Update
Le point

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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.*

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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 ± 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.

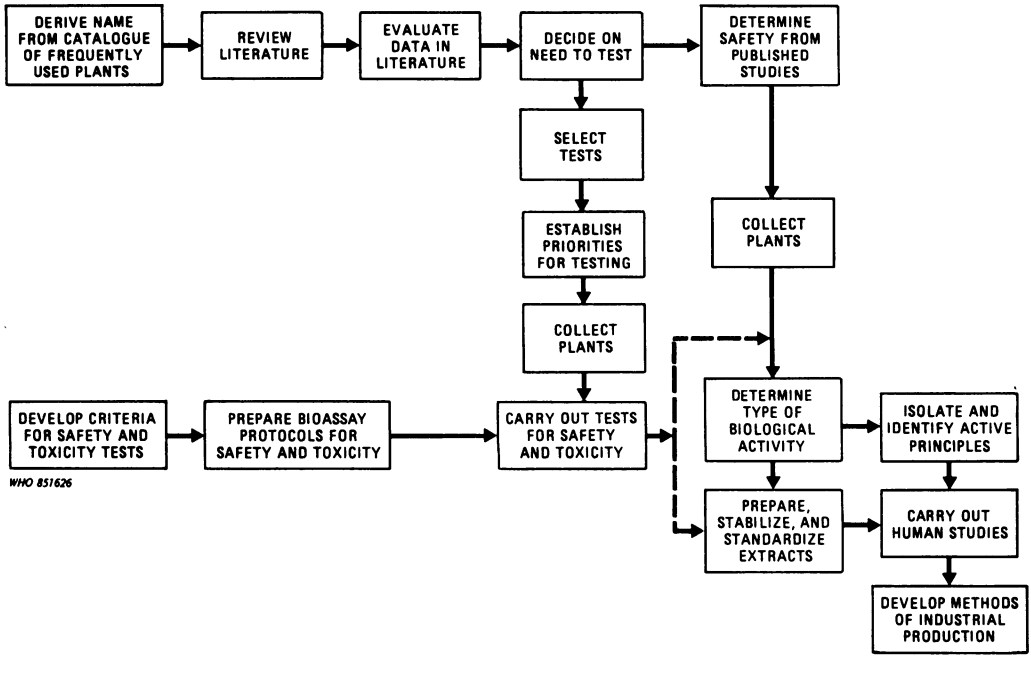

Fig 1. Flow chart of sequence for the study of plants used in traditional medicine.

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 CO_2-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 1

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

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

[a] See explanation in text (p. 966).
[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
Cocaine	Local anaesthetic	*Erythroxylum coca* Lamk.	Appetite suppressant; stimulant	Yes
Codeine	Analgesic; antitussive	*Papaver somniferum* L.	Analgesic; sedative	Yes
Colchiceine amide	Antitumour agent	*Colchicum autumnale* L.	Gout	No
Colchicine	Antitumour agent; anti-gout	*Colchicum autumnale* L.	Gout	Yes
Convallatoxin	Cardiotonic	*Convallaria majalis* L.	Cardiotonic	Yes
Curcumin	Choleretic	*Curcuma longa* L.	Choleretic	Yes
Cynarin	Choleretic	*Cynara scolymus* L.	Choleretic	Yes
Danthron (1,8-dihydroxy-anthraquinone[b]	Laxative	*Cassia* species	Laxative	Yes
Demecolcine	Antitumour agent	*Colchicum autumnale* L.	Gout	No
Deserpidine	Antihypertensive; tranquillizer	*Rauvolfia canescens* L.	Sedative; hypotensive	Yes
Deslanoside	Cardiotonic	*Digitalis lanata* Ehrh.	–	Indirect
L-Dopa[b]	Anti-Parkinsonism	*Mucuna deeringiana* (Bort) Merr.	–	No
Digitalin	Cardiotonic	*Digitalis purpurea* L.	Cardiotonic	Yes
Digitoxin	Cardiotonic	*Digitalis purpurea* L.	Cardiotonic	Yes
Digoxin	Cardiotonic	*Digitalis lanata* Ehrh.	–	Indirect
Emetine	Amoebicide; emetic	*Cephaelis ipecacuanha* (Brotero) A. Richard	Amoebicide; emetic	Yes
Ephedrine	Sympathomimetic	*Ephedra sinica* Stapf.	Chronic bronchitis	Yes
Etoposide[c]	Antitumour agent	*Podophyllum peltatum* L.	Cancer	Yes
Galanthamine	Cholinesterase inhibitor	*Lycoris squamigera* Maxim.	–	No
Gitalin	Cardiotonic	*Digitalis purpurea* L.	Cardiotonic	Yes
Glaucarubin	Amoebicide	*Simarouba glauca* DC.	Amoebicide	Yes
Glaucine	Antitussive	*Glaucium flavum* Crantz	–	No
Glaziovine	Antidepressant	*Ocotea glaziovii* Mez	–	No
Glycyrrhizin (Glycyrrhetic acid)	Sweetener; Addison's disease	*Glycyrrhiza glabra* L.	Sweetener	Yes
Gossypol	Male contraceptive	*Gossypium* species	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
Hemsleyadin	Bacillary dysentery; antipyretic	*Hemsleya amabilis* Diels	Dysentery	Yes
Hesperidin	Capillary fragility	*Citrus* species	–	No
Hydrastine	Haemostatic; astringent	*Hydrastis canadensis* L.	Astringent	Yes
Hyoscyamine	Anticholinergic	*Hyoscyamus niger* L.	Sedative	Yes
Kainic acid	Ascaricide	*Digenea simplex* (Wulf.) Agardh	Anthelmintic	Yes
Kawain[b]	Tranquillizer	*Piper methysticum* Forst. f.	Euphoriant	Yes
Khellin	Bronchodilator	*Ammi visnaga* (L.) Lamk.	Asthma	Yes
Lanatosides A, B, C	Cardiotonic	*Digitalis lanata* Ehrh.	–	Indirect
α-Lobeline	Smoking deterrant; respiratory stimulant	*Lobelia inflata* L.	Expectorant	Yes
Menthol[b]	Rubefacient	*Mentha* species	Carminative	No
Methyl salicylate[b]	Rubefacient	*Gaultheria procumbens* L.	Carminative	No
Monocrotaline	Antitumour agent (topical)	*Crotalaria sessiliflora* L.	Skin cancer	Yes
Morphine	Analgesic	*Papaver somniferum* L.	Analgesic; sedative	Yes
Neoandrographolide	Bacillary dysentery	*Andrographis paniculata* Nees	Dysentery	Yes
Nicotine	Insecticide	*Nicotiana tabacum* L.	Narcotic	No.
Nordihydroguaiaretic acid	Antioxidant (lard)	*Larrea divaricata* Cav.	Antitussive	No
Noscapine (narcotine)	Antitussive	*Papaver somniferum* L.	Analgesic; sedative	Yes
Ouabain	Cardiotonic	*Strophanthus gratus* Baill.	Arrow poison	Indirect
Pachycarpine ((+)-sparteine)	Oxytocic	*Sophora pachycarpa* Schrenk ex C.A. Meyer	–	No
Palmatine (fibraurine)	Antipyretic; detoxicant	*Coptis japonica* Makino	–	No
Papain	Proteolytic; mucolytic	*Carica papaya* L.	Digestant	Yes
Papaverine[b]	Smooth muscle relaxant	*Papaver somniferum* L.	Sedative; analgesic	No
Phyllodulcin	Sweetener	*Hydrangea macrophylla* (Thunb.) Seringe var. *thunbergii* (Siebold) Makino	Sweetener	Yes
Physostigmine (eserine)	Cholinesterase inhibitor	*Physostigma venenosum* Balf.	Ordeal poison	Indirect
Picrotoxin	Analeptic	*Anamirta cocculus* (L.) W. & A.	Fish poison	Indirect
Pilocarpine	Parasympathomimetic	*Pilocarpus jaborandi* Holmes	Poison	Indirect
Pinitol[b]	Expectorant	Several plants	–	No
Podophyllotoxin	Condylomata acuminata	*Podophyllum peltatum* L.	Cancer	Yes
Protoveratrines A & B	Antihypertensives	*Veratrum album* 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	*Ephedra sinica* Stapf.	Chronic bronchitis	Yes
Pseudoephedrine, nor-	Sympathomimetic	*Ephedra sinica* Stapf.	Chronic bronchitis	Yes
Quinidine	Antiarrhythmic	*Cinchona ledgeriana* Moens ex. Trimen	Malaria	No
Quinine	Antimalarial; antipyretic	*Cinchona ledgeriana* Moens ex. Trimen	Malaria	Yes
Quisqualic acid	Anthelmintic	*Quisqualis indica* L.	Anthelmintic	Yes
Rescinnamine	Antihypertensive; tranquillizer	*Rauvolfia serpentina* (L.) Benth. ex Kurz	Tranquillizer	Yes
Reserpine	Antihypertensive; tranquillizer	*Rauvolfia serpentina* (L.) Benth. ex Kurz	Tranquillizer	Yes
Rhomitoxin	Antihypertensive; tranquillizer	*Rhododendron molle* G. Don	Contraindicated in low blood pressure	Yes
Rorifone	Antitussive	*Rorippa indica* (L.) Hochr.	Chronic bronchitis	Yes
Rotenone	Piscicide	*Lonchocarpus nicou* (Aubl.) DC.	Fish poison	Yes
Rotundine ((+)-tetrahydropalmatine)	Analgesic; sedative; tranquillizer	*Stephania sinica* Diels	Sedative	Yes
Rutin	Capillary fragility	*Citrus* species	–	No
Salicin	Analgesic	*Salix alba* L.	Analgesic	Yes
Sanguinarine	Dental plaque inhibitor	*Sanguinaria canadensis* L.	–	No
Santonin	Ascaricide	*Artemisia maritima* L.	Anthelmintic	Yes
Scillarin A	Cardiotonic	*Urginea maritima* (L.) Baker	Cardiotonic	Yes
Scopolamine	Sedative	*Datura metel* L.	Sedative	Yes
Sennosides A & B	Laxative	*Cassia acutifolia* Delile *C. angustifolia* Vahl	Laxative	Yes
Silymarin	Antihepatotoxic	*Silybum marianum* (L.) Gaertn.	Liver disorders	Yes
Sparteine	Oxytocic	*Cytisus scoparius* (L.) Link	–	No
Stevioside	Sweetener	*Stevia rebaudiana* Bertoni	Sweetener	Yes
Strychnine	CNS stimulant	*Strychnos nux-vomica* L.	Toxic stimulant	Yes
Teniposide[c]	Antitumour agent	*Podophyllum peltatum* L.	Cancer	Yes
Δ^9-Tetrahydrocannabinol	Antiemetic; decreases ocular tension	*Cannabis sativa* L.	Euphoriant	No
(±)-Tetrahydropalmatine	Analgesic; sedative; tranquillizer	*Corydalis ambigua* (Pallas) Cham. & Schltal.	Sedative	Yes
Tetrandrine	Antihypertensive	*Stephania tetrandra* S. Moore	–	No
Theobromine	Diuretic; vasodilator	*Theobroma cacao* L.	Diuretic	Yes
Theophylline	Diuretic; bronchodilator	*Camellia sinensis* (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)	*Thymus vulgaris* L.	–	No
Trichosanthin	Abortifacient	*Trichosanthes kirilowii* Maxim.	Abortifacient	Yes
Tubocurarine	Skeletal muscle relaxant	*Chondodendron tomentosum* R.&P.	Arrow poison	Yes
Valepotriates	Sedative	*Valeriana officinalis* L.	Sedative	Yes
Vasicine (peganine)	Oxytocic	*Adhatoda vasica* Nees	Expectorant	No
Vincamine	Cerebral stimulant	*Vinca minor* L.	Cardiovascular disorders	Yes
Vinblastine (vincaleukoblastine)	Antitumour agent	*Catharanthus roseus* (L.) G. Don	Diabetes mellitus	No
Vincristine (leurocristine)	Antitumour agent	*Catharanthus roseus* (L.) G. Don	Diabetes mellitus	No
Xanthotoxin (ammoidin; 8-methoxypsoralen)	Leukoderma; vitiligo	*Ammi majus* L.	Leukoderma; vitiligo	Yes
Yohimbine	Aphrodisiac	*Pausinystalia yohimba* (K. Schum.) Pierre ex Beille	Aphrodisiac	Yes
Yuanhuacine	Abortifacient	*Daphne genkwa* Sieb. & Zucc.	Abortifacient	Yes
Yuanhuadine	Abortifacient	*Daphne genkwa* Sieb. & Zucc.	Abortifacient	Yes

Annex 2

Therapeutic indications of plant-derived drugs

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

[a] Synthetic modification of a natural product.

Annex 2: *continued*

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

Annex 3

Plants used in traditional medicine and the drugs derived from them

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

[a] See Annex 1 for plant authority names.

Annex 3: *continued on next page*

Annex 3: *continued*

Plant	Drug
Datura metel	Scopolamine
Digenia simplex	Kainic acid
Digitalis lanata	Acetyldigoxin Deslanoside Digoxin Lanatosides A, B, C
Digitalis purpurea	Digitalin Digitoxin Gitalin
Ephedra sinica	Ephedrine Pseudoephedrine Pseudoephedrine, nor-
Erythroxylum coca	Cocaine
Fraxinus rhynchophylla	Aesculetin
Gaultheria procumbens	Methyl salicylate
Glaucium flavum	Glaucine
Glycyrrhiza glabra	Glycyrrhizin
Gossypium species	Gossypol
Hemsleya amabilis	Hemsleyadin
Hydrangea macrophylla var. *thunbergii*	Phyllodulcin
Hydrastis canadensis	Hydrastine
Hyoscyamus niger	Hyoscyamine
Larrea divaricata	Nordihydroguaiaretic acid
Lobelia inflata	α-Lobeline
Lonchocarpus nicou	Rotenone
Lycoris squamigera	Galanthamine
Mentha species	Menthol
Mucuna deeringiana	L-Dopa
Nicotiana tabacum	Nicotine
Ocotea glaziovii	Glaziovine
Papaver somniferum	Codeine Morphine Noscapine Papaverine
Pausinystalia yohimba	Yohimbine
Physostigma venenosum	Physostigmine
Pilocarpus jaborandi	Pilocarpine
Piper methysticum	Kawain
Podophyllum peltatum	Etoposide[b] Podophyllotoxin Teniposide[b]
Potentilla fragarioides	(+)-Catechin
Quisqualis indica	Quisqualic acid
Rauvolfia canescens	Deserpidine
Rauvolfia serpentina	Ajmalicine Rescinnamine Reserpine
Rhododendron molle	Rhomitoxin
Rorippa indica	Rorifone
Salix alba	Salicin
Sanguinaria canadensis	Sanguinarine
Silybum marianum	Silymarin
Simarouba glauca	Glaucarubin
Sophora pachycarpa	Pachycarpine
Stephania sinica	Rotundine
Stephania tetrandra	Tetrandrine
Stevia rebaudiana	Stevioside
Strophanthus gratus	Ouabain
Strychnos nux-vomica	Strychnine
Theobroma cacao	Theobromine
Thymus vulgaris	Thymol
Trichosanthes kirilowii	Trichosanthin
Urginea maritima	Scillarin A
Valeriana officinalis	Valepotriates
Veratrum album	Protoveratrines A & B
Vinca minor	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	*In vitro*	Enhancement of drug efficacy	*5*
Angiotensin-converting enzyme inhibition	*In vitro*	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	*In vitro*	Cardiotonic	*17-19*
Benzpyrene hydroxylase (AHH) inhibition	*In vitro*	Carcinogenesis inhibition	*20*
Cell transformation	Cell culture	Carcinogenicity detection	*21, 22*
Cytotoxicity	Cell culture	Anticancer	*9, 23*
Free radicals	*In vitro*; cell culture	Anticancer	*24, 25*
HMG-CoA reductase inhibition[a]	*In vitro*	Antihypercholesterolaemic, antiatherosclerotic	*26*
Human stem cell assay	Cell culture	Anticancer	*27, 28*
Insect antifeedant	*In vitro*	Prevent crop damage and insect-borne diseases	*29, 30*
Insecticide	*In vitro*	Prevent crop damage and insect-borne diseases	*31, 32*
Molluscicide	*In vitro*	Lower incidence of snail-borne diseases, i.e., schistosomiasis	*33*
Monoamine oxidase (MAO) inhibition	*In vitro*	Antihypertensive	*34*
Mutagenicity	Cell culture or bacterial culture	Carcinogenicity detection	*35-38*
Nucleic acid biosynthesis inhibition	*In vitro*; cell culture	Antibiotic	*39, 40*
Phosphodiesterase inhibition	*In vitro*	Anticancer	*41*
Piscicide activity	*In vitro*	Predictive for molluscicide effect	*11*
Platelet aggregation inhibition	*In vitro*	Cardiovascular problems	*42*
Prostaglandin synthetase inhibition	*In vitro*	Anti-inflammatory	*43, 44*
Protease inhibition	*In vitro*	Anticancer; plant protection	*45-47*
Protein biosynthesis inhibition	*In vitro*; cell culture	Antibiotic; anticancer	*48, 49*
Sister chromatid exchange	Cell culture	Carcinogenicity detection	*50*
Tyrosine hydroxylase inhibition	*In vitro*	Antihypertensive	*51*
Unscheduled DNA synthesis	Cell culture	Carcinogenicity detection	*52. 53*

[a] β-Hydroxy-β-methylglutaryl CoA reductase.