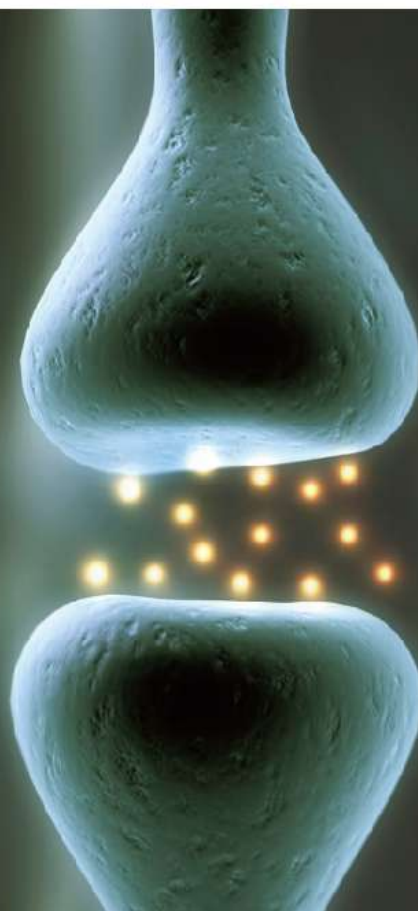


Mild Warming
Agent

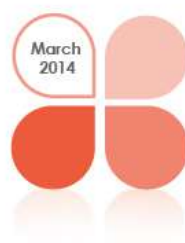


Sensory | Circulation-Enhancing Additive
Impart Exotic and Delicate **Warming** Sensation

Long-Lasting, Low-Irritation

HotFlux[®]

Vanillyl Butyl Ether





delicately warm

Relaxing.

HotFlux[®] Vanillyl Butyl Ether

Warming Agent

Mild Warming Agent

Sometimes, a small amount of additive can light up the sensory experience of a formulation. Substances known to impart a sensation of warmth upon application are called warming agents. These include capsicum (red pepper), ginger extract and vanillyl alcohol alkyl ether derivatives. Capsicum is the most used warming agent in personal care; however, it often causes skin irritation, burning and itching feelings. Often those inducing the fastest and strongest warming intensity come with short duration, especially when used at recommended levels comfortable. Alternatively, a vanillyl alcohol alkyl ether derivative, vanillyl butyl ether (VBE), was investigated as an relatively milder warming agent for personal care applications.

HotFlux[®], vanillyl butyl ether, is the kind of warming agent that has a refreshing vanilla aroma. It provides a long lasting warming effect and has a low irritation profile when compared to similar acting materials. It can be used in many types of applications, alone or together, with other warming agents. When used in such combinations, HotFlux[®] helps to reduce the irritation of the stronger materials and the blend can result in a longer lasting effect at lower usage level.

Claim Ideas for HotFlux[®]

- ◆ Impart exotic warming sensation
- ◆ Enhance microcirculation
- ◆ Help stimulate hair growth

Applications

- ◆ Massage
- ◆ Slimming
- ◆ Spa
- ◆ Pain relief
- ◆ Intimacy

Storage

- ◆ Protect from light, heat and moisture.
- ◆ Keep at temperature between 6~24°C.

Formulation Guide

- ◆ Recommended pH value range:
pH 6-6.5

INCI Declaration

- ◆ Product name : HotFlux[®]
- ◆ INCI (English) : Vanillyl Butyl Ether
- ◆ INCI (Chinese) : 香兰基丁基醚

Additional Information

- ◆ Purity (%): 98% Min
- ◆ Europe REACH registered
- ◆ China approved
- ◆ HALAL approved

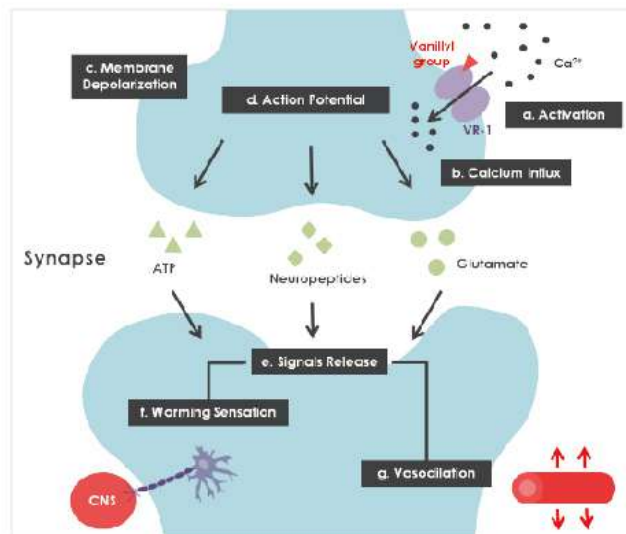


The Mechanism of Warming Sensation

The vanillyl group of HotFlux[®] is the functional group that plays key role in inducing the warming sensation via nervous system. The sensory neurons are activated through the binding of the vanillyl group to its receptor, vanilloid receptor-1 (VR-1), a non-selective cation channel that naturally responds to noxious stimuli, such as high temperatures or acidic pH. Upon ligand/receptor binding, the channel opens and leads to an influx of predominantly calcium ions through the channel pore. In turn, this action causes membrane depolarization that, once reaching a threshold, generates an action potential that is propagated along the axon to the synapse.

Activated sensory neurons will release glutamate, ATP and a variety of neuropeptides as neurotransmitters from the synapse. These neurotransmitters eventually reach the central nervous system and launch a cascade of warming sensation, which can also be similarly triggered by temperature of $\geq 43^{\circ}\text{C}$. Among the neurotransmitters, calcitonin gene-related peptide (CGRP) is one of the known neuropeptides released upon activation, which acts on vascular endothelial cells to trigger vasodilation, therefore increases the blood circulation.

The Mechanism of Warming





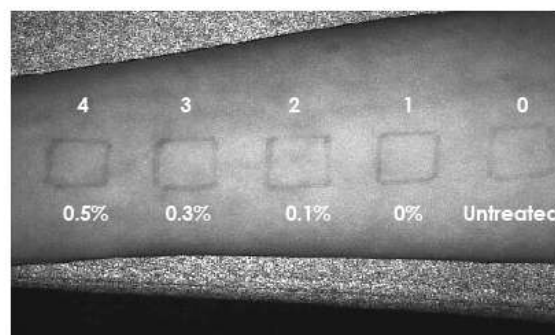
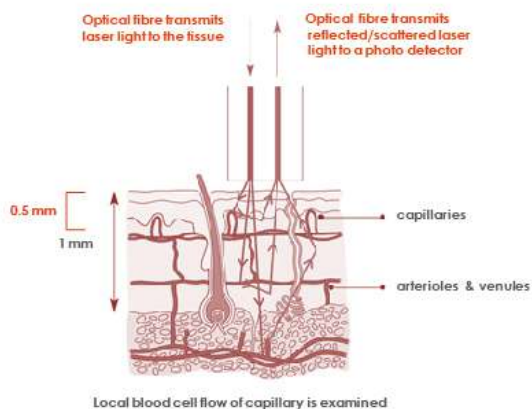
Microcirculation Enhancement Experiment

Laser Doppler Flowmetry (LDF) is an accurate and reliable method for assessing microcirculatory function. This apparatus is composed of a low-power laser and probe that takes readings and sends results to an analyzer. The apparatus can penetrate 1-4 mm of tissue, hence capable of detecting microcirculation in the capillaries residing 0.5 mm underneath the skin. The LDF quantifies the flux of red blood cells (RBCs), defined as the number of RBCs times their velocity, which determines capillaries circulation. Here, we used LDF to examine the vasodilation effects of HotFlux[®] applied at various concentrations in topical creams.

21 volunteers comprising 14 females and 7 males, age between 21 to 40 years old, were recruited in this study. Volunteers washed their forearms with a mild detergent and rested for 20-30 minutes in an air-conditioned room under constant temperature and humidity before the study commences. Their forearms, as the testing site, were maintained and monitored using laser speckle contrast imager in comparison with both the untreated and placebo areas.

Prior to application, the local blood cell flux (BCF) at tested sites was monitored until stabilized and recorded for five minutes. Four 0.01g sample creams with 0%, 0.1%, 0.3% and 0.5% of HotFlux[®] were applied to the subjects' forearm within the labeled areas, respectively. The untreated site was monitored for the relaxed state, and each site having the first five minutes serves as its own control. The laser imager assessed the HotFlux[®]-induced increase in BCF for 45 minutes continuously, and the results were analyzed in detail with specialized software.

Laser Doppler Flowmetry



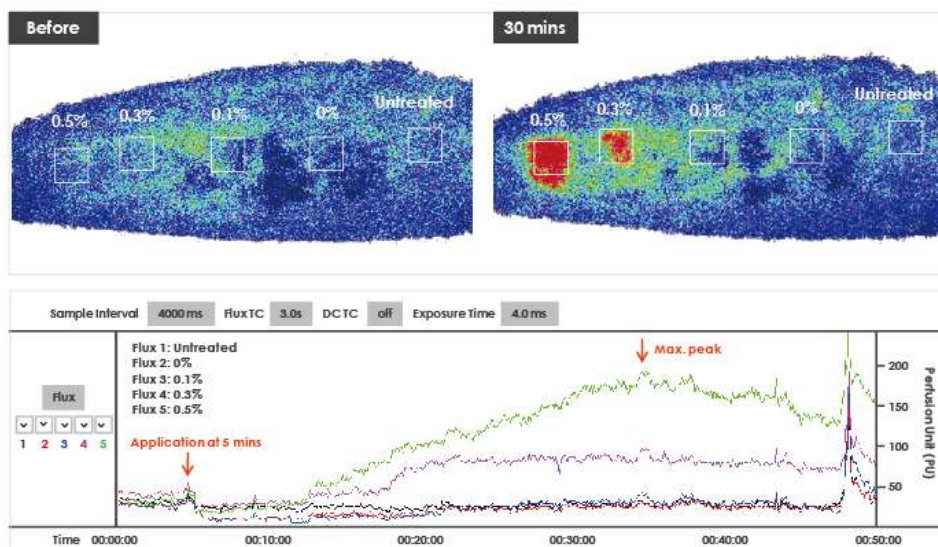


Microcirculation Enhancement

The blood flow curve diagram indicates that the perfusion unit (PU) on Y axis remained constant during the first 5 minutes before application of sample cream at all treated sites. The same constant perfusion was observed in the untreated site throughout the period of monitoring. After sample cream application, HotFlux[®] at 0.3% and 0.5% exhibit an increase in BCF as shown from the changes in the blood flow (PU) curve. On the other hand, there was no significant increase in perfusion at the untreated and placebo areas.

30 minutes after sample cream application, the increases in BCF were significant at both 0.3% and 0.5% use level of HotFlux[®]. The results also show that HotFlux[®] provides prolonged microcirculation enhancement of over 30 minutes.

Enhancement of Blood Flow





Microcirculation Enhancement

A more in-depth analysis and other parameters were also explored in this study. Upon application of sample cream, an immediate decrease in the averaged BCF in all treated sites was recorded. This is possibly due to the lower temperature of the test creams compared to skin. However, 10 minutes after application, HotFlux[®] cream demonstrated great performance in microcirculation enhancement - 0.3% and 0.5% HotFlux[®] can increase the perfusion up to 30.24% and 66.4%, respectively, throughout the whole process.

Other measurable responses following the topical application were recorded, as shown in Table 1. Results indicate that 17 out of 21 volunteers (80.95%) showed an increase in perfusion with 0.3% HotFlux[®], while with 0.5% HotFlux[®], 16 volunteers (76.19%) have increased perfusion.

The warming sensation was further evaluated via a self-assessment, where 19 volunteers felt warming sensation with both 0.3% and 0.5% HotFlux[®] application. Dose-dependent increase in warming sensation and the average BCF increase were observed. The onset time point of the perfusion increase and the peak response time were related to the dosage of applied concentration. It is also reported that the onset and maximum peak warming sensation occurred more rapidly when applied with 0.5% than 0.3% HotFlux[®]. The average duration of the perfusion in all subjects was more than 30 minutes, and no subjects reported pain or discomfort at the treatment sites throughout the process.

Enhancement of Blood Flow

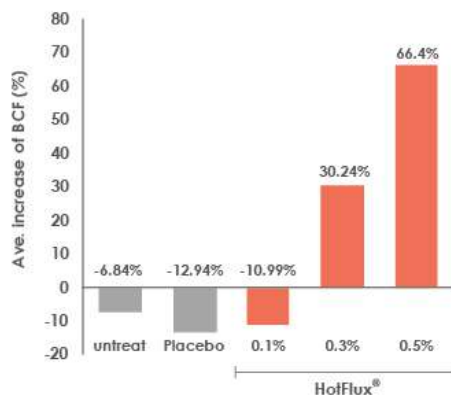


Table 1

Conc. (%)	Measurable Response (n / total)	Warming Sensation (n / total)	Ave. Percentage Increase (%)	Initial Response Time (min)	Max. peak onset time (min)	Ave. Duration Time (min)
untreated	4/21	0/21	-6.84	n.a.	n.a.	n.a.
0	3/21	0/21	-12.94	n.a.	n.a.	n.a.
0.1	5/21 (23.81%)	10/21	-10.99	14.93	28.6	>30.8
0.3	17/21 (80.95%)	19/21	30.24	10.47	23.5	>30.8
0.5	16/21 (76.19%)	19/21	66.40	9.58	22.1	>32.0

HotFlux[®]

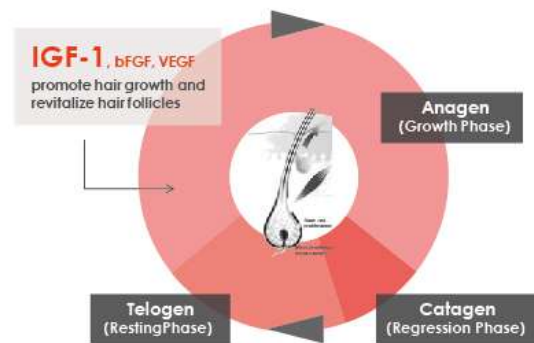
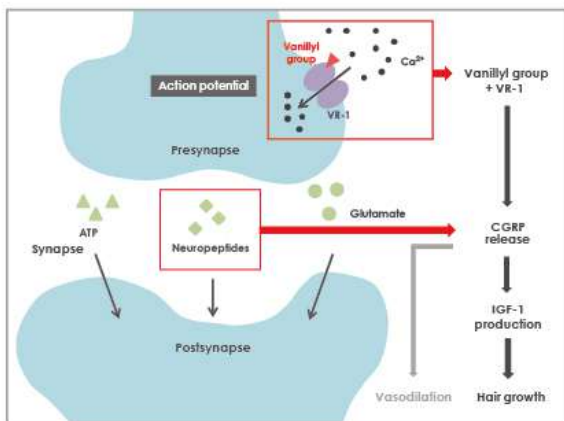
Helps Rejuvenate Hair Growth

Hair Loss: The Most Distressing Problem of the Scalp

Approximately 1.8% of the world population is experiencing hair loss, which is a common phenomenon troubling both male and female throughout their lifetime. Common causes of hair loss include stress, genetics, drugs, disease, and extensive hair styling, etc. As hair contributes to an individual's physical attractiveness and body image, hair loss could be an emotionally distressing condition that makes those affected particularly vulnerable by altering their self-esteem and overall quality of life.

Certain well-known hair loss treatments work to inhibit dihydrotestosterone (DHT), improve vasodilation, and stimulate hair stem cells. HotFlux[®], as a potential ingredient that enhances microcirculation, facilitates the delivery of nutrients to hair follicles. It also helps to increase the synthesis of insulin-like growth factor-1 (IGF-1), a growth factor that stimulates the proliferation of hair stem cells during the growth (anagen) phase of the hair cycle. Upon VR-1 activation, one of the released neuropeptides, calcitonin gene-related protein (CGRP), targets and induces an increase in the expression of IGF-1, and thus its synthesis.

The Hair Growth Cycle





Peripheral Circulation as a Key Factor for Hair Growth

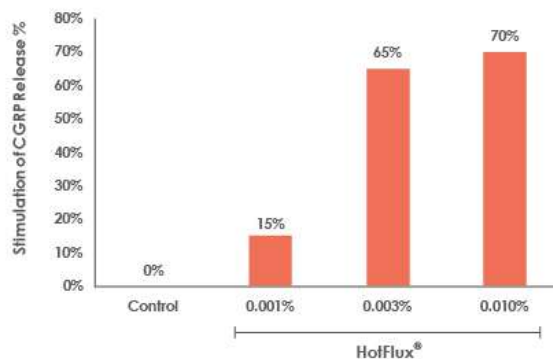
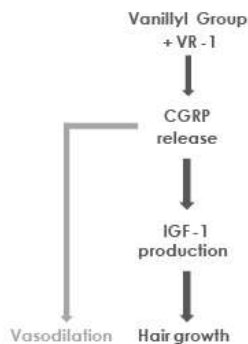
Diminished peripheral circulation has been implicated as a major cause to senescence- or age-related hair thinning. A study of young men diagnosed with male pattern baldness (androgenetic alopecia) showed that the blood flow to their scalps was an average 2.6 times lower than the normal control group, as their follicles had been deprived of blood and nutrients over an extended period of time. Another research by world's leading cosmetic company also identified diminished circulation as a critical element of the balding process that needs to be treated. Thus scalp massage is said to increase blood flow, which in turn promotes hair growth. In the light of these researches, formulating hair products with a microcirculation-stimulating active can effectively enhance the anti-hair loss effect of hair and scalp treatments.

The Effect of HotFlux[®] on CGRP Release by Sensory Neurons

It is reported that oral administration of capsaicin can improve hair growth in patients with alopecia. HotFlux[®], which contains the same vanillyl group as capsaicin, was studied to understand if similar effect exists. Different concentrations - 0.001%, 0.003% and 0.01% of HotFlux[®] was applied to an *in-vitro* primary neuron model. The release of CGRP by sensory neurons was then evaluated.

Data shows that HotFlux[®] have similar effect as capsaicin. A concentration-dependent release of CGRP by sensory neurons was observed - 15%, 65% and 70% of stimulation, respectively, without any cytotoxic effect.

Stimulation of CGRP





Claim Ideas for HotFlux®

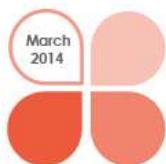
- Impart exotic warming sensation
- Enhance microcirculation
- Help stimulate hair growth

Applications

- Warming cream/ lotion (head, hand, foot and body)
- SPA product (massage, scrub)
- Slimming product
- Hair & scalp product
- Personal lubricant
- Color cosmetics (lip gloss)
- Pain-relief product (ointment, patch)
- Anti-cellulite product

Marketing Benefits

- Safer than other warming agents
- Non mutagenic and less irritating
- Longer lasting duration



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