Ben-Gurion University of the Negev
Department of Pharmacology, School of Pharmacy
Faculty of Health Sciences
Laboratory of Medicinal Chemistry and Natural Products

אוניברסיטת בן גוריון בנגב
המחלקה לפרמקולוגיה, ביה"ס לרוקחות
הפקולטה למדעי הבריאות
המעבדה לכימיה מדיצינלית וחומרי טבע

TO: LifeMel - Zuf Globus Laboratories Ltd

General report

Scientific review

TITLE:

Biological relevance of diverse natural products from LifeMel product: A general view on different classes

Ben-Shabat Shimon
Department of Pharmacology and School of Pharmacy
Ben-Gurion University of the Negev

SUBMISSION DATE: 1 April 2009

Bergman Campus, POB 653, Beer-Sheva, Israel, 84105
Tel: ***Fax:***
972-8-6479354 ***972-8-6472984***
E-mail: sbs@bgu.ac.il

קמפוס ברגמן, ת.ד. 653, באר-שבע, 84105
טל': **פקס:**
972-8-647-9354 ***972-8-647-2984***

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INTRODUCTION:

Natural products (phenolic substances, terpenoids, fatty acids etc.) have played a significant role in human disease therapy and prevention (1). Modulation of the immune system, for example, may offer novel approaches in the treatment of a variety of diseases. One strategy in the modulation and involvement of the immune system may be through the use of herbal medicines. A class of herbal medicines, known as immunomodulators, alters the activity of immune function through the dynamic regulation of informational molecules such as cytokines (2). This may offer an explanation of the effects of herbs on the immune system and other tissues. Herbal medicines contain an abundance of phenolic substances, terpenoids and other natural antioxidants that have been also associated with protection from and treatment of chronic diseases such as heart disease or cancer.

For this informal review, we will survey the primary literature on diverse classes of naturally-occurring compounds that were found in LifeMel product and we will follow their effects on the immune system, complete blood picture and cancer, taking special care to analyze research that utilized the multi-component extracts equivalent to or similar to what are used in the main plants that are used for the manufacture of LifeMel product.

Methodology

Search Strategy

The databases PubMed, SciFinder, ISI web of knowledge, and general scientific sources in the internet were searched for appropriate studies. Titles were screened for all hits to the terms that include the diverse classes of compounds with or w/o the requested activity and in comparison with the information obtained for the relevant main plants that were used in the production of LifeMel product (table 1).

Main classes	**Biological relevance**	**Main plants that were used for the feeding of the bees**
Terpenoids: Monoterpene, Sesquiterpene, Tetraterpene (carotenoids) Flavenoids; Chlorophylls Fatty acids; cinnamic acid	Immunomodulators complete blood picture cancer	Uncaria tomentosa Taraxacum officinale Eleutherococcus Senticosus

Table 1:

Bergman Campus, POB 653, Beer-Sheva, Israel, 84105
Tel: *972-8-6479354* ***Fax:*** *972-8-6472984*
E-mail: sbs@bgu.ac.il
קמפוס ברגמן, ת.ד. 653, באר-שבע, 84105
טל': *972-8-647-9354* **פקס:** *972-8-647-2984*

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1. The group of terpenoids:

The nomenclature of terpenoids depends on the number of isoprene structures and their carbon atoms in the molecule (table 2). In nature, terpenoid molecules are implicated in almost every interaction between plant and animal, plant and plant or plant and microorganisms as phytoalexins, insect antifeedants, defense agents, pheromones or signal molecules. Terpenoids can be found also in the main plants that were used for the production of LifeMel product (see above table 1). The monoterpens that were detected at LifeMel product are: carene, sabinene, terpinene, thujene, camphene, terpineol, linalool, linalyl acetate, geranyl acetate, ocimen and citral. The sesquiterpenes that were detected at LifeMel product are: cadivene, gujunene, aromadendrene and caryophyllene.

Terpenoid item	C atoms	Isoprene structures
Monoterpene: carene, sabinene, terpinene, thujene, camphene, terpineol, linalool, linalyl acetate, geranyl acetate, ocimen and citral.	10	2
Sesquiterpene: cadivene, gujunene, aromadendrene and caryophyllene	15	3
Diterpene	20	4
Triterpene	30	6
Tetraterpene (carotenoids)	40	8
Polyterpene	>40	>8

Table 2: Nomenclature of terpenoids

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1.1. Monoterpenes and Sesquiterpene

Monoterpenes and Sesquiterpene are non-nutrient dietary components and are best known as constituents of the essential oils. In general, sesquiterpenes are less volatile than monoterpenes. Monoterpenes and sesquiterpenes were investigated especially concerning their chemotherapeutic and immunomodulatory activities (3,4). Recently groups of monoterpenes and Sesquiterpene were isolated from Eleutherococcus senticosus (Siberian ginseng) a plant with well known anti-cancer and immunostimulating properties (5).

Combinations of dietary chemopreventive agents can sometimes result in significant activities at concentrations where any single agent is inactive. Many of the phytochemicals are reported to act synergistically. The molecular mechanism underlying such synergistic effects is still incomplete, but it seems that different combinations of complementary modes of actions are involved (6).

Antitumor Activity of Monoterpenes and Sesquiterpene

In animal models and at cellular level, a number of dietary monoterpenes show antitumor activities, preventing the initiation and progression of cancer and also causing regression of existing malignant tumors. Monoterpens administered as a pure chemical or in orange peel oil, inhibited the development of chemically induced rodent mammary, kidney, skin, lung and forestomach cancers in different animal models (7-13). Chemopreventive activity of carvone was observed against the development of lung and forestomach cancer (8) when administered before the carcinogen. Limonene as well as other related cyclic monoterpenes was also found to inhibit colon and breast cancer and part of them are know in clinical trails. (14-16).

Carvone, perillyl alcohol and limonene are the most common investigated monoterpenes against cancer. These monoterpens were analyzed also in Eleutherococcus senticosus (5).

Among the sesquiterpenes, the sesquiterpene lactones are widely distributed and are well known for their wide variety of biological activities (17,18). Extensive research work has been carried out to characterize the anti-cancer activity and the potential chemopreventive and chemotherapeutic application of Sesquiterpene lactones (19). The experimental evidence for the anti-cancer function of Sesquiterpene lactones obtained from both in vitro cell culture and in vivo animal models.

Immunomodolatory

There are also large group of monoterpenes, which possess antiviral and immunostimulating properties. It was shown that monoterpens from Plantago species enhanced the activity of human lymphocyte proliferation and secretion of Interferon-gamma (20). Carvone, limonene and perillic acid were found to increase the total white blood cells (WBC) count in mice (21). Administration of terpenoids to mice increased the total antibody production, antibody producing cells in spleen, bone marrow cellularity and alpha-esterase positive cells significantly compared to the normal animals.

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טל': **פקס:**
972-8-647-9354 ***972-8-647-2984***

1.2. Diterpenes

The main component of this group is the fat-soluble essential vitamin A (all-trans-retinol), the parent of a class of chemical compounds called retinoids, which have many of the structural features of vitamin A. Retinoids play an important role in regulating the growth and differentiation of normal, premalignant and malignant cell types (22). Tumor development in animal models was suppressed, e.g. in the skin, breast, oral cavity, lung, prostate, bladder, liver and pancreas (23,24). Certain retinoids showed efficacy in inhibiting the development of primary cancers of the skin, cell lung cancer and breast cancer (25,26).

In addition diterpanes are also shown to act as primary antioxidants. In this protection system of the human body, some diterpenoids are able to participate by acting as primary or synergistic antioxidants (27).

1.3. Triterpenes:

Triterpenes are precursors to steroids in both plants and animals. Triterpenoid saponins are triterpenes which belong to the group of saponin compounds that are recognized as the most active constituents in *Eleutherococcus senticosus* (28). Siberian, or Russian, ginseng consists of the dried roots and rhizome of *Eleutherococcus senticosis*, and contains phenolics (see flavonoids below), polysaccharides, and eleutherosides **(**Triterpenoid saponins**)**. Saponins are now redirected to their potential use as chemotherapeutic agents by their cytotoxicity and ability to cause cell death (29-31). The biologically active constituents in *Eleutherococcus senticosis* are a complex mixture of triterpene saponins known as ginsenosides. In a study of the anti-proliferative activity of ginsenosides using human prostate carcinoma LNCaP cell line, ginsenoside displayed growth inhibitory activity (32).

It has also been found that the known active constituents from Eleutherococcus senticosus, namely phenolics and ginsenosides exert a strong immunomodulatory effect in healthy normal subjects (32). In this study an absolute increase in all immune cells measured was detected. Several trials have supported the use of *Eleutherococcus* active extracts as adjunctive treatment in chemotherapy and radiotherapy. Studies have shown enhancement of anti-tumor and anti-metastatic actions of anti-cancer therapies, together with accelerated recovery of hematopoetic indices such as leucocyte count (32).

1.4. Tetraterpenes

Tetraterpanes are actually the carotenoids which are naturally occurring colorful components that are abundant as pigments in plants. Carotenoids are well known as antioxidant agents and act along two different main pathways – physical and chemical radical quenching (33,34). The group of carotenoids also exists in the LifMel product.

Epidemiological and intervention studies of the last years have indicated that carotenoids are potential agents for the chemical prevention of carcinogenesis (35,36). The association of different carotenoids and colon cancer is especially focused on lutein (37). The intake of carotenoids is also known to influence the development of prostate cancer, but it is mainly related to lycopene (38).

Carotenoids exhibit further biological functions which are not related to their antioxidant activities but might be of great importance in disease prevention. There has been substantial interest in carotenoids as immunomodulatory agents (39-41). β-carotene was able to enhance the cell-mediated immune responses, especially in the elderly. In particular, supplementation leads to an increase in the activity of natural killer cells and antigen presenting monocytes. Especially in patients with HIV infection, the plasma status of β-carotene is low, thus increasing the free-radical-induced peroxidation in these patients.
The immunomodulatory effect of carrot extracted Carotenoid was also assessed in rats by the analysis of immune parameters in the blood (42). Significant increases in percentage lymphocytes, monocytes neutrophils and platelet count was detected in the group that received carotenoid complex in comparison with the control group, indicating that carotenoids have clear immunomodulatory effects.

2. Flavonoids

Flavonoids belong to a group of natural substances with variable phenolic structures and are found in fruit, vegetables, grains, bark, roots, stems, flowers, tea, and wine (43). Flavonoids can be divided into various classes on the basis of their molecular structure (44). The 4 main groups of flavonoids are listed in Table 3. Flavonoids were also found in LifeMel product and in the main plants that were used for the production of LifeMel product (see above table 1).

Group	compounds
Flavones	Apigenin; chrysin; kaempferol; Luteolin; myricetin; rutin; sibelin; quercetin
Flavanones	Fisetin; hesperetin; narigin; naringenin; taxifolin
Catechins	Catechin; epicatechin; epigallocatechin gallate
Anthocyanins	Cyaniding; dephinidin; malvidin; palargonidin; peonidin; petunidin

Table 3: Main groups of flavonoids and the individual compounds.

Antitumor Activity

Amongst various modes of action, particular flavonoids can exert significant anticancer activity including anticarcinogenic properties and even a prodifferentiative activity. It has been found that the crude extract of *Taraxacum officinale* leaf decreased the growth of MCF-7 breast cancer cells and blocked the invasion of LNCaP prostate cancer cells (45).

Immune Disorders:

Using cat´s claw (*Uncaria tomentosa*) from an extract of the root bark that include flavonoids among other compounds, have reported benefits in patients with viral infections of HIV, herpes simplex, and h. zoster (46). The extract appeared to decrease the levels of neutrophils in people with high levels of these cells (>9000 cells/μL), while in people with low levels of these cells (<4000 cells/μL) neutrophil levels rose to normal. It was also shown that absolute and relative lymphocyte counts showed a significant increase (47).

Immune Modulation:

Water extracts of the bark of *Uncaria tomentosa*, that includes flavonoids among other compounds, has been used for generations as an "immuno modulator". It was shown that treatment with C-Med-100 (a stalk bark extract of *U. tomentosa)* significantly prolonged lymphocyte survival in peripheral lymphoid organs, without increasing their proliferation rate. C-Med-100 has been suggested as a potential agent for clinically accelerating the recovery of patients from leucopenia (48,49).

Other study that followed the immunomodulatory properties of kolaviron, a mixture of three related biflavonoids of *Garcinia kola Heckel* (Clusiaceae), was found that administration of kolaviron ameliorated the cyclophosphamide-induced leukopenia and increased the proportion of lymphocytes count in rats. This study indicates that flavonoids could be harnessed for possible clinical benefits to immunodeficient patients (50).

3. Fatty acids.

Fatty acids are a kind of fat or lipid. The ability of certain fatty acids to influence the immune system and the function of its various cellular components have been recognized for nearly 30 years. Most of the research on this topic has focused on one class of fatty acids, omega-3 polyunsaturated fatty acids (n-3 PUFAs). Dietary fatty acids modulate immune responses through one or more of three major molecular mechanisms: (*a*) altered membrane composition and function, (*b*) modified eicosanoid production, and (*c*) changed cytokine biosynthesis (51).

Taraxacum officinale, one of the main plants that use in the production of LifeMel product, is suggested as a food source because of the high content of minerals, fiber, vitamins and essential fatty acids (52). Unsaturated fatty acids represented 68.20% of the total, with the most prevalent being linolenic acid (50.74%), an essential fatty acid necessary for health. A high quantity of linolenic present in a diet increases the linolenic in blood platelets and reduces not only thromboxane synthesis but also aggregation, in this way reducing the thrombosis possibility (53).

4. Chlorophylls.

Chlorophyll (also found in LifeMel product) is a green pigment found in most plants, algae, and cyanobacteria and are known in a variety of medicinal uses . Chlorophyllin is a water-soluble mixture of sodium-copper salts of the chlorophyll. It has chemopreventive, antimuatgenic and anticarcinogenic properties (54). This compound may bind the carcinogen or mutagen thus reducing its bioavailability (55). In addition chlorophyllin exhibited protection against radiation and chemical induced cytogenetic damage (56). It was found to inhibit radiation induced single strand breaks in plasmid pBR322 DNA (56). Chlorophyllin was found to act as an immunomodulator and also aginst modification of radiation induced immunosuppression (57).

5. Cinnamic acid.

Cinnamic acids' derivatives are known for their biological activities, usually related to the immune system and can also act as anti cancer agents (58). The active compound 4-methyl cinnamic acid was found in LifeMell product.

6. Metals.

Metals in general are important in biological systems. Several metals, such as: Iron, Manganese, Molybdenum**,** Selenium, Zinc and Copper, were detected in high levels in the LifMell product. The levels of the metals in the LifeMell product were found to be 3-10 fold higher than the levels in diverse honey samples from the market. Metals are in general present in protein complexes and use in diverse cell enzymes including anti-oxidant enzymes (59). Metals are also vital for the functioning of DNA and RNA polymerases which rule the biosynthesis of proteins. It is well known that Fe-containing compounds play an important part in the functioning of the immune system (59).

In summary we can say that in analytical measurements, that were carried out in parallel, to the LifeMell product and to various honey samples from the market, it was shown that the lifemell product contains diverse natural products (such as: terpenoids, flavenoids, chlorophylls, fatty acid etc.) with potential biological activities and that are not existing in other honey samples from the market that were analyzed.

Bergman Campus, POB 653, Beer-Sheva, Israel, 84105
Tel: ***Fax:***
972-8-6479354 ***972-8-6472984***
E-mail: sbs@bgu.ac.il
קמפוס ברגמן, ת.ד. 653, באר-שבע, 84105
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Bergman Campus, POB 653, Beer-Sheva, Israel, 84105
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E-mail: sbs@bgu.ac.il
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טל': **פקס:**
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