

Phytor Ltd.
Biotechnology Park (JBP)
Ein Kerem campus, Jerusalem, Israel



Tel: 02-6711911
Fax: 153-2-6711911
e-mail: phytor1@gmail.com



Consulting in Human Health, Toxicology & Regulatory Affairs

Phytor Ltd.

Consultant: Dr. Yehoshua Maor (Ph.D, M.Sc.,B.Pharm.)

JBP Building – Ein Kerem Campus

9112001 Jerusalem – ISRAEL

Phone: +972-2-6711-911

Fax: +972-153-2-6711-911

e-mail: phytor1@gmail.com

Jerusalem, Israel June 20, 2020

Expert opinion on the toxicological aspects and risk assessment of the product *FLORMEL*, a nutritional supplement from Zuf Globus

Expert opinion on the toxicological aspects and risk assessment of the product *FLORMEL*, a nutritional supplement from Zuf Globus.

This initial review relates only to the toxicological aspects and risk assessment of the inactive substances used in the formulation of *FLORMEL*, a nutritional supplement from Zuf Globus. This independent opinion has been done on the request of Zuf Globus as represented by Mr. Arik Fahima.

Dr. Yehoshua Maor

Expert in pharmacology, toxicology and regulation of medicines and nutritional supplements.

About my training:

- Bachelor's degree in Pharmacy (B.Pharm , Brazil)
- Medicinal Chemistry degree (M.Sc., Hebrew University)
- PhD in Medicinal Chemistry and Molecular Biology (PhD, Hebrew University)
- Post - Doctoral School of Medicine and Harvard University, Boston, USA, on Pharmacology of cardiovascular
- Coordinator of the Center of Excellence for Research in Agriculture and Environmental Health of the Hebrew University of Jerusalem (HU CEAEH) in the Rehovot campus and lecturer of Toxicology at the Faculty of Medicine in the Ein Kerem campus - Jerusalem.
- Senior consultant at Phytor Ltd. Engaged in consulting in pharmacology, toxicology and regulatory aspects of new drugs and chemical substances of medicinal plants.
- Member of the SOT (Society of Toxicology)
- Member of the ICRS (International Cannabinoid Research Society)

Product Name: *FLORMEL*

Manufacturer: Zuf Globus

Product Description: beehive product and herbal tinctures in a bottle containing 15 ml.

Directions of Use: Add 20 drops to a spoon of water. Rinse mouth for 30 seconds and swallow. Avoid eating or drinking for 30 minutes after the use. 2-3 times a day.

Product Summary:

FLORMEL is a product from Zuf Globus which aims at promoting and keeping proper oral health when the balance of the oral cavity has been disrupted. The product is recommended for those who need complementary treatment in cases of gingival recession, bleeding gingiva, aphthous stomatitis and may also serve as a first aid for toothaches. Due to its antibacterial properties it can also be an agent in preventing tooth decay (dental caries). *FLORMEL* herbal and beehive components support a healthy oral cavity.

FLORMEL is comprised by a unique blend of herbs which are known for their biological activities on the oral cavity. In addition, *FLORMEL* has in its composition, propolis and a small amount of *DefenseMel* which act as immunomodulators and adaptogens with strong antioxidant and anti-inflammatory activities. The biological activities produced by the chemical constituents of these herbs and propolis are recorded on the WHO monographs and are corroborated by numerous peer-reviewed scientific publications.

Herbal components in the bees' feed:

The herbal components in this product were not added to the beehive product. Instead, they were added to the bees' feed and based on this nutrition, the bees produced the beehive product which contains the herbal compounds or their metabolites as can be seen in the chromatographic analysis, in the end of this document.

| | Botanical name | Part of the plant |
|----|------------------------------|--------------------------|
| 1 | Uncaria tomentosa | Barks |
| 2 | Echinacea purpurea | Roots |
| 3 | Sambucus nigra | Flower |
| 4 | Polygonum aviculare | leaves |
| 5 | Eleutherococcus senticosus | roots |
| 6 | Eucalyptus globulus | leaves |
| 7 | Salvia officinalis | leaves |
| 8 | Ceratonia siliqua | Fruit |
| 9 | Beta vulgaris | Root |
| 10 | Medicago sativa | leaves |
| 11 | <i>DefenseMel (HIZUKMEL)</i> | beehive product |
| 12 | Propolis | beehive product |

After thoroughly reviewing the scientific literature and professional, this document will refer only to the following aspects relating to *FLORMEL* product components:

1. The amount of active substance in the plant before and after preparation of the beehive product
2. Reaction between components
3. Usual doses and toxicity of formula or component
4. Warnings (if any) about the product
5. Levels of safety

1. Active substances in the plants before and after preparation of the beehive product

The amount of active ingredient in the plants before and after preparation of the beehive product can vary with the harvest season, cultivation location, and other factors.

As for herbal medicines, the active ingredient is sometimes known and sometimes requires co - factors (other materials in the plant that are active together synergistically) to achieve therapeutic goals. This leads to complications in tagging the active ingredient. One-way manufacturers have found to solve the problem of labeling is selecting the marker element (the most active component in the plant) and perform standardization of the cursor element.

However, official standardization by government agencies such as the Ministry of Health, has not been achieved yet, and therefore not required by the health of natural herbal products manufacturers in Israel or in Europe. Consequently, various companies use different markers, or different levels of the same markers, or different methods of testing marker compounds.

Both the Israeli Ministry of Health and EMEA/EFSA do not publish a list of active substances in plants. Instead, they provide a list of plants approved for use.

2. Reaction between components

The components of the bees' feed go through the bees' digestive system and produce metabolites which are still present and stable in the final product.

A fingerprint of the herbal compounds still can be observed in the chromatogram (HPLC), which indicates the ability of these compounds to exert their pharmacological activities as recorded in the pharmacopeia and other officially accepted sources.

The matrix of the beehive product is very stable and there is no interaction between the chemical compounds during the shelf life, as can be seen in the stability tests performed on the beehive products.

3. Usual doses and toxicity of formula or components

The recommended daily dose of the product allows the use of a reasonable and absolutely safe margin of toxicity. The product can be safely administered up to 10 ml a day for an adult, without any fear of side effects or toxicity.

The dilution of the herbal components by the bees' processing of the bees' feed relatively weakens the toxicity of the formula thus requiring relatively large amounts the product in order to exert its pharmacological properties. To the best of my knowledge, from the toxicological standpoint, there is no fear of toxicity or poisoning from taking this product.

4. Warnings (if any) about the product

Pregnant women, lactating women, patients taking prescription drugs, children- should consult their family practitioner prior to taking this product.

5. Level of safety

Based on a critical evaluation of available public data sources listed in the bibliographic sources and above, as an expert in toxicology I have reached the conclusion that the active ingredients used in the formulation of *FLORMEL* is safe for human use especially when followed the instructions for use from the manufacturer. The formulation possesses a wide safety margin concerning its risk of toxicity.

In conclusion, since these substances have been certified by the Ministry of Health and possess a long history of safe use by humans, the review of the substances and the product allows me to state that the product has a high safety level, once it is administered in accordance with the use and guidance of the Ministry of Health.

Sincerely,


פיטאור בע"מ
514486240 .פ.ח
PHYTOR LTD.

Yehoshua Maor
Ph.D., M.Sc., B.Pharm.

Product HPLC Analysis Results:

Product preparation

FLORMEL was diluted 1:10000 in HPLC grade water, centrifuged, and supernatant was taken for RP-HPLC analysis.

HPLC conditions

Dionex ultimate 3000 system and a phenomenex C-18 (4.6 x 250) Luna column were used. The mobile phase consisted of acetonitrile and water (95:5 v/v). The mobile phase was delivered at a flow rate of 2.0 ml/min in the isocratic mode. Detection was carried out at 202 nm.

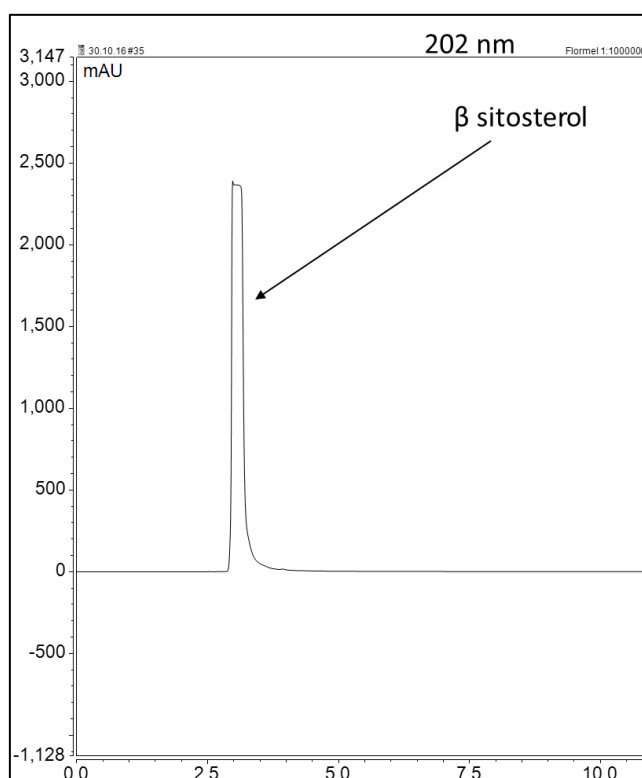


Figure 1: Chromatogram of the product *FLORMEL* and an example of a main herbal component, according to its retention time for the relevant HPLC program. The number on the upper right side represents the optimal wave length for the detection of the desired compound.

Bibliographic References in addition to the EMEA document regarding the herbal substances in the formula.

- Adom MB. et al. Chemical constituents and medical benefits of *Plantago major*. *Biomed Pharmacother.* 2017.
- Blumenthal M, editor. *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines.* The American Botanical Council, 1998.
- Bradley PR, editor. *British Herbal Compendium, Vol I.* Bournemouth: British Herbal Medicine Association, 1992.
- British Herbal Pharmacopoeia.* Keighley: British Herbal Medicine Association, 1983.
- British pharmacopoeia. Vol. I (International edition and addendum).* London, Her Majesty's Stationery Office, 1995.
- Chen XP. et al. Phytochemical and pharmacological studies on *Radix Angelica sinensis*. *Chin J Nat Med.* 2013.
- ESCOP monographs on the medicinal uses of plant drugs. Fascicule 3. Devon, European Scientific Cooperative on Phytotherapy, 1997.
- European pharmacopoeia, 3rd ed.* Strasbourg, Council of Europe, 1996.
- Gardiner P, Phillips R, Shaughnessy AF. *Herbal and Dietary Supplement drug Interactions in Patients with Chronic Illnesses*, *Am Fam Physician.* 2008;77:73-78.
- Guidelines for Herbal ATC Classification, The Upsala Monitoring Centre. WHO Collaborating Centre of International Drug Monitoring. 2004.
- Hansel R. *Phytopharmaka*, 2nd ed. Berlin, Springer-Verlag, 1991.
- Herbal ATC Index*, The Upsala Monitoring Centre. WHO Collaborating Centre of International Drug Monitoring. 2004.
- Irfan M. et al. Adaptogenic effects of *Panax ginseng* on modulation of cardiovascular functions. *Journal of Ginseng Research.* 2020.

Izzo AA. *Interactions between Herbs and Conventional Drugs: Overview of the Clinical Data*, Med Princ Pract 2012; 21: 404-428.

Li Y. et al. Antitumour Activities of Sesquiterpene Lactones from *Inula helenium* and *Inula japonica*. Z Naturforsch C J Biosci. 2012.

Martindale, *The Extra Pharmacopoeia*: 30th Edition. (Reynolds JEF, editor). London: The Pharmaceutical Press, 1993

Mills SY. *The dictionary of modern Herbalism* Wellingborough:Thorsons, 1985

Newall CA, Anderson LA, Phillipson JD. *Herbal Medicines: A Guide for Health Care Professionals*.London: Pharmaceutical Press, 1996

Niroumand MC., Heydarpour F. and Farzaei MH. Pharmacological and Therapeutic Effects of *Vitex agnus-castus* L.: A Review. Pharmacognosy Reviews. 2018.

Prasanth D S N B K, Rao AS and Yejella RP. Assessment of Pharmacognostic, Phytochemical and Physicochemical Standards of *Aralia racemosa* (L.) root. Indian Journal of Pharmaceutical Education and Research. 2016.

Sowndhararajan K. et al. An overview of neuroprotective and cognitive enhancement properties of lignans from *Schisandra chinensis*. Biomedicine & Pharmacotherapy. 2018.

Tierra M (Editor) *American Herbalism: Essays on Herbs and Herbalism*, Crossings Press, 1992.

Yamauchi Y, Ge YW, Yoshimatsu K, et al. Memory Enhancement by Oral Administration of Extract of *Eleutherococcus senticosus* Leaves and Active Compounds Transferred in the Brain. Nutrients, 11(5). pii: E1142. 2019

<http://reference.medscape.com/drug-interactionchecker>

<http://abc.herbalgram.org/site/PageServer?pagename=Monographs>