



TO: FlorMel - Zuf Globus Laboratories Ltd

Scientific review

TITLE:

**Anti-inflammatory and antimicrobial activity of diverse
terpenoids found in ZufGlobus product (FlorMel)**

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Essential oils, odorous and volatile products of plant secondary metabolism, have a wide application in folk medicine, food flavouring and preservation. The anti-inflammatory and antimicrobial properties of essential oils have been known for many centuries. In recent years a large number of essential oils and their constituents have been investigated for their anti-inflammatory activity and for their antimicrobial properties against some bacteria and fungi. Essential oils contain variable mixtures of principally terpenoids, specifically monoterpenes [C₁₀] and sesquiterpenes [C₁₅].

This report reviews part of the recent reports dealing mostly with terpenoids with anti-inflammatory, antibacterial and antifungal activities. The short review will be focused on some specific terpenoids (especially monoterpenes and sesquiterpenes) that exist in "FlorMel", a product that is in use for dental hygiene and manufactured by Zuf-Globus Laboratories. The terpenoids in "FlorMel" were detected by "The national residue control laboratory at Bet Dagan" by Prof. Stefan Soback (Table 1). Titles were screened for all hits to the terms that include the diverse compounds with or w/o the requested activities. **(The compounds in bold that mention below were detected at FlorMel product).**

Table 1: Terpenoids that were detected in FlorMel.

Terpenes:	α -pinene; phellandren; bisabolene
Terpene ketone:	Camphor; β -ionone;
Terpenes alcohols:	isomenthol; linalool oxid; α -terpineol; cis-sabinol
Sesquiterpenes:	patchoulane; junipene; santalol; capnellane-5- α -ol



1. Anti-inflammatory activity of terpenoids (general view):

Many essential oils have been used for treatment of inflammation, including some terpenoids that have been found to inhibit inflammatory cytokine (1, 2). Interleukin 6 (IL-6), which has been considered a proinflammatory cytokine, plays an important role in immune and inflammatory responses, such as tumor necrosis factor-alpha (TNF- α), a cytokine involved in systemic inflammation, and IL-1 β (3-5). A large number of studies found that essential oil containing terpenoids can inhibit the IL-6, TNF- α and IL-1 β protein expression in very significant way (6, 7).

Linalool:

Linalool and Linalool oxide are the principal components of many essential oils known to possess several biological activities, attributable to these monoterpene compounds. The linalool plays a major role in the anti-inflammatory activity displayed by some essential oils containing it. Examination of linalool and its related derivatives on carrageenin-induced edema (a known model of inflammation) exhibited significant anti-inflammatory activity (8).

Terpineol:

Terpineol is a naturally occurring monoterpene alcohol with low toxicity that has been isolated from a variety of sources. It occurs as a mixture of three isomeric hydrocarbons and used as an antiseptic compound. Its anti-inflammatory activity was established in several papers. Studies on the IL-6 formation revealed that α -terpineol had an inhibiting effect. This anti-inflammatory effect of α -terpineol on IL-6 formation was verified and it was found that α -terpineol inhibited the gene expression of the IL-6 receptor (9).



Bisabolene and bisabolol:

The sesquiterpene bisabolene and its alcohol bisabolol have been isolated from the essential oils of a variety of plants, shrubs and trees (10, 11). Bisabolol is a natural antioxidant agent, capable of reducing ROS and consequent inflammation (12). Bisabolol is frequently used in pharmaceutical and cosmetic products due to its anti-inflammatory mode of action (13). Bisabolol is also well-known for its wound-healing and anti-inflammatory properties in vivo (14). It was shown that (-)- α -Bisabolol significantly inhibited 5-lipoxygenase and cyclooxygenase (COX) in human blood cells (10).

Capnellenes:

Capnellenes are a tricyclic skeleton typical of sesquiterpenes. Anti-inflammatory activities of this group of compounds were tested using LPS (lipopolysaccharide) -stimulated cells. Stimulation of cells with LPS resulted in up-regulation of the pro-inflammatory iNOS and COX-2 proteins. Capnellene significantly reduced the levels of the iNOS protein compared with control cells stimulated with LPS (15).

2. Anti-bacterial and anti-fungal activity of terpenoids (general view):

The antimicrobial properties of plant volatile oils and their constituents from a wide variety of plants have been assessed and reviewed in many papers (16, 17). Plant volatile oils (mostly monoterpenes and sesquiterpenes) have potential in medical procedures and applications in the cosmetic, food and pharmaceutical industries (18, 19).

Dental plaques are understood to be biofilm composed of many species of bacteria, and the adhesive ability of these bacteria seems to be an important pathogenic factor. A great number of



studies are dealing with the inhibitory effect of essential oil on the adhesion of different bacteria (19, 20). It was shown that many essential oil exhibited growth-inhibiting and bactericidal effect on various bacteria, and also adhesion inhibiting effects. These essential oils seem to be promising for oral care at concentration at which they have little effect on human cells (20).

Anti bacterial activity and adhesion inhibiting effects of essential oils and their constituents were examined by *determination of minimal inhibitory dose (MID)*. Among **terpene alcohols**, the highest activity was demonstrated by geraniol. **Menthol**, α -**Terpineol** and **linalool** showed moderate activity and were comparable to each other. The activity of terpene ketones, menthone and **camphor** as well as terpene ether (1,8-cineole) was active but somewhat weaker than the terpene alcohols (20, 21).

The most abundant oil components in many essential oils are **α and β -phellandrenes**, a cyclic monoterpenes. **α -Phellandrene and β -phellandrene** have shown in vitro antifungal and antimicrobial activity against diverse bacteria (22-24). It was found that the bacteria are more susceptible to the poisoning effect of the cyclic monoterpenes at higher doses (22). The presence of monoterpene hydrocarbons in agar medium has been demonstrated to inhibit the mycelia growth of the bacteria (22).

3. Anesthetic activity of terpenoids from essential oils:

Menthol, **isomentol** and **α -terpineol** are a fragrant monoterpene alcohols derived from different essential oils and have been used for centuries as a local anesthetic, a topical analgesic and gastric sedative agents (25, 26). Investigations of this monoterpene alcohol's neuroactive properties have revealed effects on neuronal intracellular signaling and modulating neurotransmitter-gated currents. It was shown that (+)-menthol may share sites on the receptor with the known intravenous anesthetic propofol (26).



4. Inhibitory Effect of Propolis on Dental Caries Formation:

Propolis, the resinous hive product collected by bees, is known to possess antibacterial, anti-inflammatory, and anesthetic activities (27, 28). The constituents of propolis vary widely due to climate, season, location and year, and its chemical formula is not stable (29). The most important pharmacologically active constituents in propolis are aromatics (mostly monoterpenes and sesquiterpenes) and flavanoids (flavones, flavonols, flavonones) (30). In rats given water containing propolis, the total *S. sobrinus* (bacteria that is associated with the development of dental caries) counts in dental plaque did not change, while the severity of enamel and superficial dentine lesions was markedly decreased compared with the control group (30). No toxic effects of propolis were observed in rats under the conditions studied (30). These results are in agreement with other authors who state that propolis could be an effective agent for controlling dental caries (31, 32).

In summary, the overall picture of the FlorMel, due to the substances found in it and their health properties, is that it could be effective in treating medical problems in the mouth cavity including dental caries.



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