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Expert opinion on the toxicological aspects and risk assessment of the product *LADYMEL-DAY*, a nutritional supplement from Zuf lab

Expert opinion on the toxicological aspects and risk assessment of the product *LADYMEL-DAY*, a nutritional supplement from Zuf lab.

This initial review relates only to the toxicological aspects and risk assessment of the inactive substances used in the formulation of *LADYMEL-DAY*, a nutritional supplement from Zuf lab. This independent opinion has been done on the request of Zuf lab 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: *LADYMEL-DAY*

Manufacturer: Zuf lab

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

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

Product Summary:

LADYMEL-DAY is a product from Zuf which aims at balancing the level of female hormones mainly during perimenopause and menopause when hormonal balance can be disrupted. The product is recommended for healthy women during perimenopause and menopause, who wish to modulate the hormonal balance thus helping the woman to cope with symptoms like hot flashes, nervousness and restlessness that are associated with menopause and PMS. *LADYMEL-DAY* components support a healthy female hormonal system and fight agents caused by stress.

The bees' feed utilized for producing *LADYMEL-DAY* is comprised by a unique blend of herbs which are known for their biological activities on the female hormonal system. The biological activities produced by the chemical constituents of these herbs are recorded on the WHO monographs and are corroborated by numerous peer-reviewed scientific publications.

The product is offered in two versions (day and night). The elements of each formula take into consideration the natural biological clock and the female circadian rhythms determining the sleep patterns which involve the control of the production of melatonin.

LADYMEL-DAY herbal components assist to adapt to many and varied environmental and psychological stresses by supporting the female hormonal system during menopause and PMS.

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	Trifolium pratense	Leaves
2	Vitex agnus-castus	Fruits
3	Matricaria recutita	Flowers
4	Eleutherococcus senticosus	All plant
5	Calendula officinalis	Leaves, Flowers
6	Medicago sativa	Leaves
7	Mentha piperita	Leaves
8	Actaea racemosa	Root

After thoroughly reviewing the scientific literature and professional, this document will refer only to the following aspects relating to *LADYMEL-DAY* 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.

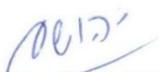
4. Warnings (if any) about the product

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 *LADYMEL-DAY* 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.


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PHYTOR LTD.

Sincerely,

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

Product HPLC Analysis Results:

Plant	Product
<i>Vitex agnus cactus</i>	<i>LADYMEL-DAY</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

LADYMEL-DAY 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

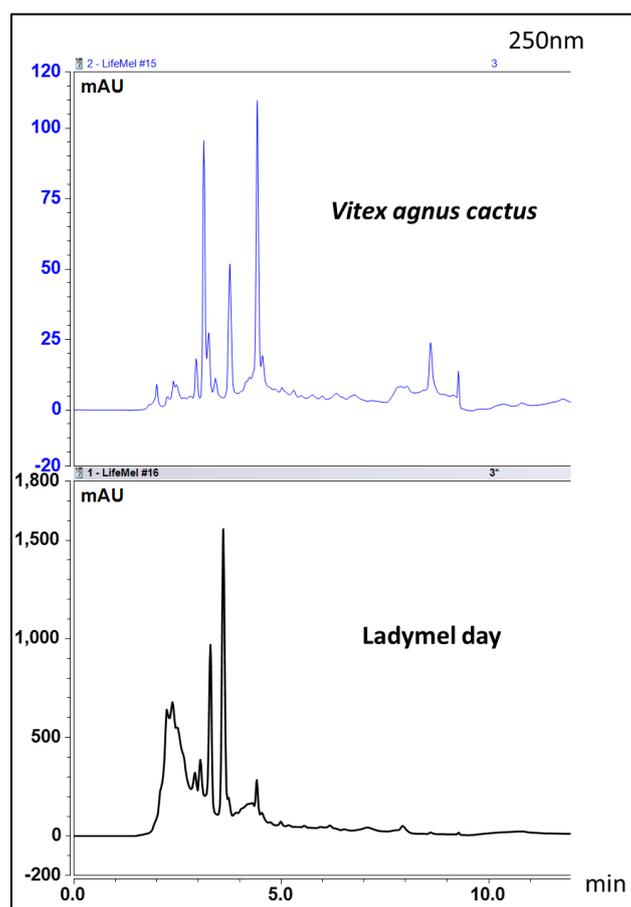


Figure 1: Chromatogram of the product *LADYMEL-DAY* and its main herbal component. The number on the upper right side represents the optimal wave length for the desired compounds detection

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herbal substances in the formula**

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