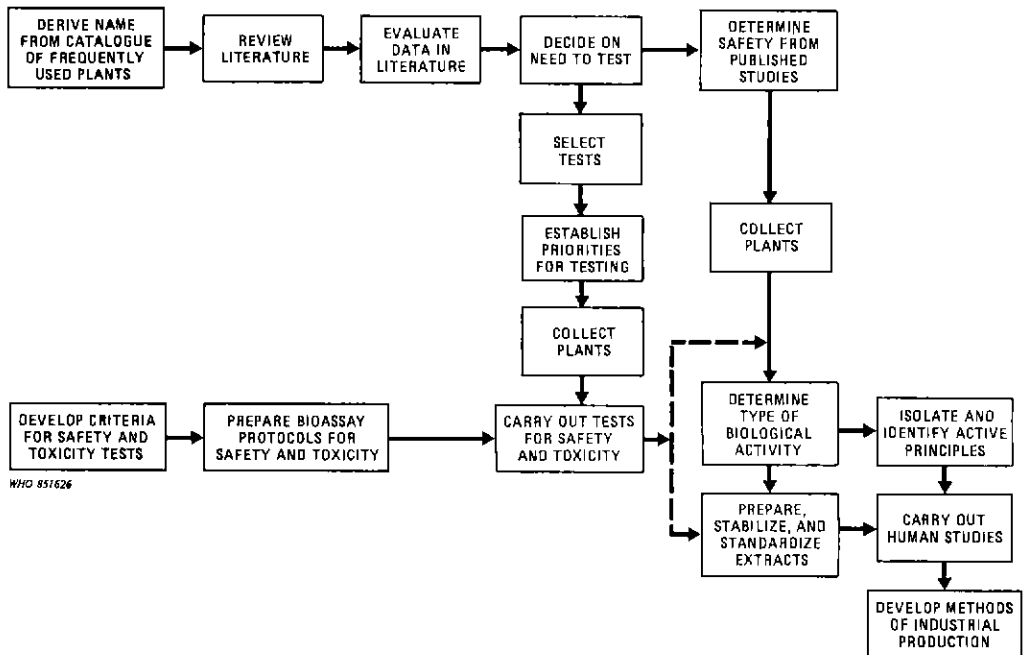


Fig 1. Flow chart of sequence for the study of plants used in traditional medicine.

Simplified pharmacological pre-screening of plant extracts

One point that should be noted about the biological activity data on plant extracts reported in the literature is the difficulty of reproducing many of the results. In general, the more sophisticated the bioassay, the lower the chance of being able to reproduce the data, but the reason for this remains elusive. Many of the reports on the pharmacological testing of crude plant extracts have been published by investigators working in laboratories in developing countries. One explanation might therefore be that laboratory animals in some developing countries are undernourished and thus respond biochemically in a different way from animals that have a better nutritional intake. It is also possible that low-grade laboratory animal infections, especially parasitic infestations, which may not manifest themselves visibly, could cause animals to respond abnormally to the action of drugs. The inability to reproduce experiments involving the biological evaluation of plant extracts has also been attributed to variation in the chemical constituents due to the age of the plants, the time of year or season when they were collected, or the geographical area where they were collected. Although chemical variation in plants is well known, we are unaware of reliable experimental data indicating that this is the reason for the inability to reproduce the biological effects of plant extracts.

Scientists are generally reluctant to accept data on the effects of crude plant extracts in humans or in intact animals unless an explanation of the reported effects is also given. Conversely, data from mechanistic studies (usually *in vitro*) on crude plant extracts rarely attract much interest in the absence of evidence demonstrating the effects in an intact animal or human subject.

In most developing countries, chemical and botanical expertise is usually readily available but experienced pharmacologists are rare. If trained pharmacologists are in short supply or if they are not interested in collaborative efforts to discover new drugs from plants, it is feasible for chemists to set up and implement certain *in vitro* bioassays (sometimes referred to as "pre-screens") or cell-culture systems that can provide valuable information. Similarly, pharmacologists may find it more convenient and economical to study drug effects *in vitro* as an alternative to using intact laboratory animals in their research. There are sufficient bioassay techniques described in the literature to enable almost any biological activity of interest to be studied without using intact animals. Indeed, there is a worldwide trend to avoid experimenting on intact animals in the early stages of drug development. Some of the "pre-screens" rely on chemical or biochemical expertise rather than on pharmacological knowledge and training and hence should be managed by chemists. A few of these bioassays are listed in Annex 4.

Most of the "pre-screens" indicated in Annex 4 can be performed using relatively simple equipment. Virtually all assays can be conducted using tissue culture equipment, a CO₂-incubator, an inverted microscope, a sterile hood, a cell counter, water baths, dry air incubators, an autoclave, a recording spectrophotometer, and a liquid scintillation counter. However, many of the *in vitro* "pre-screens" can be effectively carried out without some or all of this equipment. Thus, the chemist who does not have collaborating biologists could set up one or more bioassays that facilitate the isolation of biologically active molecules. These compounds are usually likely to be chemically complex and possess novel structures that are interesting from the scientific point of view.

The "pre-screens" listed in Annex 4 have all been successfully employed for the biological evaluation of crude extracts and may need only slight modification to adapt them to laboratories where conditions are not the best. The information provided in the cited references should be adequate to set up the bioassay systems, as well as to facilitate an understanding of the basic principles involved.

CONCLUSION

Scientists in developing countries are entering an era in which plants can be expected to occupy a prominent position in the list of national priorities. This type of drug research could lead to industrial development in the country where the discoveries are made. The source of starting materials is normally abundant and readily available since in most developing countries the flora remains virtually unexploited, and we believe that over the next two decades many useful drugs will be isolated from plants. The majority of these discoveries should and will be made by enthusiastic, energetic, and highly motivated scientists in developing countries.

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Annex I

Sources, action and uses of plant-derived drugs and their correlations

Drug	Action or clinical use	Plant source	Traditional use	Correlation ^a
Acetyldigoxin	Cardiotonic	<i>Digitalis lanata</i> Ehrh.	—	Indirect
Adoniside	Cardiotonic	<i>Adonis vernalis</i> L.	Heart conditions	Yes
Aescin	Anti-inflammatory	<i>Aesculus hippocastanum</i> L.	Inflammations	Yes
Aesculetin	Antidysentery	<i>Fraxinus rhynchophylla</i> Hance	Dysentery	Yes
Agrimophol	Anthelmintic	<i>Agrimonia eupatoria</i> L.	Anthelmintic	Yes
Almalicine	Circulatory disorders	<i>Rauwolfia serpentina</i> (L.) Benth ex Kurz	Tranquillizer	Indirect
Allantoin ^b	Vulnery	Several plants	—	No
Allyl isothiocyanate ^b	Rubefacient	<i>Brassica nigra</i> (L.) Koch	Rubefacient	Yes
Anabasine	Skeletal muscle relaxant	<i>Anabasis aphylla</i> L.	—	No
Andrographolide	Bacillary dysentery	<i>Andrographis paniculata</i> Nees	Dysentery	Yes
Anisodamine	Anticholinergic.	<i>Anisodus tanguticus</i> (Maxim.) Pascher	Menngitis symptoms	Yes
Anisodine	Anticholinergic	<i>Anisodus tanguticus</i> (Maxim.) Pascher	Menngitis symptoms	Yes
Arecoline	Anthelmintic	<i>Areca catechu</i> L.	Anthelmintic	Yes
Asiaticosidi ^c	Vulnery	<i>Centella asiatica</i> (L.) Urban	Vulnery	Yes
Atropine	Anticholinergic	<i>Atropa belladonna</i> L.	Dilate pupil of eye	Yes
Benzyl benzoate ^b	Scabicide	Several plants	—	No
Berberine	Bacillary dysentery	<i>Berberis vulgaris</i> L.	Gastric ailments	Yes
Bergenin	Antitussive	<i>Ardisia japonica</i> Bl.	Chronic bronchitis	Yes
Borneol ^b	Antipyretic; analgesic, anti-inflammatory	Several plants	—	No
Bromelain	Anti-inflammatory, proteolytic agent	<i>Ananas comosus</i> (L.) Merrill	—	Indirect
Caffeine	CNS stimulant	<i>Camellia sinensis</i> (L.) Kuntze	Stimulant	Yes
Camphor	Rubefacient	<i>Cinnamomum camphora</i> (L.) J.S Presl	—	No
(+)-Catechin	Haemostatic	<i>Potentilla fragarioides</i> L.	Haemostatic	Yes
Chymopapain	Proteolytic, mucolytic	<i>Carica papaya</i> L.	Digestant	Yes
Cissampelline	Skeletal muscle relaxant	<i>Cissampelos pareira</i> L.	—	No

^a See explanation in text (p. 966).

^b Now also produced commercially by synthesis

Annex 1: continued

Drug	Action or clinical use	Plant source	Traditional use	Correlation
Cocaine	Local anaesthetic	<i>Erythroxylum coca</i> Lamk		Yes
Codeine	Analgesic; antitussive	<i>Papaver somniferum</i> L.	Appetite suppressant, stimulant	Yes
Colchicine amide	Antitumour agent	<i>Colchicum autumnale</i> L.	Gout	No
Colchicine	Antitumour agent, anti-gout	<i>Colchicum autumnale</i> L.	Gout	Yes
Convallatoxin	Cardiotonic	<i>Convallaria majalis</i> L.	Cardiotonic	Yes
Curcumin	Choleretic	<i>Curcuma longa</i> L.	Choleretic	Yes
Cynarin	Choleretic	<i>Cynara scolymus</i> L.	Choleretic	Yes
Danthron (1,8-dihydroxy-anthraquinone) ^b	Laxative	<i>Cassia species</i>	Laxative	Yes
Demecolcine	Antitumour agent	<i>Colchicum autumnale</i> L.	Gout	No
Deserpidine	Antihypertensive, tranquilizer	<i>Rauwolfia canescens</i> L.	Sedative, hypotensive	Yes
Deslanoside	Cardiotonic	<i>Digitalis lanata</i> Ehrh.	—	Indirect
L-Dopa ^b	Anti-Parkinsonism	<i>Mucuna deeringiana</i> (Bort) Merr	—	No
Digitalin	Cardiotonic	<i>Digitalis purpurea</i> L.	Cardiotonic	Yes
Digitoxin	Cardiotonic	<i>Digitalis purpurea</i> L.	Cardiotonic	Yes
Digoxin	Cardiotonic	<i>Digitalis lanata</i> Ehrh.	—	Indirect
Emetine	Amoebicide; emetic	<i>Cephaelis specazuana</i> (Brotero) A. Richard	Amoebicide, emetic	Yes
Ephedrine	Sympathomimetic	<i>Ephedra sinica</i> Stapf	Chronic bronchitis	Yes
Etoposide ^c	Antitumour agent	<i>Podophyllum peltatum</i> L.	Cancer	Yes
Galanthamine	Cholinesterase inhibitor	<i>Lycoris squamigera</i> Maxim	—	No
Gitalin	Cardiotonic	<i>Digitalis purpurea</i> L.	Cardiotonic	Yes
Glaucaubin	Amoebicide	<i>Samarouba glauca</i> DC	Amoebicide	Yes
Glaucine	Antitussive	<i>Glaucium flavum</i> Crantz	—	No
Glaziovine	Antidepressant	<i>Ocotea glaziovii</i> Mez	—	No
Glycyrrhizin (Glycyrrhetic acid)	Sweetener; Addison's disease	<i>Glycyrrhiza glabra</i> L.	Sweetener	Yes
Gossypol	Male contraceptive	<i>Gossypium species</i>	Decreased fertility observed	Yes

^b Now also produced commercially by synthesis^c Synthetic modification of a natural product.

Annex 1 continued

Drug	Action or clinical use	Plant source	Traditional use	Correlation
Hemilevadin	Bacillary dysentery; antipyretic	<i>Hemileya amabilis</i> Diels	Dysentery	Yes
Hesperidin	Capillary fragility	<i>Citrus</i> species	—	No
Hydrastine	Haemostatic; astringent	<i>Hydrastis canadensis</i> L.	Astringent	Yes
Hyoscycamine	Anticholinergic	<i>Hyoscyamus niger</i> L.	Sedative	Yes
Kamnic acid	Ascaricide	<i>Digenea simplex</i> (Wulf.) Agardh	Anthelmintic	Yes
Kawain ^b	Tranquillizer	<i>Piper methysticum</i> Forst. f.	Euphoriant	Yes
Khellin	Bronchodilator	<i>Ammi visnaga</i> (L.) Lamk	Asthma	Yes
Lanatosides A, B, C	Cardiotonic	<i>Digitalis lanata</i> Ehrh	—	Indirect
α -Lobeline	Smoking deterrent, respiratory stimulant	<i>Lobelia inflata</i> L.	Expectorant	Yes
Menthol ^b	Rubefacient	<i>Mentha</i> species	Carminative	No
Methyl salicylate ^b	Rubefacient	<i>Gaultheria procumbens</i> L.	Carminative	No
Monocrotaline	Antitumour agent (topical)	<i>Crotalaria sessiliflora</i> L.	Skin cancer	Yes
Morphine	Analgesic	<i>Papaver somniferum</i> L.	Analgesic, sedative	Yes
Neoandrographolide	Bacillary dysentery	<i>Andrographis paniculata</i> Nees	Dysentery	Yes
Nicotine ^b	Insecticide	<i>Nicotiana tabacum</i> L.	Narcotic	No.
Nordihydroguaiaretic acid	Antioxidant (lard)	<i>Larrea divaricata</i> Cav	Antitussive	No
Noxaprine (narcotine)	Antitussive	<i>Papaver somniferum</i> L.	Analgesic; sedative	Yes
Ourarian	Cardiotonic	<i>Strophanthus gratus</i> Baill.	Arrow poison	Indirect
Pachycarpin: (+)-sparteine	Oxytocic	<i>Sophora pachycarpa</i> Schrenk ex C. A. Meyer	—	No
Palmatine (fluraurine)	Antipyretic, detoxicant	<i>Coptis japonica</i> Makino	—	No
Papain	Proteolytic; mucolytic	<i>Carica papaya</i> L.	Digestant	Yes
Papaverine ^b	Smooth muscle relaxant	<i>Papaver somniferum</i> L.	Sedative; analgesic	No
Phylloulcin	Sweetener	<i>Hydrangea macrophylla</i> (Thunb.) Seringe var. <i>thunbergii</i> (Siebold) Makino	Sweetener	Yes
Physostigmine (eserine)	Cholinesterase inhibitor	<i>Physostigma venenosum</i> Balf.	Ordeal poison	Indirect
Picrotoxin	Analeptic	<i>Anamirta cocculis</i> (L.) W. & A	Fish poison	Indirect
Pilocarpin ^b	Parasympathomimetic	<i>Pilocarpus jaborandi</i> Holmes	Poison	Indirect
Pinitol ^b	Expectorant	Several plants	—	No
Podophylotoxin	Condylomata acuminata	<i>Podophyllum peltatum</i> L.	Cancer	Yes
Protoveratrine A & B	Antihypertensives	<i>Veratrum album</i> L.	Hypertension	Yes

^b Now also produced commercially by synthesis.

Annex 1 continued on next page

Annex 1: continued

Drug	Action or clinical use	Plant source	Traditional use	Correlation
Pseudoephedrine	Sympathomimetic	<i>Ephedra sinica</i> Stapf.	Chronic bronchitis	Yes
Pseudoephedrine, nor-	Sympathomimetic	<i>Ephedra sinica</i> Stapf.	Chronic bronchitis	Yes
Quinidine	Antiarhythmic	<i>Cinchona ledgeriana</i> Moens ex Trimmen	Malaria	No
Quinine	Antimalarial, antipyretic	<i>Cinchona ledgeriana</i> Moens ex Trimmen	Malaria	Yes
Quisqualic acid	Anthelmintic	<i>Quisqualis indica</i> L.	Anthelmintic	Yes
Rescinnamine	Antihypertensive, tranquilizer	<i>Rauwolfia serpentina</i> (L.) Benth. ex Kurz	Tranquilizer	Yes
Reserpine	Antihypertensive; tranquilizer	<i>Rauwolfia serpentina</i> (L.) Benth. ex Kurz	Tranquilizer	Yes
Rhomitoxin	Antihypertensive, tranquilizer	<i>Rhododendron molle</i> G. Don	Contraindicated in low blood pressure	Yes
Rorifone	Antitussive	<i>Rorippa indica</i> (L.) Hochr	Chronic bronchitis	Yes
Rotenone	Piscicide	<i>Lonchocarpus nicou</i> (Aubl.) DC	Fish poison	Yes
Rotundine (+)-tetrahydropalmatine)	Analgesic; sedative, tranquilizer	<i>Stephania sinica</i> Diels	Sedative	Yes
Rutin	Capillary fragility	<i>Citrus</i> species	—	No
Salicin	Analgesic	<i>Salix alba</i> L.	Analgesic	Yes
Sanguinane	Dental plaque inhibitor	<i>Sanguinaria canadensis</i> L.	—	No
Santonin	Ascariocide	<i>Artemisia maritima</i> L.	Anthelmintic	Yes
Scillarin A	Cardiotonic	<i>Urginea maritima</i> (L.) Baker	Cardiotonic	Yes
Scopolamine	Sedative	<i>Datura metel</i> L.	Sedative	Yes
Sennosides A & B	Laxative	<i>Cassia acutifolia</i> Delle <i>C. angustifolia</i> Vahl	Laxative	Yes
Silymarin	Antihepatotoxic	<i>Silybum marianum</i> (L.) Gaertn.	Liver disorders	Yes
Sparteine	Oxytocic	<i>Cytisus scoparius</i> (L.) Link	—	No
Stevioside	Sweetener	<i>Stevia rebaudiana</i> Bertoni	Sweetener	Yes
Strychnine	CNS stimulant	<i>Strychnos nux-vomica</i> L	Toxic stimulant	Yes
Temposide ^c	Antitumour agent	<i>Podophyllum peltatum</i> L.	Cancer	Yes
Δ^8 -Tetrahydrocannabinol	Antiemetic; decreases ocular tension	<i>Cannabis sativa</i> L.	Euphoriant	No
(\pm)-Tetrahydropalmatine	Analgesic; sedative, tranquilizer	<i>Corydalis ambigua</i> (Pallas) Cham & Schltal.	Sedative	Yes
Tetraandrine	Antihypertensive	<i>Stephania tetrandra</i> S Moore	—	No
Theobromine	Diuretic; vasodilator	<i>Theobroma cacao</i> L.	Diuretic	Yes
Theophylline	Diuretic, bronchodilator	<i>Camellia sinensis</i> (L.) Kuntze	Diuretic; stimulant	Yes

^c Synthetic modification of a natural product.

Annex 1: continued

Drug	Action or clinical use	Plant source	Traditional use	Correlation
Thymol	Antifungal (topical)	<i>Thymus vulgaris</i> L	—	No
Trichosanthin	Abortifacient	<i>Trichosanthes kirilowii</i> Maxim.	Abortifacient	Yes
Tubocurarine	Skeletal muscle relaxant	<i>Chondodendron tomentosum</i> R.&P	Arrow poison	Yes
Valepotriates	Sedative	<i>Valeriana officinalis</i> L	Sedative	Yes
Vasicine (pegamine)	Oxytotic	<i>Adhatoda vasica</i> Nees	Expectorant	No
Vincamine	Cerebral stimulant	<i>Vinca minor</i> L	Cardiovascular disorders	Yes
Vinblastine (vincal leukoblastine)	Antitumour agent	<i>Catharanthus roseus</i> (L.) G. Don	Diabetes mellitus	No
Vincristine (leurocristine)	Antitumour agent	<i>Catharanthus roseus</i> (L.) G. Don	Diabetes mellitus	No
Xanthotoxin (ammoidin, 8-methoxyypsoralen)	Leukoderma; vitiligo	<i>Ammi majus</i> L	Leukoderma; vitiligo	Yes
Yohimbine	Aphrodisiac	<i>Pausinystalia yohimiba</i> (K. Schum.) Pierre ex Belle	Aphrodisiac	Yes
Yuanhuacine	Abortifacient	<i>Daphne genkwa</i> Sieb. & Zucc.	Abortifacient	Yes
Yuanhuadine	Abortifacient	<i>Daphne genkwa</i> Sieb. & Zucc.	Abortifacient	Yes

Annex 2

Therapeutic indications of plant-derived drugs

Therapeutic indication	Drug	Therapeutic indication	Drug			
Abortifacient	Trichosanthin Yuanhuacine Yuanhuadine	Cerebral stimulant	Vincamine			
Analgesic	Borneol	Chemotherapy	Agrimophol			
	Codeine		Arecoline			
	Morphine	Quisqualic acid				
	Rotundine	Emetine				
	Salicin (±)-Tetrahydropalmatine	Antiamoebic	Glaucarubin Kaicic acid Santonin			
Analeptic	Picrotoxin	Antidysentery	Aesculetin Andrographolide Berberine Hemsleyadin Neoandrographolide			
Antiarrhythmic	Quinidine	Antifungal Antimalarial Antitumour	Thymol Quinine Colchicine amide Colchicine Demecolcine Etoposide ^a Monocrotaline Teniposide ^a Vinblastine Vincristine			
Anticholinergic	Anisodamine		Choleretic	Curcumin Cynarin		
	Anisodine			Cholinesterase inhibitor	Gаланthamine Physostigmine	
	Atropine				Circulatory disorders	Ajmalicine
	Hyoscyamine					CNS stimulant
Antidepressant	Glaziovine					Condylomata acuminata
	Antiemetic			Δ ⁹ -Tetrahydrocannabinol		
	Antigout			Dental plaque inhibition	Sanguinarine	
Antihepatotoxic	Colchicine				Detoxicant	
Antihypertensive	Silymarin				Diuretic	Theobromine Theophylline
	Deserpidine	Emetic			Emetine	
	Protoveratrine A & B		Expectorant	Pinitol		
	Rescinnamine	Haemostatic	(±)-Catechin Hydrastine			
	Reserpine			Insecticide	Nicotine	
	Rhomitoxin		Laxative		Danthron Sennosides A & B	
Tetrandrine	Leukoderma			Xanthotoxin		
Anti-inflammatory		Aescin		Local anaesthetic	Cocaine	
		Borneol			Male contraceptive	Gossypol
		Bromelain	Oxytocic	Pachycarpine Sparteine Vasicine		
Antioxidant	Nordihydroguaiaretic acid	Parasympathomimetic	Philocarpine			
Anti-Parkinsonism	L-Dopa		Piscicide	Rotenone		
Antipyretic	Borneol			^a Synthetic modification of a natural product.		
Antitussive	Hemsleyadin					
	Palmatine					
	Quinine					
	Bergenin					
Aphrodisiac	Codeine					
	Glaucine					
	Noscapine					
	Rorifone					
Astringent	Yohimbine					
	Hydrastine					
Bronchodilator	Khellin					
	Theophylline					
Capillary fragility	Hesperidin					
	Rutin					
Cardiotonic	Acetyldigoxin					
	Adoniside					
	Convaliatoxin					
	Deslanoside					
	Digitalin					
	Digitoxin					
	Digoxin					
	Gitalin					
	Lanatosides A,B,C					
	Ouabain					
	Sciliarin A					

Annex 2: *continued*

Therapeutic indication	Drug	Therapeutic indication	Drug
Proteolytic	Bromelain Chymopapain Papain	Sweetener	Glycyrrhizin Phylloolucin Stevioside
Respiratory stimulant	α -Lobeline	Sympathomimetic	Ephedrine Pseudoephedrine Pseudoephedrine, nor-
Rubefacient	Allyl isothiocyanate Camphor Menthol Methyl salicylate	Tranquillizer	Deserpidine Kawain Rescinnamine Reserpine Rhomitoxin Rotundine (\pm)-Tetrahydropalmatine
Scabicide	Benzyl benzoate	Vasodilator	Theobromine
Sedative	Rotundine Scopolamine (\pm)-Tetrahydropalmatine Valepotriates	Vitiligo	Xanthotoxin
Skeletal muscle relaxant	Anabasine Cissampeline Tubocurarine	Vulnerary	Allantoin Asiaticoside
Smoking deterrent	α -Lobeline		
Smooth muscle relaxant	Papaverine		

Annex 3

Plants used in traditional medicine and the drugs derived from them

Plant ^a	Drug	Plant	Drug
<i>Adhatoda vasica</i>	Vasicine	<i>Cassia acutifolia</i>	Sennosides A & B
<i>Adonis vernalis</i>	Adoniside	<i>Cassia angustifolia</i>	Sennosides A & B
<i>Aesculus hippocastanum</i>	Aescin	<i>Cassia species</i>	Danthron
<i>Agrimonia eupatoria</i>	Agrimophol	<i>Catharanthus roseus</i>	Vinblastine Vincristine
<i>Ammi majus</i>	Xanthotoxin	<i>Centella asiatica</i>	Asiaticoside
<i>Ammi visnaga</i>	Khellin	<i>Cephaelis ipecacuanha</i>	Emetine
<i>Anabasis aphylla</i>	Anabasine	<i>Chondodendron tomentosum</i>	Tubocurarine
<i>Ananas comosus</i>	Bromelain	<i>Cinchona ledgeriana</i>	Quinidine Quinine
<i>Anamirta cocculus</i>	Picrotoxin	<i>Cinnamomum camphora</i>	Camphor
<i>Andrographis paniculata</i>	Andrographolide Neoandrographolide	<i>Cissampelos pareira</i>	Cissampeline
<i>Anisodus tanguticus</i>	Anisodamine Anisodine	<i>Citrus species</i>	Hesperidin Rutin
<i>Areca catechu</i>	Arecoline	<i>Colchicum autumnale</i>	Colchicine amide Colchicine Demecolcine
<i>Ardisia japonica</i>	Bergenin	<i>Convallaria majalis</i>	Convallatoxin
<i>Artemisia maritima</i>	Santonin	<i>Coptis japonica</i>	Palmatine
<i>Atropa belladonna</i>	Atropine	<i>Corydalis ambigua</i>	(\pm)-Tetrahydropalmatine
<i>Berberis vulgaris</i>	Berberine	<i>Crotalaria sessiliflora</i>	Monocrotaline
<i>Brassica nigra</i>	Allyl isothiocyanate	<i>Curcuma longa</i>	Curcumin
<i>Camellia sinensis</i>	Caffeine Theophylline	<i>Cynara scolymus</i>	Cynarin
<i>Cannabis sativa</i>	Δ^9 -Tetrahydrocannabinol	<i>Cytisus scoparius</i>	Sparteine
<i>Carica papaya</i>	Chymopapain Papain	<i>Daphne genkwa</i>	Yuanhuacine Yuanhuadine

^a See Annex 1 for plant authority names.

Annex 3: *continued*

Plant	Drug	Plant	Drug
<i>Datura metel</i>	Scopolamine	<i>Physostigma venenosum</i>	Physostigmine
<i>Digenia simplex</i>	Kainic acid	<i>Pilocarpus jaborandi</i>	Pilocarpine
<i>Digitalis lanata</i>	Acetyldigoxin Deslanoside Digoxin Lanatosides A, B, C	<i>Piper methysticum</i>	Kawan
<i>Digitalis purpurea</i>	Digitalin Digitoxin Gitalin	<i>Podophyllum peltatum</i>	Etoposide ^b Podophyllotoxin Teniposide ^b
<i>Ephedra sinica</i>	Ephedrine Pseudoephedrine Pseudoephedrine, nor-	<i>Potentilla fragarioides</i>	(+)-Catechin
<i>Erythroxylum coca</i>	Cocaine	<i>Quisqualis indica</i>	Quisqualic acid
<i>Fraxinus rhynchophylla</i>	Aesculetin	<i>Rauvolfia canescens</i>	Deserpidine
<i>Gaultheria procumbens</i>	Methyl salicylate	<i>Rauvolfia serpentina</i>	Ajmalicine Rescinnamine Reserpine
<i>Glaucium flavum</i>	Glaucine	<i>Rhododendron molle</i>	Rhomitoxin
<i>Glycyrrhiza glabra</i>	Glycyrrhizin	<i>Rorippa indica</i>	Rorifone
<i>Gossypium species</i>	Gossypol	<i>Salix alba</i>	Salicin
<i>Hemsleya amabilis</i>	Hemsleyadin	<i>Sanguinaria canadensis</i>	Sanguinarine
<i>Hydrangea macrophylla</i> <i>var thunbergii</i>	Phylloulcin	<i>Silybum marianum</i>	Silymarin
<i>Hydrastis canadensis</i>	Hydrastine	<i>Simarouba glauca</i>	Glaucarubin
<i>Hyoscyamus niger</i>	Hyoscyamine	<i>Sophora pachycarpa</i>	Pachycarpine
<i>Larrea divaricata</i>	Nordihydroguaiaretic acid	<i>Stephania sinica</i>	Rotundine
<i>Lobelia inflata</i>	α -Lobeline	<i>Stephania tetrandra</i>	Tetrandrine
<i>Lonchocarpus nicou</i>	Rotenone	<i>Stevia rebaudiana</i>	Stevioside
<i>Lycoris squamigera</i>	Galanthamine	<i>Strophanthus gratus</i>	Oubain
<i>Mentha species</i>	Menthol	<i>Strychnos nux-vomica</i>	Strychnine
<i>Mucuna deeringiana</i>	L-Dopa	<i>Theobroma cacao</i>	Theobromine
<i>Nicotiana tabacum</i>	Nicotine	<i>Thymus vulgaris</i>	Thymol
<i>Ocotea glaziovii</i>	Glaziovine	<i>Trichosanthes kinlowii</i>	Trichosanthin
<i>Papaver somniferum</i>	Codeine Morphine Noscapine Papaverine	<i>Urginea maritima</i>	Scillaric acid
<i>Pausinystalia yohimba</i>	Yohimbine	<i>Valeriana officinalis</i>	Valepotriates
		<i>Veratrum album</i>	Protoveratrine A & B
		<i>Vinca minor</i>	Vincamine
		Several plants	Allantoin Benzyl benzoate Borneol Pinitol

^b Synthetic modification of a natural product.

Annex 4
Examples of *in vitro* bioassays for determining useful drug effects or improvement of health

Type assay	Type system	Implied useful effect	References
Adenosine deaminase inhibition	<i>In vitro</i>	Enhancement of drug efficacy	5
Angiotensin-converting enzyme inhibition	<i>In vitro</i>	Antihypertensive	6
Antibacterial activity	Bacterial culture	Anti-infective	7, 8
Antifungal activity	Fungal culture	Anti-infective	7, 8
Antimitotic activity	Cell culture	Anticancer	9-11
Antimutagenic activity	Cell culture or bacterial culture	Anticancer	12-15
Antiviral	Cell culture	Anti-infective, anticancer	7, 16
ATPase inhibition	<i>In vitro</i>	Cardiotonic	17-19
Benzopyrene hydroxylase (AHH) inhibition	<i>In vitro</i>	Carcinogenesis inhibition	20
Cell transformation	Cell culture	Carcinogenicity detection	21, 22
Cytotoxicity	Cell culture	Anticancer	9, 23
Free radical	<i>In vitro</i> , cell culture	Anticancer	24, 25
HMG-CoA reductase inhibition ^a	<i>In vitro</i>	Antypercholesterolaemic, antiatherosclerotic	26
Human skin cell assay	Cell culture	Anticancer	27, 28
Insect antifeedant	<i>In vitro</i>	Prevent crop damage and insect borne diseases	29, 30
Insecticide	<i>In vitro</i>	Prevent crop damage and insect borne diseases	31, 32
Molluscicide	<i>In vitro</i>	Lower incidence of snail borne diseases, i.e., schistosomiasis	33
Monoamine oxidase (MAO) inhibition	<i>In vitro</i>	Antihypertensive	34
Mutagenicity	Cell culture or bacterial culture	Carcinogenicity detection	35-38
Nucleic acid biosynthesis inhibition	<i>In vitro</i> , cell culture	Antibiotic	39, 40
Phosphodiesterase inhibition	<i>In vitro</i>	Anticancer	41
Plasmodic activity	<i>In vitro</i>	Predictive for molluscicide effect	11
Platelet aggregation inhibition	<i>In vitro</i>	Cardiovascular problems	42
Prostaglandin synthetase inhibition	<i>In vitro</i>	Anti-inflammatory	43, 44
Protease inhibition	<i>In vitro</i>	Anticancer, plant protection	45-47
Protein biosynthesis inhibition	<i>In vitro</i> , cell culture	Antibiotic, anticancer	48, 49
Sister chromatid exchange	Cell culture	Carcinogenicity detection	50
Tyrosine hydroxylase inhibition	<i>In vitro</i>	Antihypertensive	51
Unscheduled DNA synthesis	Cell culture	Carcinogenicity detection	52, 53

^a β -Hydroxy- β -methylglutaryl CoA reductase.

