HYPERICUM PERFORATUM L. IN MODERN PHYTOTHERAPY

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Hypericum perforatum L. is a known medicinal herb having choleretic, cholagogue, healing antimicrobial, antiviral, antimycotic and antidepresive actions.

The plant is recommended in modern medicine especially for its antidepresive effect and it is intensively studied for its antiviral effect, demonstrated especially on some retroviruses, inclusively HIV-1. Scientist opinion has recently changed in favour of phytomedicines especially in developed countries where active population manifested a significant increase in the psychotic mood because of psychic, physical and intellectual stress. Extracts of *Hyperici herba*, especially standardized in hypericin or hyperforin are used in the treatment of depression. The first tests concerning the clinical application on the extract of *Hyperici herba* were realized between 1979-1989, but unfortunately most of the patients received compound medicines preparations (*Hypericum perforatum* L. and *Valeriana officinalis* L.), the efficiency of this extract being proved much more later.

Clinical studies were realized in other to analyse if the extracts of *Hypericum* would be more efficient than the placebo ones, if they would be as efficient as standard, antidepresive ones, if they would have less secondary side effects than standard antidepresive medicines, if they would be more efficient in minor to medium or severe depression.

The effects of the treatment that was realized by Harrer and Somer, 1993, in double studies, placebo controlled on 105 patients who suffered of depression and who have been treated for four weeks with 900mg of standardized extract have been assessed taking into consideration Hamilton Scale of Depression after two and four weeks respectively, the values resulted in the active group were between 15.81-9.64 or 7.17 and in the placebo group were between 15.83-12.28 or 11.30.

Hubner et all, 1993 obtained similar results after double studies that were placebo controlled with extract of *Hypericum perforatum* LI 160, 900mg/day for four weeks, the parameters followed being Hamilton Depression Scale (HAMD), Global Clinical Impressions (GCI), the symptoms of neuro-vegetative system.

The treatment with *Hypericum perforatum* extract brings an important improvement in the cognitive performances (Lehrl et al, 1993).

The extract of *Hypericum* had no efficiency on patients diagnosed with severe depression in a study developed in eleven academical centres from USA (Shelton et al, 2001).

St. John’s wort a herbal antidepresive remedy should also be analysed from the point of view of its possibility to cause emotional changes.

There was the risk that *Hypericum* should induce hypomania taking into consideration the fact that most of the patients were given this remedy without any formal psychitriatic assessments (Nieremberg et al, 1999).

There are also necessary through studies to compare the extracts of *Hypericum* with standard antidepresive with well defined groups of patients on longer periods of time (Lindek et all, 2000).

One obtained a decrease of Hamilton score (from 20,2 to 8,8 at *Hypericum* and from 19,4 to 10,7 to Imipramin), in a double study on patients suffering of depression, treated for six weeks with 900mg of *Hypericum* extract or with 75 mg of Imipramine (Vorbach et al, 1991).

The efficiency of *Hypericum* extract is comparable to that of Maproline, both treatments also improving cognitive functions (Harrer et al, 1993; Johnson et al, 1993).

The treatment with *Hypericum* extract has determined a significant development in the depressive symptoms (anxiety, self disbelief, diminish activity) in minor to moderate depressive discordance and which have been comparable to that of Amitriptiline or a Desipramin (Harald et al, 1996).

Extensive clinical studies proved that one of five patients has resisted to the effect of antidepresive of synthesis and 50% of those suffering of depression were compatible to a placebo treatment.

Some depressive patients manifested the tendency of a not taking the medicines constantly or not dosing them and some others had side effects because of cyclical, antidepresive (sleeplessness, gastro-intestinal haemorrhages, cardiotoxicity).

In Germany, for example, 25% of antidepresive prescriptions have been let towards phytomedicines, patients expressed their desire to use an alternating treatment to which they manifested no pharmacodependence and which could be interrupted without difficulties.

One of the reasons for which people chose to use St. John’s wort as their own medication in minor depression instead of seeing a doctor was represented by safety, trust in herb remedies and access, most of the patients considered unimportant to communicated primary medicine doctor that they used St. John’s wort (Wagner et all., 1999).

Standard preparations of *Hypericum perforatum* influence different neurotransmithing systems which a implied in depression by many processes of action: MAO inhibition (monoaminoxydaze) and COMT (catecol -O-methyltransferaze), the induction of free 6-interleukin from monocytes, the reduction of alpha frequency and the increase of theta and betha ones of sleep, influencing the metabolism of serotonin-melatonin.

The most quoted mechanism of action has been MAO inhibition an/or COMT, the enzymes responsible in the catabolism of biological amines.

The pharmacological models used frequently to demonstrate possible antidepresive activity are the examination of the behaviour of a mouse in a new environment and the measurement of one metabolite of biological amines.

A standardized extract of hypericine given to mice as determined an increase in the action of their exploring in a new environment and measurement of some metabolite of biological amines.

The dosage of a standard hypericine extract in a clinical lest on women who suffered of depression has determined a significant increase in the urine of 3-metoxy-4-hidroxyphenylglicol, the main metabolite of noradrenaline (Muldner an Zoller, 1984).

Some authors considered a MAO inhibitory element as being hypericine (Suzuki et al 1984) and the others confirmed MAO antagonism as being a possible process of action but a probable result of flavones and xanthones (Demish et al 1989; Sparenberg et al 1993).

The antidepresive effect of the species of *Hypericum perforatum* is not due to the inhibition including the serotonin in the area of synapsis as it happens with new synthetic antidepresive medicines (Buturovic et al, 2004).

Nowadays it is considered that the substance that is the most antidepresive one of the phytocomplex of *Hypericum* extracts is hyperforin.

The medicine's antidepresive action that conditioned standard extracts of *Hypericum* belonging to the phytocomplex but its intensity depended on the content of hyperforin, hypericin, pseudohypeericin, procyamidin B_2 rutozid 2,3,6,7 – trihydroxixanthone.

This toxic action of hypericin was noticed for the first time in one of Cirillo's study, in 1787. That is why the plant has been considered dangerous in Australia and it is listed in Common Poisonous Plants and Mushrooms of North America by Turner and Szczawinski.

When they ingest a large amount of plant, the herbivorous especially cows, sheep, goats, horses and also rabbits, rats may present psychomotor anxiety or some pigmentations like those caused by burns and in some serious cases haemolysis, epileptic crises even death.

There have been skin ulcerations, fatigue to mice treated hypodermically with hypericin and exposed to electric light. This phenomenon was not recorded to human beings, in the doses recommended for depression even of there was a possibility from a theoretical point of view.

Side phytotoxic effects were few and they never induced death in AIDS researches which implied 30 to 35 higher intravenous doses, higher than those recommended in case of depression.

A study on human kerotinocytes cells cultures demonstrates that usual therapeutic doses of *hypericum* extract have been 20 to 30 times under phytotoxicity level (Siegers et al, 1993).

Some authors warn the persons who are white-skin of the fact that when they use *hypericum* extract they shall not wish themselves by exposing to sun UV rays during the therapy and they shall not also use tetracyclines and chlorpromazine at the same time.

In a study referring to the assessment of *hypericum* extract's advantages and disadvantages, Woelch et al, 1999, recorded side effects to 2.4% of patients (gastro-intestinal inflammations; 0.6% allergical reactions; 0.4% psychic fatigue 0.3%) effects that disappeared after the and of treatment.

When referring to hypericin's secondary effects Jenike MD, the publisher of the Journal of Geriatric Psychiatry and Neurology recommended as suitable the choice of *Hypericum perforatum* in the treatment of minor and medium depression to the aged.

If we dowel on daily illness of 12 million of American people, 1.2 million of Canadians who are suffering of depression and to people who are not given any treatment for depression, the advantages will over weight possible rich of using *Hypericum*.

There were found interactions of *Hypericum* with digoxina *Hypericum perforatm* extract inducing some izoenzymes of cytochrom P450, in the last few years.

The some thing is still available even for theophilin, anticoagulants, oral contraceptives, cyclosporina, indinavir which are metabolized with P450 cytochrom. It has been proved *in vitro* that hypericin has mutagenic and cancerigenic effects but they were not confirmed *in vivo*. It is recommended that *hypericum* extract shall not be give to pregnant women (it manifested an uterotonicã activity during animal experiments) and to women who are nursing (it inhibits the prolactin hormone secretion).

The medicines based on *hypericum* extract are not connected with other MAO antidepresive because they patent their actions.

Hypericum perforatum's antidepresive activity has been assessed by clinical tests. The main condition of this efficient antidepresive treatment was that the preparation should contain standard vegetal extracts.

LI-160 purified extract of the species, standardized in hypericin and the special one WS 5572 purified and standardized in hyperforin are obtained by the extraction of vegetal material, by processing the resulted fluid extracts, by concentrating extract extra/ballast substances.

The extracts standardized in hypericin are compounds of some antidepresive remedies: Hyperforat, Jarsin, Psychotonin and Life 600 contain standardized extracts in hypericin flavones and hyperforin.

The suitable dose, based on the most part of medical clinic studies is of 300mg, 3 times a day (almost 0.2-1mg hypericin) and 4g of vegetal material (to grown-up, people little children, shall be given 900mg/day, children-600mg/day and teenagers shall be given a full dose).

Studies demonstrated that effect was gradual than that of the antidepresive prescribed. Antidepresive action manifested in 8 to 10 days from the beginning of treatment and lasted 4 to 6 weeks maximum, *Hypericum* should be given for 6-18 months as in the case of other antidepresive.

Hawing as a starting point the fact that *Hypericum perforatum* L. is used in traditional medicine, in healing wounds, burns, some studies have demonstrated that John's wort extracts have an antibacterial action.

Two Russian *Hypericum perforatum* preparations, for example, worldwide prescribed novoimanina and imanina have been tested in infections with *Staphylococcus aureus in vivo* and *in vitro* and they proved to be more efficient than sulphonilamida.

The main antibiotic element of novoimanina has been hyperforin. When studying antimicrobial activity of three species of *Hypericum* that originated in Turkey (*H. calycinum*, *H. avicularifolium* and *H. triquetrifolium*), Sakar, 1990, noticed that the extracts of three species had an active action on *Staphylococcus aureus* and *Mycobacterium smegmatis*.

Hypericum perforatum proved to have an antimicrobial efficiency in a study about *in vitro* testing the extracts of seven species of *Hypericum* belonging to Mediteranean flora on a colony of bacteria taken from human skin (Michel et al, 2002).

On acknowledging the recommendation of Dioscorides, the famous Ancient Greek botanist, the value of *hypericum* extract in the treatment of premenstrual syndrome (the improvement of depressive mood, of anxiety, of social interaction has been an encouraging one (Stevinson and Ernst, 2000).

Nowadays the antiviral activity of the substances of *Hypericum perforatum* L. extract has been intensively studied.

Lavie et al 1986 were the first who demonstrated that hypericine and pseudohypericine were efficient antiviral agents in vesicular stomatites, flu virus and simple type I and II, herpes virus.

The some authors recorded the activity of 2 compounds against infections with *in vivo* retrovirus.

Some other experimental data assessed the fact that hypericin and pseudohypericin inhibited retroviral infections by unconventional mechanisms. Now it is studies the application of these compounds in AIDS disease.

Hypericin proved to have antitumoural properties, inhibiting *in vitro* the disimination of tumoural cells from brain, longs and skin.

By monitoring hypericin cytotoxic effects on *in vivo* experimental models, using Biosenzal, a standardized phytopharmaceutic preparation on 8mg% of hypericin as assessed (its role of being a modulator of cells dissemination) (Sobotovic et al, 2002).

Conladis, 2004, tested methanolic extracts of *Hypericum perforatum* samples apatherd from different regions of Greek on cultures of human hepatic cells and on human carcinomas in order to determine cytotoxic activity.

Antioxidant properties of these extracts are to be assessed.

We can say that today the plant has its important role in modern phytopharmacy *Hypericum perforatum* being consideration as a medicinal herb, and nowadays it is use especially as an antidepresive element and it's an extensive study for its antiviral and antitumorale effect.

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