Second-Generation Cosmeceutical Cytokinin: Pyratine

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Cytokinins are a class of phytohormones that promote cell division in plants and human keratinocytes. Two cytokinin ingredients, kinetin and zeatin, have been used in cosmeceuticals as active ingredients since the early 2000s after bursting onto the skin care scene as antiaging alternatives for sensitive skin. A second-generation cytokinin, Pyratine-6, featuring a tetrahydropyranyl moiety (Figure 1), has been commercially available to physicians in North America since early 2008 in a cream and lotion form. It is still early, but clinical studies and clinical experiences indicate Pyratine-6 has a positive effect on photodamage and the signs and symptoms of rosacea.

History of Cytokinins

Fifty-four years ago, kinetin was first isolated from autoclaved herring sperm DNA and showed cell division–promoting effects.[1] In 1954, Professor Folke Skoog developed a technique for the generation and culture of wound tumor tissue from isolated tobacco shoots.[2] This callus grew in the presence of yeast extract, coconut milk, or old DNA preparations. Fresh DNA only stimulated plant growth after being autoclaved. This led to the conclusion that one of the breakdown products of DNA was required for stimulation of plant cell growth and division. After isolation and characterization, this substance was identified as kinetin or 6-furfurylaminopurine.[3]

Since the mid-1990s there has been great interest in these compounds as antiaging skin actives for cosmeceuticals. Kinetin has been shown to induce differentiation of human keratinocytes undergoing aging in vitro.[4] In another in vitro evaluation, a reconstructed skin equivalent was supplemented with kinetin in culture medium and showed an increase in Ki-67 positive cells, filaggrin and laminin 5, and fibrillin and elastin fiber. The position of elastin fiber was organized more perpendicular to the dermoepidermal junction.[5] Kinetin has been isolated from plant extracts,[6] as well as from human urine,[7] and is now believed to be a natural by-product of DNA damage in all human cells, which increases in proportion to oxidative stress. At the time, very little was known of the clinical significance of a topically applied product to skin. According to a report of tests on human fibroblasts with pyranyl kinetin,[8] fibroblasts produce more collagen and elastin, antioxidant effects were noted, and prevention of reversion of actin patterns was documented, which helps maintain cell structure and delay the senescence of cells by removing cellular debris.

Clinical Studies

Early animal studies in hairless dogs showed a reduction of hyperpigmentation and wrinkling between 50 to 100 days.[9] The histologic correlates were confirmed to be a reduction in stratum corneum width and melanin granule number in keratinocytes, as well as larger numbers of fine collagen and elastic fibers that were densely aligned. There were no histologic abnormalities in the epidermis and the dermis.

An open-label clinical study conducted at the University of California, Irvine, recruited 17 participants with type I or II rosacea. Participants were to apply kinetin lotion to their skin twice daily along with a sunscreen containing SPF 30 for 12 weeks.[10] On average, results revealed a 32% reduction of erythema, and 58.8% of the participants showed moderate to marked improvement. There was no reduction in inflammatory lesions. Symptoms of burning, stinging, and dryness were reduced in a statistically significant fashion. At the end of the treatment, 88.2% of subjects rated skin tolerance as good and 100% rated cosmetic acceptability as good to very good. There were no study-related adverse events. There was a reduction in skin mottling and roughness but no apparent clinical reduction in wrinkling.

The company that developed the kinetin-containing line Kinerase recently launched a second cytokinin agent Pyratine-6, formed from the fusion of a tetrahydropyranol group with the kinetin molecule. According

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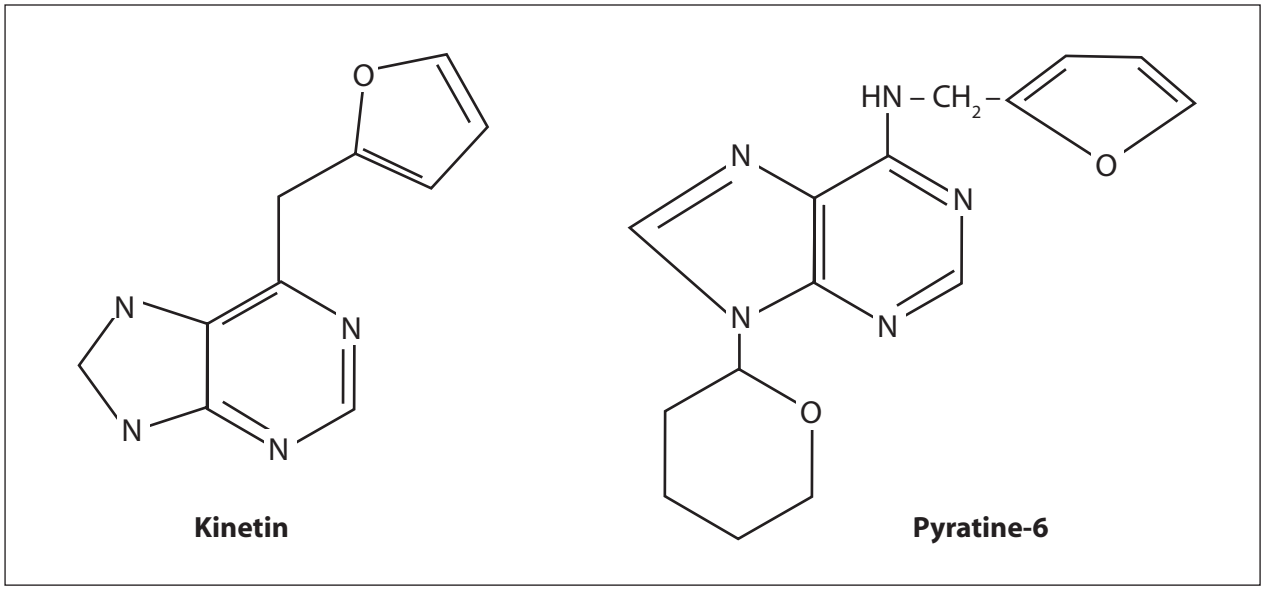

Figure 1. Chemical structure of kinetin and Pyratine-6.

to the company, an independent research laboratory conducted similar testing on human participants who applied Pyratine-6 twice weekly to the face for 12 weeks. At 8 weeks, they found a 22% improvement in fine wrinkles, an 86% improvement in skin roughness, and a 24% improvement overall in aging skin.[11] New testing methods not available at the time of kinetin's evaluation, such as the NOVA Dermal Phase Meter for measuring the skin's moisture content, were utilized and revealed a 35% increase in the skin's moisture after 8 weeks. According to this report, experts evaluated a 42% reduction in erythema after 2 weeks (Figure 2) and a 45% reduction in acne lesions after 12 weeks.

Forty women with mild to moderate facial photodamage were enrolled in a 12-week, open-label trial to determine the antiaging potential of Pyratine-6 0.1% lotion. Significant changes in skin roughness and erythema were noted after 2 weeks, whereas significant changes in fine wrinkling (Figure 3) and mottled pigmentation were noted after 4 weeks.[12] Results of this trial are noted in Figure 4.

Figure Not Available Online

Figure 2. Female patient with acne and rosacea before (A) and 52 weeks posttreatment with Pyratine-6 (B).

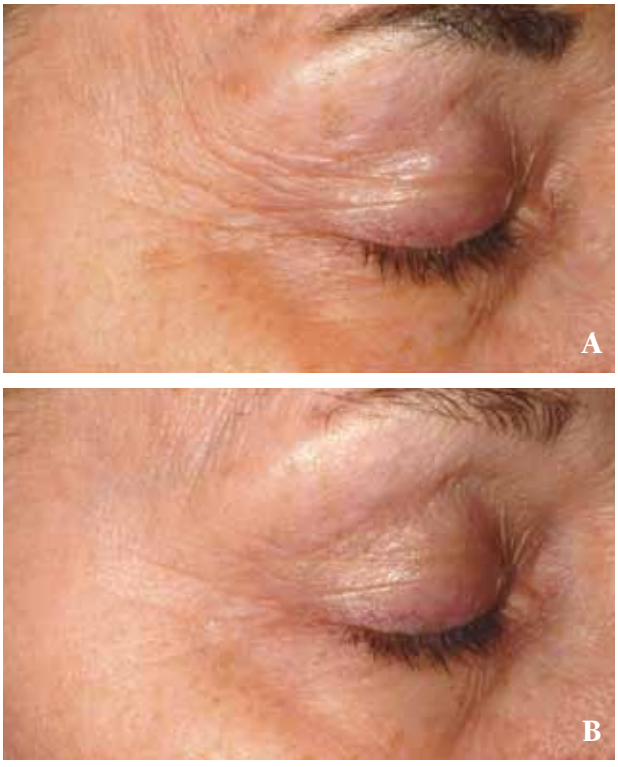

Figure 3. Female patient with fine wrinkling before (A) and 4 weeks posttreatment with Pyratine-6 (B).

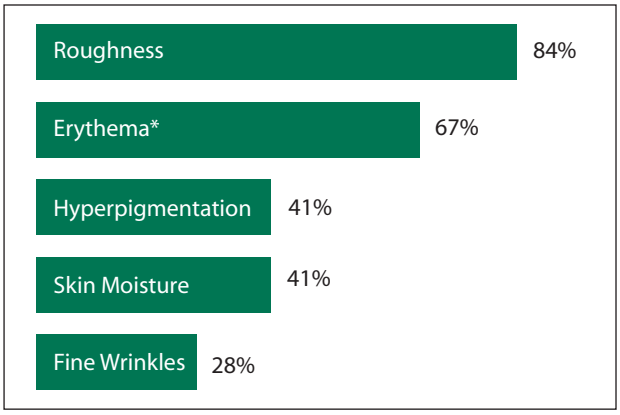

Figure 4. Results of a 12-week, open-label trial to determine the effects of Pyratine-6 0.1% lotion in 40 women with mild to moderate facial photodamage. Asterisk indicates participants with erythema at baseline.

A lotion with a higher strength, containing 0.125% furfuryl tetrahydropyranyladenine, has been tested in a 12-week, open-label study to determine its efficacy in patients with mild to moderate rosacea.[13] Twenty-four healthy male and female participants with moderate erythematotelengiectatic rosacea, papulopustular rosacea, or both, with a mean age of 51 years were enrolled in the study. All participants applied the lotion twice daily to the face. Eighty-eight percent of participants had mild to moderate rosacea. After 12 weeks, there was a reduction in erythema and papules, with an overall clinical improvement in 80% of participants, as well as a significant reduction in transepidermal water loss. A follow-up extension study[8] of 18 participants using the lotion for 48 weeks revealed a 90% improvement in lesions, a 48% improvement in erythema, and a 28% improvement in telangiectasia.

Clinical Usage

Kinetin and zeatin have been widely used as moisturizing and antiaging agents during the last 6 years. Pyratine-6 has been commercially available since September 1, 2008. In the cosmeceutical boutique of the author's practice, Pyratine-6 was found to be highly replenished. Obviously not a scientific measure, the rate of replenishment in the author's boutique is a testimonial to patients' perceptions of a product's effectiveness. Pyratine-6 is expensive and, notwithstanding the placebo effect, patients seem to be discerning.

The author began recommending Pyratine-6 as an adjunctive therapy for patients with rosacea after initially thinking it was similar to kinetin, a highly tolerated, mildly beneficial moisturizer for patients with sensitive skin and rosacea. After a couple of months, patients were expressing very positive feedback, especially patients with long-term rosacea who had plateaued and were seeking new and more effective products. The author started using Pyratine-6 then, not as adjunctive therapy but as a substitution, for patients who found either metronidazole 1% gel or azelaic acid 15% gel drying or irritating. Again the author received positive feedback, even from these patients with very sensitive skin. After 6 months of experience with this cosmeceutical, the author now uses it as a first line therapy for rosacea and recommends it regularly as an antiaging treatment for patients with sensitive skin. Patients have liked it and tolerated it, have noticed a real improvement in the signs and symptoms of rosacea, and have noticed an improvement in how their skin looks and feels.

Recently, the higher concentration product, Pyratine-XR, was released for specific use in patients with rosacea. The author looks forward to utilizing this agent in the future as well as other cytokinins in the pipeline. Further testing in a multicenter, randomized, placebo-controlled fashion would be welcomed and is now justified by this early work and experiences. Determining the mechanism of action for reduction of erythema could further our knowledge of the etiology of rosacea.

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