

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

July 19, 2020

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

Expert opinion on the toxicological aspects and risk assessment of the product *GASTOMEL*, 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 *GASTOMEL*, 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 ICERS (International Cannabinoid Research Society)

Product Name: *GASTOMEL*

Manufacturer: Zuf Globus

Product Description: Beehive product in a jar
containing 120 gr.

Directions of Use: One teaspoon, twice a day
before meals.

Product Summary:

The gut-brain axis is the biochemical signaling that takes place between the gastrointestinal tract and the central nervous system. The digestive system is now seen as having a strong influence on our nervous, hormonal and immune systems and therefore playing a fundamental role on our overall health. *GASTOMEL* is a product from Zuf recommended for those who wish to strengthen the digestive system and therefore the biochemical signaling that stems from this system. *GASTOMEL* should be taken continuously as a dietary supplement in order to support a healthy digestive system. The blend of herbs which comprise the bees' feed used in the production of *GASTOMEL* possess bioactive substances, such as terpenes, which promote digestive enzymes, act as analgesic and antiseptic. The herbal components of *GASTOMEL* are cited in numerous experimental reports including the WHO monographs. In addition, the biological activities of the herbs composing the bees' feed of *GASTOMEL* are all corroborated by 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	Propolis	
2	Angelica atropurpurea	Root, Leaves, stalk
3	Laurus nobilis	Leaves
4	Salvia officinalis	Leaves, Flowers
5	Hydrangea arborescens	Roots
6	Opuntia ficus Indica	Flowers, Fruits
7	Medicago sativa	Flowers, stalk

After thoroughly reviewing the scientific literature and professional, this document will refer only to the following aspects relating to *GASTOMEL* 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 4 teaspoons 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.

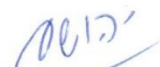
5. Level of safety

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 *GASTOMEL* 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,

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


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

Product HPLC Analysis Results:

Component	Product
Propolis	<i>GASTOMEL</i>

Plant extraction

25 ml of HPLC grade boiling water were poured into glass erlenmeyer containing 1 g of the desirable plant material and the erlenmeyer flasks were shaken for 1 hour. Then, samples from the extractions were centrifuged, and the supernatants were subjected for RP-HPLC analysis.

Product preparation

GASTOMEL was diluted 1:3 in HPLC grade water, centrifuged, and supernatant was taken for RP-HPLC analysis.

HPLC conditions

A Dionex ultimate 3000 system and a phenomenex C-18 (4.6 x 250) Luna column were used. Mobile phase consisting of a gradient (Table 1) of purified water acidified with 0.05% of acetic acid, (Phase A) and acetonitrile (Phase B). The flow rate and column oven temperature were 1mL/min and 40°C respectively. Optimal detection wavelength was chosen for each plant and its related product.

Table 1

Time (min)	Phase A %	Phase B %
0	74	26
1	58	42
4.5	56	44
4.8	10	90
6	10	90
6.5	74	26
8	74	26
10	74	26

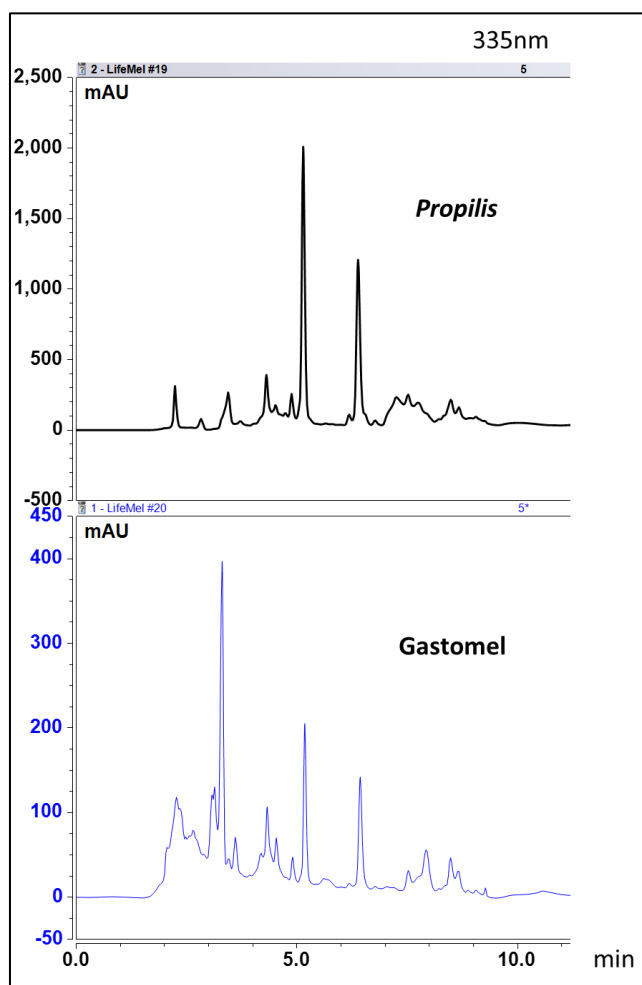


Figure 1: Chromatogram of the product *GASTOMEL* and its main herbal component. The number on the upper right side represents the optimal wave length for the desired compounds detection

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

- Blumenthal M, editor. The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines. The American Botanical Council, 1998.
- Bora KS. and Sharma A. Phytochemical and pharmacological potential of *Medicago sativa*: a review. Pharm Biol. 2011.
- 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.
- 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.
- Galati EM. et al. Biological Activity of *Opuntia ficus indica* Cladodes II: Effect on Experimental Hypercholesterolemia in Rats. Journal of Pharmaceutical Biology. 2003.
- Gardiner P, Phillips R, Shaughnessy AF. *Herbal and Dietary Supplement drug Interactions in Patients with Chronic Illnesses*, Am Fam Physician. 2008;77:73-78.
- Ghorbani A. and Esmaeilzadeh M. Pharmacological properties of *Salvia officinalis* and its components. J Tradit Complement Med. 2017.
- Gouws C. et al. The effects of Prickly Pear fruit and cladode (*Opuntia* spp.) consumption on blood lipids: A systematic review. Complementary Therapies in Medicine. 2020.
- Guidelines for Herbal ATC Classification, The Uppsala 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.

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

Kim SH. et al. Prickly pear cactus (*Opuntia ficus indica* var. *saboten*) protects against stress-induced acute gastric lesions in rats. J Med Food. 2012.

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

Mikaili P. and Shayegh J. *Medicago sativa*: A historical ethnopharmacology and etymological study of the alfalfa. Research Opinions in Animal and Veterinary Sciences. 2011.

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

Mota da Silva L. et al. Propolis and Its Potential to Treat Gastrointestinal Disorders. Evid Based Complement Alternat Med. 2018.

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

Qnais EY. et al. Antidiarrheal activity of *Laurus nobilis* L. leaf extract in rats. J Med Food. 2012.

Tierra M (Editor) *American Herbalism: Essays on Herbs and Herbalism*, Crossings Press, 1992. Food. 2012.

Wagh VD. Propolis: a wonder bees product and its pharmacological potentials. Adv Pharmacol Sci. 2013 .

Wang K. et al. *Angelica sinensis* polysaccharide attenuates concanavalin A-induced liver injury in mice. International Immunopharmacology. 2016 .

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

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