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GLOBAL PROGRAMME ON AIDS AND TRADITIONAL MEDICINE PROGRAMME

Report of a WHO Consultation on Traditional Medicine and AIDS: Clinical Evaluation of Traditional Medicines and Natural Products

Geneva, 26-28 September 1990

CONTENTS

1. INTRODUCTION

Human immunodeficiency virus (HIV) infection and the consequent acquired immunodeficiency syndrome (AIDS) pose an unprecedented challenge to health planners, clinicians, other health workers, scientists and the community at large. The World Health Organization (WHO) currently estimates that more than 8 million people are already infected with HIV and about 1 million adults have suffered or are suffering from AIDS.

Persons with AIDS are seeking many different treatments, some using plant products, with the hope of obtaining either a cure or relief of symptoms. There is scientific evidence, based on *in vitro* studies, that some medicinal plants do in fact have inhibitory effects on HIV. A consultation on *in vitro* screening of traditional medicines for anti-HIV activity, held in Geneva from 6 to 8 February 1989, offered promise that scientifically valid collaborative studies of traditional medicines, particularly medicinal plants, might lead to effective and affordable therapeutic agents.[1]

Against this background, the Global Programme on AIDS (GPA) Biomedical Research Unit, and the Traditional Medicine Programme (TRM) of the World Health Organization (WHO) convened a consultation in Geneva from 26 to 28 September 1990, with the objective of developing guidelines on the clinical evaluation of the safety and possible efficacy of traditional remedies in the treatment of persons with AIDS.

The consultation was attended by ten participants from eight countries (Annex 1). Opening the meeting, Dr Hu Ching-Li, Assistant Director-General of WHO, cited the growing menace posed by AIDS and emphasized the limitations of existing drug therapy. Traditional medicines, which are being used empirically in many countries for the treatment of AIDS, therefore need to be evaluated clinically to establish their safety and possible efficacy in the treatment of AIDS and AIDS-related diseases.

Dr O. Akerele, Programme Manager, TRM, outlined the activities of the programme with particular reference to the collaborative activities with GPA.

Dr J. Esparza, Acting Chief, Vaccine Development, GPA, welcomed the participants on behalf of GPA and provided information on the general goals and current activities of the programme.

2. BACKGROUND INFORMATION

2.1 Traditional medicine products used in HIV infection and disease

Several countries have traditional medicine products that are used in the treatment of HIV infection and to ameliorate symptoms and prolong the life of persons with AIDS.

In vitro anti-HIV activity has been reported for the following Chinese medicinal plants: *Glycyrrhiza uralensis, Hypericum perforatum, Viola yedoensis, Alternanthera philoxeroides, Andrographis paniculata, Arctium lappa, Lithospermum erythrorhizon, Coptis chinensis, Epimedium grandiflorum, Lonicera japonica* and *Prunella vulgaris*.

The protein trichosanthin (compound Q or GLQ 223), isolated from the Chinese herb *Trichosanthes kirilowii*, has been used not only in China as an abortifacient, but also to treat patients with AIDS in unofficial trials in the United States of America. Compound Q has also been approved for limited clinical trial by the United States Food and Drug Administration. It has been reported to interfere with the replication of HIV, and selectively to eliminate infected cells.

Kampo is a pharmacotherapeutic branch of Oriental medicine that originated in ancient China and is still being used today in Japan. Originally Kampo medicines consisted of a variety of crude drugs prepared in several hundred different combinations as decoctions, powders or pills. Today, however, the extracts of crude drugs are formulated under strict quality control using state-of-the-art technology. Kampo medicines play a large role in modern medical care in Japan and are expected to continue to do so in future.

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[1] **Bulletin of the World Health Organization**, **67**(6): 613-618 (1989).

One Kampo medicine, **Sho-saiko-to**, has been used to treat a number of different diseases, including viral hepatitis. It has been reported that **Sho-saiko-to** (which contains glycyrrhizin) has an immunoenhancing effect on the interleukin cascade. Thus, **Sho-saiko-to** might have potential for use in the treatment of some phases of HIV infection. This medicine also has anti-inflammatory activity and induces the production of lipocortin, a protein produced by the cell nucleus. This is only one example of a Kampo medicine with pharmacological activities that could be useful in the treatment of persons with AIDS.

2.2 Summary of immunological aspects and considerations

WHO has proposed that the following prognostic categories of the disease should be used in describing the course of HIV infection and disease: (1) asymptomatic/persistent generalized lymphadenopathy; (2) early (mild) disease; (3) intermediate (moderate) disease; and (4) late (severe) disease (AIDS) (see Annex 3). After becoming infected with human immunodeficiency virus type 1 (HIV-1), persons may remain asymptomatic for years before the onset of AIDS. During this asymptomatic phase there may be functional abnormalities of both T-cells and B-cells, even if lymphocyte numbers remain normal. At present, it is not clear whether the immune system abnormalities in either the asymptomatic phase or clinical AIDS are due solely to the direct effects of HIV-1 or whether they also reflect defects existing prior to infection in the host immunoregulatory mechanisms.

One characteristic feature of retrovirus infections is the ability of the virus to insert a DNA copy of its viral RNA genome into the genome of the host cell. During HIV infection, the integrated proviral genome may remain in an inactive state until appropriate activating signals stimulate viral expression. Because of the possibility of induction of HIV expression by T-cell activating factors, such as mitogens and antigens, it is recommended that in clinical trials with traditional medicines with a known immunomodulating effect, antivirals should also be given. On the other hand, the development of humoral and cell-mediated responses against HIV soon after acquisition of infection with HIV clearly demonstrates the ability of the immune system to counteract HIV-1 infection. Immunostimulators might, therefore, also be considered for clinical testing, either alone or together with a specific antiretroviral agent for the treatment of patients in stages of the disease with a small virus burden, e.g., in the asymptomatic phase.[1]

Drugs active against HIV enzymes (e.g., reverse transcriptase inhibitors) may also benefit patients with AIDS. However, screening for anti-HIV activity using single-cell immune cultures may be of only limited value, because the pathogenesis of AIDS involves several types of immune cells and complex relations among the cytokines of the immunological network.

Animal models will play a central role in AIDS research in the coming years. Important models include HIV-infected chimpanzees, immunodeficiency virus-infected simian monkeys, and ungulates and cats with HIV-related lentivirus infections. However, animal models may not exhibit all the features of human HIV infection.

2.3 Current drug-screening activities

Medicinal plants that have been used as anti-infective agents in the prevailing systems of traditional medicine in different geographical areas are being systematically collected in order to evaluate their anti-HIV potential. For this purpose a collaborative project has been established between the WHO Collaborating Centre for Traditional Medicine at the University of Illinois, Chicago, USA, and the WHO Collaborating Centre for AIDS at the National Bacteriological Laboratory in Stockholm, Sweden. The preparation of primary extracts is being coordinated by the Chicago group, and the extracts are then sent to the Stockholm facility for anti-HIV testing *in vitro*. The two centres have so far evaluated 36 extracts representing 18 plant species. Activity has been found in extracts from two species, which are of great interest because of their low toxicity.

The finding of two active species in 18 samples represents a high rate of success. If the initial project goal of collecting 200 samples by the end of 1990 is attained, a projected total of about 11-12 active plant

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[1] Report of a WHO informal consultation in preclinical and clinical aspects of the use of immunomodulators in HIV infection, Geneva, 3-5 April 1989, **AIDS**, **4**(12): WHO1-WHO14.

species can be expected to serve as candidates for bioassay-directed fractionation and eventual isolation of active principles. It is WHO's policy to ensure that the benefits from the development of drugs as a result of collaborative efforts such as this one are, as far as possible, made widely available on an equitable basis.

In addition, bimonthly and annual reports to WHO on anti-HIV active compounds of known structure and natural product extracts having anti-HIV and related activities (e.g., reverse transcriptase inhibition, other enzyme inhibitions, etc.) are provided through a computerized data base, NAPRALERT (Natural Products Alert), established by the WHO Collaborating Centre in Chicago.

The plant-derived chemicals of known structure listed in Table 1 are those reported to date to have anti-HIV activity.

Table 1. Phytochemicals that inhibit HIV *in vitro*[a]

Compound	Compound class
Arabinitol, L: 1,4-dideoxy-1,4-imino:	Carbohydrate
Castanospermine	Indolizidine
Castanospermine, 6-0-Butyryl:	Indolizidine
Colchicine	Alkaloid
Fucitol, L: N-(5-carboxylmethyl-l-pentyl)-1-5-amino:	Carbohydrate
Glycycoumarin	Coumarin
Glycyrrhizin	Triterpene
Glycyrrisoflavone	Flavonoid
Gossypol	Sesquiterpene
Gossypol, (+):	Sesquiterpene
Gossypol, (-):	Sesquiterpene
Hypericin	Quinoid
Hypericin, pseudo:	Quinoid
Licochalcone A	Flavonoid
Licoflavonol, Iso:	Flavonoid
Licopyranocoumarin	Coumarin
Nojirimycin, 1-deoxy:	Carbohydrate
Oenothein B	Tannin
Papaverine	Isoquinoline
Viola yedoensis polysaccharide	Polysaccharide
Prunellin	Polysaccharide
Punicalin	Tannin
Quinic acid, 1,3,4,5-tetra-O-galloyl:	Tannin
Quinic acid, 3,4,5-tri-O-galloyl:	Tannin
Quinic acid, 3,4-di-O-galloyl-5-O-galloyl:	Tannin
Quinic acid, 3,5-di-O-galloyl-4-O-galloyl:	Tannin
Quinic acid, 3-O-digalloyl-4,5-di-O-galloyl:	Tannin
Ricin A Chain	Peptide
Soybean saponin B-1	Triterpene
Soybean saponin B-2	Triterpene
Sulfapatrinoside I	Triterpene
Sulfapatrinoside II	Triterpene
Trichosanthin, alpha: (GLQ223)	Protein

[a] Excludes sulfated polysaccharides.

3. PRECLINICAL CONSIDERATIONS

The participants discussed a variety of issues related to the preclinical stages in the development of traditional medicines and other natural products for the treatment of AIDS. The major points are summarized below.

3.1 Botanical verification

The performance of a clinical trial under controlled conditions requires a constant supply of a product whose botanical identification and characterization can be verified. Lack of assurance of plant species identity is arguably the most serious deficiency of commercial herbal products. If there is no reliable chemical basis for determining identity, and botanical morphology is destroyed during formulation by such processes as powdering and extraction, only **independent botanical certification** can provide the necessary assurance.

A botanical certification scheme, organized along the lines of the WHO certification scheme for pharmaceutical products, would be an invaluable international stimulus towards botanical quality assurance. Each professional grower/supplier of medicinal plant material would be required to submit to the designated national botanical authority an appropriate sample of the plant, in a state of sufficient integrity to allow physical identification for confirmation of species identity. If appropriate, a certificate would then be issued indicating the currently accepted Latin binominal, and synonyms, with associated authority, and its usual common names, as well as the site and date of harvest of the crop. Professional growers could be registered with the national authority and samples for testing could be collected by trained inspectors or qualified botanists. Plant products with established pharmacological activity would be standardized on the basis of correlation of activity with levels of their known active constituent(s) or with appropriate chemical profiles. The products would also be checked for the presence of "characterizing substances", where applicable, for further confirmation of botanical origin. The part(s) of the plant used to make each preparation should be indicated, as well as detailed instructions for harvesting (e.g., stage of growth), storage and processing, prior to and following formulation.

3.2 Pharmacological activity

Before a new drug of known chemical structure is tested in a clinical trial, there must be adequate data from *in vivo* and/or *in vitro* studies to validate its claimed therapeutic efficacy. In the case of known herbal remedies, such evidence may be available from the current practices of traditional health practitioners or from reports in the literature.

Establishing a correlation of pharmacological activity with some component in the plant is an invaluable aid to assuring comparability between preparations of a medicinal plant product. In the case of HIV infection, a number of *in vitro* approaches are available for evaluating antiviral activity. The *in vitro* anti-HIV assay could also lead to a chemical assay for active constituent(s).

3.3 Safety

There are several aspects of safety that need to be considered for herbal products that are candidates for a clinical trial. The first requirement is to identify any potential toxicity by undertaking an extensive search of the literature and evaluating performance in preclinical toxicological tests. The range of preclinical tests available for the evaluation of a synthetic drug before beginning clinical trials is well known. What is not known, however, is whether such preclinical tests need to be so extensive for traditional medicines.

The use of traditional plant remedies over a long period of time may provide important information on the pharmacological effects in humans of a particular group of chemical compounds - information that is usually not available when testing begins on a new synthetic drug. Because herbal remedies have often been used for centuries, their preparation having been described in classical texts of traditional medicine, they cannot be considered "new drugs" in the same sense as new drug candidates from the pharmaceutical industry, which are usually pure and well characterized chemical entities, never before used in humans. Testing requirements formulated by regulatory authorities to ensure the safety of "new drugs" are therefore not necessarily applicable to traditional remedies. A more limited range of preclinical toxicological tests may be adequate for traditional remedies. Consideration must also be given to the cost of performing extensive

animal toxicological tests in developing countries, particularly where laboratory infrastructure is limited. Further, such tests require time that cannot be justified when no other treatment is available. Thus, limited animal testing of a herbal medicine may be justified by the remedy's previous use in human disease and the fatal character of AIDS.

Because of time-tested usage, national drug testing policies may permit some herbal remedies to be submitted directly to clinical evaluation without prior preclinical or toxicological tests. Other remedies may need at least some preclinical toxicological testing. The requirements for testing will be determined for each country, by its own authorities, in the context of its own regulations, and on the basis of pertinent scientific data on the herbal preparation and its history of use in humans.

When a traditional remedy results in promising activity, either in a bioassay or a human study, further investigation may yield a chemically defined active principle, which might then be considered a "new drug" that would have to be tested for safety and efficacy as prescribed by drug regulatory authorities. Such active agents, however, would probably be given special ("fast-track") consideration because of the urgent need for new drugs effective against AIDS.

A second safety consideration is the prompt recognition of any toxic events that may occur during the course of a clinical trial. It may be particularly difficult to recognize toxic events during a clinical trial in persons with AIDS because of the large number of organ systems usually involved in the disease state and the presence of secondary disease/opportunistic infections. Thus, adverse side effects may be masked by the normal progression of AIDS and related diseases and it may be difficult to determine whether a new drug actually accelerates the progress of the disease. It is also possible that the incidence and extent of drug toxicity may be increased in organ systems that are compromised by AIDS or AIDS-related diseases, a problem that even extensive testing in animals may fail to predict.

All patients with AIDS, and particularly those entering clinical trials, must be carefully screened for underlying diseases that may not yet have become clinically important. Such diseases are particularly important when they may compromise either liver or renal function and thus prevent adequate drug elimination. Overall health status must therefore be well characterized at the time that a patient is evaluated for entrance to a study.

Because there is always the possibility of an adverse drug reaction during the testing of a new drug, the study design must include a plan for managing patients who experience some manifestation of drug toxicity. Such problems may be exacerbated in AIDS patients because of their susceptibility to secondary infections, which may require treatment with additional drugs. Additional diseases and the drugs used to treat them increase the likelihood of adverse drug interactions as well as adverse reactions to the drugs themselves. The preclinical plan must address these possibilities.

4. CLINICAL CONSIDERATIONS

Every clinical trial must be conducted according to a protocol that is written and approved before the study starts. The most satisfactory protocols are those that are designed with the collaborative effort of a team of experts representing various disciplines. The trial protocol should include a justification for the trial, and should clearly define the question that the trial is designed to answer. The study population must also be clearly defined, indicating both inclusion and exclusion criteria and the procedures to be used for recruiting study participants and allocating them to various treatment protocols. Study patients should have confirmed HIV infection, either asymptomatic or early symptomatic; in most cases, children and pregnant or lactating women should be excluded. Patients may be recruited from voluntary testing centres and from clinics treating either AIDS or other sexually transmitted diseases. Appropriate informed consent must be obtained from each patient, and each patient should have the opportunity to receive appropriate counselling. The protocol should define appropriate clinical monitoring to detect toxicity as well as to determine efficacy and a plan to deal with drug toxicity should it occur.

An accurate record must be kept for each patient in the study, which should include documentation of informed consent, a medical history, details of treatment received and succinct reports of all physical examinations, follow-up evaluations and laboratory test results.

Efficacy should be judged on the basis of such defined end-points as specific clinical symptoms or signs, the development of particular opportunistic infections, or defined prognostic laboratory markers. Safety should be monitored on the basis of either symptoms or signs, particular attention being given to end-points that may signal forms of toxicity that might be anticipated. Laboratory indicators of liver, renal, cardiac and haematological toxicity should also be monitored.

Evaluation of the trial should be undertaken using appropriate statistics.

Ideally, the study design should be blind, randomized and placebo-controlled. A cross-over design may present problems in interpretation of study results, both because of uncertainty concerning the time course over which a drug may act and because a patient's status may change during the two phases of the study.

Every effort must be made to address the problems concerning preparation, quality control and dose standardization for herbal preparations, and to find a satisfactory placebo.

5. RECOMMENDATIONS

A place for traditional herbal remedies in the health care system will be established only if recommendations for their use are based on studies that make them credible and acceptable. Thus, studies with herbal medicines must satisfy the same criteria of efficacy and safety as do the drugs that are products of the modern pharmaceutical industry.

In this context, the consultation drew up a series of guidelines for clinical trials with traditional medicine products used in the treatment of AIDS and AIDS-related diseases, which are presented in Annex 2.

The consultation also made the following recommendations:

(1) This report should be given wide distribution so that the guidelines can be readily and immediately applied in countries where potential remedies may exist.

(2) The guidelines should be used as the basis for the development of clinical trials for the evaluation of traditional medicines and natural products.

(3) WHO should monitor the impact of the use of the guidelines at the country level to determine any needs for revision.

(4) A second consultation should be convened in two years' time to revise the guidelines on the basis of experience in their use.

(5) The WHO Traditional Medicine Programme, together with the WHO Global Programme on AIDS, should jointly identify appropriate institutions in developing countries where clinical evaluation of traditional medicines and natural products for AIDS could be carried out.

(6) Other consultations should be convened by the WHO Traditional Medicine Programme, in collaboration with appropriate WHO programmes, to adapt the guidelines for the clinical evaluation of traditional medicines for other primary disease states that are of concern in developing countries, such as malaria and other parasitic diseases.

ANNEX 1

LIST OF PARTICIPANTS

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