

DEVELOPMENT OF NEW DRUGS FROM PLANT ORIGIN

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Abstract

The scope of this paper is to trace some considerations about possible trends on the development of new drugs from plant origin. Some examples used come from results of research work done in the Laboratory of Galenical Development.

1. Introduction

Phytopharmaceutical drugs, also called, herbal preparations, phytomedicinal remedies and phytotherapics, represent a rich area of products and a rational and true alternative of therapeutical agents. Recent information shows a promising market for such drugs. Only as an example, can be mentioned the participation of phytopharmaceutical drugs in the Brazilian market, which reaches about nine billion dollar including all produced drugs. One of every four drugs registered in Brazil contains at least one component from plant origin.

The New World trend considers as Phytopharmaceutical drug, those products, which contain, as active ingredients, exclusively, material from plant origin. Another tendency is the production of products with only one plant - monodrugs preparation - instead of the combination of many plant drugs which quality can be easier evaluated by current laboratory methodologies.

Products containing therapeutically active materials from other origins as from synthetic, animal or mineral would not be recognized as Phytopharmaceutical Drug. Isolated substances from plant origin, called Phytopharmacon or Phytopharmaca, would not be recognized as a Phytopharmaceutical Drug.

Although it is sometimes difficult for many Pharmacologists to accept a plant drug, which is a complex mixture of substance, as a single drug, we know very well, that the final effect is the resultant of this complexity.

We also have some difficulty to understand the role of some substances, which, despite of their lack of pharmacological effect, are co-responsible for the activity of some plants. I remember a paper appeared in Germany at the end of the sixties, describing the action of *Crataegus oxyacantha* products. The total extract was the only, which showed efficacy. Purified extracts failed totally.

Of course plants and medicinal plants represent a rich source of therapeutically active substances and also of pharmaceutical excipients. The world sees nowadays a lot of research trying to find new chemical entities from plants. The reason for such tendency is very easy to understand. The organic synthesis failed in this field. The investment done for the discovery of a new molecule is higher everyday. Synthesis turns no more profitable.

Active substances from plant origin make a long list. To enumerate all of them it will be tedious. Only as some examples of active substances from plant origin, acevaltrate from

the roots of *Valeriana officinalis*, can be mentioned. Together with other valepotriates, are the responsible for the light sedative effect of the preparations of such plant.

Yohimbine, an indole alkaloid from the cortex of the African *Pausynistalia yohimbe*, acts as sympatholytic, vasodilatant and hypotensive. The indication as aphrodisiac is not rational, due to the central toxic effect of such substance.

Solasodine, a steroidal alkaloid from the Solanaceae, although lacking a therapeutical indication is used for the synthesis of steroidal hormones. Many other substances have found similar application.

The production of substances from the secondary metabolism of plants through cell and tissue cultures and the chemical modification of the original molecule are fields with promising results.

Of course medicinal plants and products derived thereof are actually indicated and sold for many diseases and other physiological disorders. Some of them present ambitious indications, they pretend to heal pathological conditions, they are not able to do. We can everyday find in the newspaper announcements about AIDS cure, recuperation of virginity and so on, by products based on plants.

Some perspectives of the use of medicinal plants, however, find support on new research results, as we can read in current scientific publications. One of the uses studied refers to the improvement of the body's ability to answer correctly against immunological signals. Immunomodulation means helping the organism to promote an adequate immunological response. This can be done through suppression of the immunological response or through the stimulation of the immunological response. Some plants present such unspecific (non-specific) immunomodulation. Responsible for this effect could be polysugars like, for example, heteroglucans. Prof. Dr. Wagner from Munich worked on such subject, on a plant from our Region, *Achyrocline satureioides*. Results obtained in our laboratory confirmed the immunomodulatory effect of aqueous preparations from the floral summits of this Compositae/Asteraceae. Of course a lot of work has to be done, in order to improve this activity for future purpose. This is pointed out by recent results of the discussion about the use of *Echinacea*.

In this area we have also to remember the possibility of using Lectines, as for example those found in *Viscum album*. Although known since the end of the last century, few results have been found in order to introduce such substances as a valid drug.

The utilization of medicinal plants as behavior adapters is known just for a long time. The use of plant beverages in some Indians ceremonies and the toxic drug scene in our days demonstrate the potentiality and the danger of such indication. The lack of a synthetic substance with adequate safety in the actual therapy for minor behavior disorders or discomfort encouraged the search of alternative products, mainly from plant origin. As examples we have *Passiflora* and *Hypericum*. Both plants present however paraeffects, which can reduce their therapeutical application. Another problem noted for *Passiflora* is the establishment of the differences between the pharmacological value of each species and the determination of the real active substances (today flavonoids). New plants, some of them from the Amazon Rainforest, stay under research for such application area, as for example the "hayuasca" or "ahyahuasca" [*Banisteriopsis caapi*], which contains harmane alkaloids.

The improvement of greater resistance against stress and adverse physiological conditions conducted to the search of new products called adaptogens. Some examples are *Panax*, the Brazilian *Pfaffia* and *Eleutherococcus*.

Population all over the world is getting older. In other words, the development of products related to elderly, improving a better quality of life, have to be seriously considered.

The better knowledge of the efficacy and toxicity will lead to new applications of medicinal plants and products derived thereof.

Of course, not only new indications will result from deeper studies on old products and new plants. Technological modifications will also lead to products with improved efficacy, such as those caused by managing the bioavailability. In this area I will like to show some results from the work we have done in our Laboratory in Porto Alegre, south Brazil.

A possible way to improve the aqueous solubility of poor soluble substances with therapeutic activity is their inclusion in cyclodextrins. Flavonoid aglycones, such as quercetin, are an example of such substances. The addition of cyclodextrins increases dramatically the dissolved quantity of quercetin in water. Quercetin is presented in a wide number of medicinal plants.

The higher aqueous solubility of the complexed quercetin improves its bioavailability. As consequence a better bioavailability can be expected for such product.

Technological transformations can also affect the pharmaceutical activity of products derived from medicinal plants, improving at the same time pharmaceutical characteristics, as for example was demonstrated to the dried extracts of *Achyrocline satureioides*, a plant widely used in southern South America. The drying procedure not only maintained the same pharmacological effect, but also improved a better stability of the marker substances.

Another example denotes the effect of technological process and of the adjuvant addition on the stomach ulcers protective action of dried products from *Maytenus ilicifolia* (Celastraceae). Spray-dried or lyophilized products showed an intense activity. For the spray-dried products the concentration of drying excipients influenced the pharmacological effect.

Spray drying is a technique able to modify or to manage solid particle characteristics, which are directly involved in the dissolution process, such as particle size and distribution, so as particle shape, surface and structure. Not only the concentration of solids in the feed solution, but also the concentration and type of the added excipients can affect such attributes. Hollow particles with rough surfaces will promote differentiated bioavailability behavior.

Technological procedures can also influence the quality of the drug and of the products derived thereof. Drying of maté leaves conducted to different content of xanthine in dependence of the drying conditions. The solvent medium choice can lead to distinct activities for the same plant material.

New products with higher aggregate value do not only represent a greater benefit for the pharmaceutical industry, but also for the population, which needs drugs with improved quality, efficacy and safety, and leases the acceptance of phytopharmaceutical drugs. The positive consequences are easy to understand: wider and greater interest on medicinal plants.

Our Laboratory at the School of Pharmacy at the Federal University Rio Grande do Sul, southern Brazil is dedicated since 1984 to study the technological development of products derived from medicinal plants. Today the group is based on five Ph.D. searchers, two of them formed at German universities and three at French universities. I will like to express my gratitude to my M.Sc.-students that did the hard lab work.

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3. References

- Ammon H.P.T. and Kaul R., 1994. Crataegus. Teil 2: Wirkungen auf das Herz. Dtsch. Apoth. Ztg., 134 (27): 2521-2535.
- Campos A. M., 1996. Desenvolvimento de extratos secos nebulizados de *Ilex paraguariensis* St. Hil. Aquifoliaceae (erva-mate). Porto Alegre: Curso de Pós-graduação em Ciências Farmacêuticas, UFRGS. M.Sc.-Dissertation.
- Carvalho E.L.S., 1997. Desenvolvimento do produto seco nebulizado de *Maytenus ilicifolia* Martius ex. Reiss. - Celastraceae (espinheira-santa). Porto Alegre : Curso de Pós-Graduação em Ciências Farmacêuticas da UFRGS. M.Sc.-Dissertation.
- De Souza K.C.B., 1997. Desenvolvimento de metodologias analíticas e tecnológicas na obtenção de extratos secos nebulizados de *Passiflora edulis* variedade *flavicarpa*. Porto Alegre: Curso de Pós-Graduação em Ciências Farmacêuticas da UFRGS. M.Sc.-Dissertation.
- Carvalho E.L.S., Martins A.G., Bassani V.L., Gonzáles Ortega G., Petrovick P.R., Guterres S.S., 1997. Anti Ulcer Activity of Dried Extracts from *Maytenus ilicifolia* in Rats. In: WOCMAP, 2, Mendoza, *Abstracts*, Mendoza, p. P-339.
- Santos A.L.G., 1996. Estudo tecnológico e biológico de soluções extrativas aquosas de *Achyrocline satureioides* (Lam.) DC., Asteraceae. Porto Alegre: Curso de Pós-Graduação em Ciências Farmacêuticas da UFRGS. M.Sc.-Dissertation.
- Soares L.A.L., 1997. Padronização do extrato aquoso e desenvolvimento do produto seco por aspersão de *Phyllanthus niruri* L. - Euphorbiaceae (Quebra-Pedra). Porto Alegre: Curso de Pós-Graduação em Ciências Farmacêuticas da UFRGS. M.Sc.-Dissertation.
- Teixeira H., 1995. Avaliação da influência de adjuvantes farmacêuticos sobre as características físicas, químicas, tecnológicas e farmacológicas de extratos secos nebulizados de *Achyrocline satureioides* (Lam.) DC. Compositae - marcela. Porto Alegre: Curso de Pós-Graduação em Ciências Farmacêuticas da UFRGS. M.Sc.-Dissertation.
- Vinadé E.R.C., 1995. Características de solubilidade e de passagem de quercetina através de membranas poliméricas. Porto Alegre: Curso de Pós-Graduação em Ciências Farmacêuticas da UFRGS. M.Sc.-Dissertation.