

Guidelines for the Assessment of the Efficacy of Phytomedicines in the Netherlands.

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The CTF, the Dutch Committee for the Assessment of Phytotherapeutics, is an independent foundation of civil law, founded by a joint initiative of the organisation of the pharmaceutical industries Nehoma and the Dutch Scientific Association for Phytotherapy. The assignment of the committee is to develop guidelines with a view to a future registration of Phytotherapeutics, to start the assessment of Phytotherapeutics and to support by education all who are involved in Herbal Medicines, professionals and Industrials, familiarise them with the fact that in the future, registration of Herbal Medicines is inevitable. The Dutch Ministry of Health enables the CTF to fulfil its task by financial support. Before we talk about the guidelines for assessing the efficacy of Phytotherapeutics, we have to discuss three major starting points.

1) Each Herbal Medicinal Product has to be considered as a single product.

Herbal medicinal products are only identical when:

- a) They are prepared from the same parts of the same plant species.
- b) The products are prepared following exactly the same procedures.
- c) The fingerprints of the products are identical.
- d) The standardisation of components is identical
- e) The way of administration and the prescribed dosage are identical.

Instead of a standardisation of a component by a chemical analysis, a bioassay may be used. When two products do not meet these requirements we have to consider them as two different herbal medicinal products. Each will have to prove its own efficacy.

2) The quality of the Herbal Medicinal Product has to be defined.

Because each herbal medicinal product has to be considered as a single product, any product has to be described exactly by the data of its quality including source, preparation procedures, standardisation and analytical data. It is important that all the studies have been done consistently with the same herbal medicinal product.

3) The Safety of the Herbal Medicinal Product

The Dutch Committee for Assessment of Phytotherapeutics holds that safety of herbal medicinal products prevails over efficacy. In general the Registration Committees will weigh the efficacy of a medicine versus the adverse effects of a medicine. As a general rule the Dutch Committee has stated that the use of herbal medicinal products with an incidence of Serious Adverse Effects (as defined by the CPMP) higher than 1: 2000 should be considered unsafe and should not be used.

The Assessment of the efficacy of Herbal Medicinal Products

For the assessment of Phytotherapeutics the Dutch Committee uses three categories A, B, and C. This classification is totally based on the strength of the evidence for the efficacy of the herbal medicinal product and corresponds with the definitions of the types of evidence and the grading of recommendation set out in the following table originating from the US Agency for Health Care Policy and Research (AHCPR) and WHO.

Table 1: Grading and definition of types of evidence.(1)

Grade	Definition of type of evidence
A , (Evidence levels 1 a and 1b) .	Requires at least one randomised-controlled trial as part of the body of literature of overall good and consistency addressing the specific recommendation.
B , (Evidence levels II a, II b, III .	Requires availability of well-conducted clinical studies, but no randomised clinical trials on the topic of recommendation.
C , (Evidence level IV)	Requires evidence from expert's committee reports or opinions and / or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

I will give you more details about the categories

Category C, corresponds with Grade C, corresponds with traditional use

A herbal medicinal product is assigned to Category C when no studies of good quality are available, but there is evidence available that this product has been used for a long time for the specific recommendation. These data from the literature must have been published in reliable, authoritative sources. The product under assessment should be identical with the products described in the literature as stated before as one of the starting points. That means that plant material, preparation procedure and dosage, as far they are set out, should be identical. We are aware that this requirement may give rise to problems due

to the fact that in older literature the herbal medicinal product seldom is described in a proper way.

Because no clinical studies are available, there is no proof for efficacy and it is possible that future clinical studies will show that the product is ineffective. In the patient-leaflet a disclaimer that the efficacy is not proven should be included.

Examples of herbal medicinal products in Category C are Hops, Lavender and Passionflower for insomnia and restlessness; Caraway, Fennel and Anise for gastric-intestinal complaints.

Category B, corresponds with evidence level Grade B, corresponds with plausible efficacy.

A herbal medicinal product is assigned to Category B when the efficacy of the product is made plausible by one hypothesis generating study and at least one hypothesis confirming study for the specific recommendation. The hypothesis confirming study usually will be a clinical study which meets the requirements of the evidence level Grade B. That means a randomised double blind study is not required.

For Category B there is just as for Category C no sufficient proof of efficacy and it is still possible that future clinical studies will show that the product is ineffective. Therefore the Dutch Committee for the Assessment of Phytotherapeutics, on the basis of the studies that are available speaks of plausible efficacy.

As an example: the herbal medicinal product prepared from the roots of *Echinacea purpurea* (Coneflower). This product contains polysaccharides which have been shown to have a stimulating influence on the activity of the macrophages in vitro. This may be considered as a hypothesis generating study. A limited clinical study evidence grade level B is then sufficient for an assignment to Category B.

Further examples of herbal medicines that may be assigned to Category B are: Valerian as a sedative, Garlic for the prevention of arteriosclerosis, Ginger roots for nausea, Arnica as a local application for

contusion and Coneflower (Echinacea) for influenza and flue.

Category A, corresponds with evidence level Grade A, corresponds with proven efficacy.

A herbal medicinal product is assigned to Category A when the efficacy of the product is proven by one hypothesis generating study and at least one hypothesis confirming study for the specific recommendation. The hypothesis confirming study usually will be a clinical study that meets the requirements of the level of evidence Grade A. That means that the study will be controlled, randomised and double blind.

Examples of the Category A are herbal medicinal products prepared from Ginkgo biloba for peripheral circulatory problems and cognitive dysfunction, St Johns Wort (Hypericum perforatum) for mild and moderate depression, Hawthorn (Crataegus species) for coronary insufficiency, Kawa Kawa for anxiety, Sabal for benign prostate hypertrophy and Chestnut for peripheral venous insufficiency.

More about the concept of hypothesis generating and hypothesis confirming studies.

The Dutch Committee for the Assessment of Phytotherapeutics has elaborated the requirements for the evidence levels grade A and grade B more explicitly than the W.H.O. and the US agency for Health Care Policy and Research have done. The CTF requires a hypothesis generating study as well as a hypothesis confirming study, arguing from the principle that a statistic significant effect may only be accepted as a definitely established fact when there is also a plausible causality for this effect or when this effect is confirmed in a second independent study.

As hypothesis generating data for Category A and Category B the Committee will accept:

- Well-documented literature surveys.
- In vitro and in vivo studies of pharmacodynamic effects published in an acknowledged scientific

journal.

- Description of efficacy in generally accepted authoritative sources.
- A clinical study.

The herbal medicinal products used in these sources need not to be completely identical with the product under assessment.

In case there are no literature data available, for example for a new medicinal product from a herb with no traditional use, we need a hypothesis generating study. That means an in vitro or in vivo study of their pharmacodynamic effect. The hypothesis confirming study usually will be a clinical study with the herbal medicinal product under assessment addressing the specific recommendation. For an assignment to Category A two independent clinical studies with a grade of evidence A are also acceptable.

As we stated already in the beginning of this presentation each herbal medicinal product has to be considered as a single product. If it can be proved that the herbal medicinal product under assessment is identical with an other herbal medicinal product that has been assigned to Category A or B, these data may be considered as hypothesis confirming. Analytical methods or a proper bioassay are essential for proving this “phyto-equivalence”.

Conclusion

In the guidelines of the Dutch Committee for the Assessment of Phytotherapeutics, the classification of herbal medicinal products is totally based on the strength of evidence for the efficacy of the product. Due to this classification the prescriber and the user of herbal medicinal products will get honest and clear information about the expected therapeutic effect. It will require the utmost exertion and large investments from the authorities as well as from the producers of herbal medicinal products to realise this classification. But first they need to show their good will. Where there is a will, there is a way!

Literature:

1) Draft points to consider on the evidence of safety

and efficacy required for well-established herbal medicinal products in bibliographic applications (EMA/HMWPG/23/99). London.