

\*\*\*

**L-5-HYDROXYTRYPTOPHAN**  
**GRIFFONIA SEED EXTRACT**

\*\*\*

# LINNEAssure™ Extracts

For the assurance of quality

## L-5-Hydroxytryptophan (Griffonia Seed Extract):

Linnea L-5-Hydroxytryptophan (5-HTP) is a natural extract from the seeds of the Griffonia simplicifolia tree found principally in the West African countries of Ghana, Ivory Coast and Togo. Traditional African uses for the plant include the use of the stem and roots as chewing sticks, leaves to aid in the healing of wounds whilst the leaf juice is used as an enema and for the treatment of kidney ailments. A decoction of the stems and leaves is also used to stop vomiting, to treat congestion of the pelvis and as an aphrodisiac. The bark-pulp is applied as a plaster to soft chancres <sup>(1)</sup>.

From the 1960's chemical investigations <sup>(2)</sup> on Griffonia simplicifolia seed have resulted in the detection and isolation of several indole derivatives including 5-hydroxy-L-tryptophan, indole-3-acetylaspartic acid and 5-hydroxy indole-3-acetic acid (5-HIAA).

The discovery that the seeds of the Griffonia simplicifolia contained high concentrations of 5-HTP was of threefold interest. Firstly it indicated the presence of an unusual metabolic system which might be of value in comparative and phylogenetic studies. Secondly it provided an unusually favourable opportunity to study the hydroxylation of tryptophan in a plant and thirdly, it offered a possible explanation of one or more of the medicinal and physiological properties attributed to the plant by the native peoples of West Africa <sup>(2)</sup>.

Research during the period from 1970 to 1980<sup>(2,13)</sup>, showed 5-HTP to possess antidepressant activity. 5-HTP was found to be more effective than the tricyclic synthetic drugs which were considered the standard of care at that time. As a consequence during the 1980's a number of medicinal specialities containing 5-HTP as the active ingredient were registered and launched on the market.

The leading antidepressants available in the 1990's have been the selective serotonin re-uptake inhibitors (SSRIs). While these have revolutionised the treatment of depression and are certainly effective for reducing depression, they are far from perfect because like most drugs, they have some undesirable side effects.

Depression occurs, at least in part, because of a relative lack of serotonin in certain crucial synapses in the brain. SSRIs help by blocking the "re-uptake" of serotonin molecules that have been released into the synapse. This effectively increases the amount of serotonin available to stimulate serotonin receptors. A more natural alternative to SSRIs may be a metabolic precursor to the neurotransmitter serotonin. The amount of serotonin available can be increased in a synapse by supplying more of the raw materials for endogenous manufacturing of serotonin. These raw materials include the immediate metabolic precursor 5-HTP, which the body uses to make 5-hydroxytryptamine (5-HT), otherwise known as serotonin.

# LINNEAssure™ Extracts

For the assurance of quality

## Part of Plant Used :

Seed

## Formula :

C11 H12 N2 O3

## Iupac name :

L-5-Hydroxy-tryptophan

## Synonyms :

Oxitriptan, L-5-HTP

## Product Category:

Antidepressant. Antiepileptic

## Normal Dosage:

100 mg orally by tablet or capsule

# LINNEAssure™ Extracts

For the assurance of quality

## **LINNEAssure™ 5-HTP:**

- ❑ LINNEAssure™ 5-HTP is pharmaceutical grade and manufactured under strict GMP.
- ❑ All LINNEAssure™ extracts comply with pharmaceutical standards of low residual solvents, microbiology and levels of impurities.
- ❑ LINNEAssure™ 5-HTP is characterised as an odourless white to pale grey crystalline powder. LINNEAssure™ 5-HTP is notable for its light and consistent colour profile.
- ❑ LINNEAssure™ 5-HTP corresponds to is the quality upon which the efficacy of European pharmaceutical preparations with Griffonia seed extract is established.

# Bibliographical Summary -

---

## PHARMACOLOGICAL ACTIVITIES

# LINNEAssure™ Extracts

For the assurance of quality

## Pharmacological Activities

### Mechanism of action

5-HTP derives from the essential aminoacid (AA) tryptophan known to be the precursor of the biological amine 5-HT, or serotonin, which plays a significant role as a neuromediator in the modulation of several specific activities at the CNS level such as,

- Control of pain threshold
- Sleep phasing
- Regulation of neuroendocrin pituitary gland activity
- Modulation of motor integrating mechanisms of extra-pyramidal system
- Neuronal excitability
- Thermal regulation
- Regulation of eating
- Sexual and aggressive behaviour

Serotonin is endogenously synthesised from tryptophan usually contained in several foods (mainly meat and dairy products). Tryptophan is available in the plasma both free or bound to plasma proteins and only minimal quantities of the free form is passing the blood/brain barrier in competition with other aminoacids. Tryptophan is transformed into 5-HTP by the L-tryptophan-hydroxylase and then to 5-HT (serotonin) by L-aminoacid-decarboxylase. Once formed 5-HT is inactivated and transformed by mitochondria MAO enzymes into 5-HIAA. Only 1% of the total amount of tryptophan is transformed into serotonin.

However, the administration of 5-HTP causes instead a significant increase in serotonin levels as it easily passes through the blood/brain barrier as:

- 5-HTP is not bound to plasma proteins
- 5-HTPit is not competing with other amino acids
- 5-HTP can not be transformed by pyrrolase into nicotinic acid as happens to tryptophan.

---

## CLINICAL USE

---

# LINNEAssure™ Extracts

For the assurance of quality

## Clinical Use

### Depression

The aminic hypothesis of depression <sup>(3,4,5)</sup> is based on the observation that some substances affecting the mood either in a depressive sense (i.e. reserpine), or in an anti-depressive way (MAO Inhibitors, tricyclic drugs) are interfering with the metabolism of biological amines. A clear reduction of the serotonin CNS levels has been observed in patients affected by depression.

The antidepressant efficacy of 5-HTP has been studied in more than 500 patients treated with doses ranging from 50 mg/day to 600 mg/day for a duration of 4 weeks to 8 months <sup>(6 - 18)</sup>.

The mean recommended dosage in monotherapy or in combination with tricyclic drugs is 100 mg TID. Higher dosages can be administered with a titration up to a total daily dose of 600 mg.

In the open-label studies the treatment with 5-HTP was considered effective in the reduction of the depression scales (Hamilton's Rating Scale for Depression, Zung's Depression Status Inventory, Clinical Global Impression Scale, Mini Mental State, etc.) and for a reduction in depression symptoms. A marked improvement was observed in 70% of the patients treated.

In the controlled studies 5-HTP proved superior to placebo and showed a clear anti-depressant effect both in monotherapy and in association with other anti-depressant drugs.

### Migraine, cephalalgia and pain syndromes

Many Authors in the past have demonstrated serotonin may play a role in the genesis of the migraine attack <sup>(19,20,21)</sup>. It was observed that during the attack the plasma levels of serotonin are significantly reduced while its main metabolic product 5-HIAA is increasingly excreted in the urine. Serotonin and its precursor 5-HTP also play a part as analgesic substances <sup>(22)</sup>.

It has been postulated that in migraine both a reduction of serotonin levels and a malfunctioning of the antinociceptive system are involved. The clinical experience with 5-HTP in migraine is based on several trials conducted in more than 400 adult patients treated with doses of 300-400 mg/day up to a maximum of 1500 mg/day for at least 6 weeks up to 24 months and in more than 150 paediatric patients (aged 6-14 years) treated with doses ranging from 5 to 10 mg/kg/day for 6 weeks to 3 months <sup>(23 - 32)</sup>.

In all the open-label trials and in those vs. placebo the treatment with 5-HTP was shown to significantly improve the symptom scores (migraine index, pain score, etc.) and the frequency and severity of the headache.

# LINNEAssure™ Extracts

For the assurance of quality

Almost 74% of patients were considered as responder to treatment with an improvement of the symptoms in 86% of cases. 5-HTP was shown to be superior to ASA and as effective as dihydroergotamine.

## **Parkinson's disease (PD)**

In this degenerative disease of the CNS where dopamine depletion is considered the main pathophysiological factor, also a reduction of serotonin in the CNS may play a role in its genesis.

In the treatment of PD by levo-Dopa patients can show amplified clinical symptoms of serotonin decrease. Indeed dopamine and serotonin synthesis is based on the activity of the enzyme L-AA-decarboxylase. The chronic administration of l-Dopa is competitively utilising the enzyme to produce dopamine with a progressive reduction in the serotonin production. This is causing the appearance of hyperkinetic syndrome and psychosis in the patients <sup>(33,34)</sup>.

Some Authors <sup>(35,36)</sup> have reported that doses of 100-300 mg /day of 5-HTP concomitantly administered to l-Dopa in PD patients gave good clinical effects on tremors and depression together with an activity on rigidity and akinesia.

## **Sleep disorders**

Serotonin, as other neuromediators, is involved in the regulation of the hypnotic activity.

The duration and the quality of the sleep and its REM phase are related also to the activity of serotonin. Several studies <sup>(37 - 40)</sup> with mean doses of 300 mg/day in adults and 100 mg/day in pediatric patients showed a positive effect of 5-HTP in regulating the sleep patterns.

---

# PHARMACOKINETICS

---

# LINNEAssure™ Extracts

For the assurance of quality

## Pharmacokinetics

5-HTP is well and rapidly absorbed and unlike its precursor is not bound by plasma proteins and it is rapidly decarboxylated. I.P administration of 5-HTP at doses of 25-50-100 mg/kg in rats induced a dose proportional increase in the cerebral 5-HTP levels, reaching its maximum level at 30 minutes after dosing.

In mice the dose of 1 g/kg enhanced the cerebral serotonin levels from 0.58 µg to 20 µg. In monkeys the dose of 30 mg/kg increased in one hour the serotonin levels from two to six fold depending on the cerebral region explored.

The urinary excretion of the metabolite 5-HIAA, that is usually at a constant rate in controls, was considerably increased in those animals receiving a single dose of 50-100-200 mg/kg of 5-HTP and reached the top after 24 hours after dosing. Multiple dose administration of 10 and 25 mg/kg of 5-HTP reached the maximal urinary excretion of 5-HIAA after 6 days with a progressive reduction in the following days.

In humans the pharmacokinetics was studied after oral doses of 50 to 200 mg TID and after an i.v. dose of 0.2 mg/kg<sup>(41)</sup>. The systemic availability of 5-HTP ranged from 47 to 84% with a mean value of 69.2%. The absorption is rather slow with a Tmax of 1.8-3.3 hours after dosing.

---

## SAFETY PROFILE

---

# LINNEAssure™ Extracts

For the assurance of quality

## **Safety**

The administration of the drug could induce nausea, occasionally vomiting and some other minor GI disturbs such as abdominal cramping and pain, diarrhoea that in general lessen or disappear once the steady state dose is reached. Mild and transient variations in blood pressure could also be observed, while rare adverse effects are insomnia, headache and palpitations.

No significant laboratory changes were observed in all the clinical studies.

---

## BIBLIOGRAPHY

---

## Bibliography

- 1) Dwuma-Badu D. et al. Constituents of West African Medicinal Plants. XYG. Griffonin and Griffonilide, Novel Constituents of Griffonia simplicifolia. Lloydia Vol. 39(6), 1976.
- 2) Fellows L.E. et al. Phytochemistry 9:2389-2396; 1970
- 3) Van Praag H.M. Aromatic Amino Acid Hydroxylases and Mental Disease. Ed. by M.B.H. Youdim, 1979 by John Wiley & Sons Ltd.
- 4) Barchas J. et al. Academy Press, New York 1977
- 5) Mendels J. et al. Br J Psychiatry 126:241-248, 1979
- 6) Angst J. Arch Psychiatr Nervenkr 224(2):175-186; 1977
- 7) Nardini M. et al. Int J Clin Pharmacol Res 3(4):239-250; 1983
- 8) Rousseau J. Clin Ther 9(3):267-272; 1987
- 9) Mendlewicz J. et al. J Affect Disord 2(2):137-146; 1980
- 10) Kahn R.S. et al. Int Clin Psychopharmacol 2(1):33-45; 1987
- 11) Westenberg H.G.M. Psychopharmacol. 98(2):283-285; 1989
- 12) Den Boer J.A. et al. Psychiatry Research 31(3):267-278; 1990
- 13) Byerley W.F. et al. J Clin Psychopharmacol 7(3):127-137; 1987
- 14) Agren H. et al. Acta Psychiat Scand 83(6):449-455; 1991
- 15) Conte G. Br J Psychiatry 152:720; 1988
- 16) Zmilacher K. et al. Neuropsychobiology 20(1):28-35; 1988
- 17) Van Hiele L.J. Neuropsychobiology 6(4): 230-240; 1980
- 18) Van Praag H. M. et al. Schweiz Rundschau Med Prax 77(34a):40-46; 1988
- 19) Sicuteri F. et al. Arch Allergy 19:55-58; 1961
- 20) Curran D.A. et al. Lancet 1:1393; 1972
- 21) Anthony M. et al. Arch Neurol 16(5):544-52; 1967
- 22) Sicuteri F. Background to Migraine 5:45-56; 1973
- 23) Longo G. et al. Pediatr Med Chir 6(2):241-245; 1984
- 24) De Benedittis G. et al. Clin J Pain 2:123-129; 1986
- 25) Centonze V. et al. G Neuropsicofarmacol 4(6):212-214; 1982
- 26) Cassa D. et al. Comptes Rendus du 2eme Congres de la Societe de Neurologie infantile, Genova 4-6/12/1981
- 27) Bono G. et al. Cephalagia 4(3):159-165; 1984
- 28) Romiti A. et al. Algos 3(3):256; 1986
- 29) Boiardi A. et al. J Neurol 225(1):41-46; 1981
- 30) Lendvai D. et al. Aggior Ped 38:25-28; 1987
- 31) Lendvai D. et al. Riv Pediat Siciliana 38(4):188-193; 1983
- 32) Bono G. et al. G Neuropsicofarmacol 4(2); 1982
- 33) Birkmayer W. et al. In Siegfried J. (Ed.) Parkinson's disease Hans Huber, Bern, vol. 1, pp. 176-185, 1972
- 34) Birkmayer W. et al. J Neurol Trans 33:163-178; 1972
- 35) Sano I. et al. Munch Med Wschr 114(40):1717-1719; 1972
- 36) Bastard J. et al. Nouv. Presse Med 5(29):1836-1837; 1976
- 37) Zarcone V.P. et al. Serotonin and Behavior: 499-505; 1973
- 38) Soulairac A. et al. Congrès de Psychiatrie et de Neurologie – Monaco 1973 – LXX Session
- 39) Bouchard J.M. et al. Inform Psychiatr 53(2):215-219; 1977
- 40) Herbaut M. Actualités psychiat (Suppl. Ther.);7(2):66-70; 1977