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Current Science on the Hair Growth Promoting Effects of Procyanidins: a review of the medical literature in 2007

In 1999, a group of scientists at Tsukuba Research Laboratories in Ibaraki, Japan published the first studies showing hair growth promoting effects of procyanidin chemicals extracted from apples.

Since these first reports were published, multiple studies in cells, animals and human clinical trials have confirmed the effectiveness of procyanidins to intensively and safely promote hair growth.

Herein we review the available published literature, with emphasis on both results of these inquiries, and the current understanding of the mechanisms by which procyanidins promote hair growth and follicle production.

J Invest Dermatol. 1999 Mar;112(3):310-6.

Procyanidin oligomers selectively and intensively promote proliferation of mouse hair epithelial cells in vitro and activate hair follicle growth in vivo.

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We have previously reported that proanthocyanidins extracted from grape seeds possess growth-promoting activity toward murine hair epithelial cells in vitro and stimulate anagen induction in hair cycle progression in vivo. This report constitutes a comparison of the growth-promoting activity of procyanidin oligomers and the target cells of procyanidins in the skin. Results show that procyanidin dimer and trimer exhibit higher growth-promoting activity than the monomer. The maximum growth-promoting activity for hair epithelial cells with procyanidin B-2, an epicatechin dimer, reached about 300% (30 microM) relative to controls (= 100%) in a 5 d culture. Optimum concentration of procyanidin C-1, an epicatechin trimer, was lower than that of procyanidin B-2; the maximum growth-promoting activity of procyanidin C-1 was about 220% (3 microM). No other flavonoid compounds examined exhibit higher proliferative activities than the procyanidins. In skin constituent cells, only epithelial cells such as hair keratinocytes or epidermal keratinocytes respond to procyanidin oligomers. Topical application of 1% procyanidin oligomers on shaven C3H mice in the telogen phase led to **significant hair regeneration** [procyanidin B-2, 69.6% +/- 21.8% (mean +/- SD); procyanidin B-3, 80.9% +/- 13.0%; procyanidin C-1, 78.3% +/- 7.6%] on the basis of the shaven area; application of vehicle only led to regeneration of 41.7% (SD = 16.3%). In this paper, we demonstrate the hair-growing activity of procyanidin oligomers both in vitro and in vivo, and their potential for use as agents to induce hair growth.

EXCERPT: "We report here that procyanidin oligomers possess selective and intensive growth-promoting activity with respect to hair epithelial cells in vitro and stimulate anagen induction *in vivo*."
RESULTS: "Procyanidin dimer and trimer selectively and intensively promote growth of hair epithelial cells."

Highlights of this study:

- ⇒ **The first published report of the hair growth effects of procyanidin compounds from apples**
- ⇒ **Hair growth activity shown in both test tube (*in vitro*) and animals (*in vivo*)**
- ⇒ **Describes "significant hair regeneration" *in vivo***
- ⇒ **Procyanidins twice as effective as minoxidil *in vitro***
- ⇒ **Procyanidins shown as effective as minoxidil in anagen induction *in vivo***

"Procyanidin oligomers... induce anagen phase efficiently in hair cycle progression in the murine model to the same degree as minoxidil."

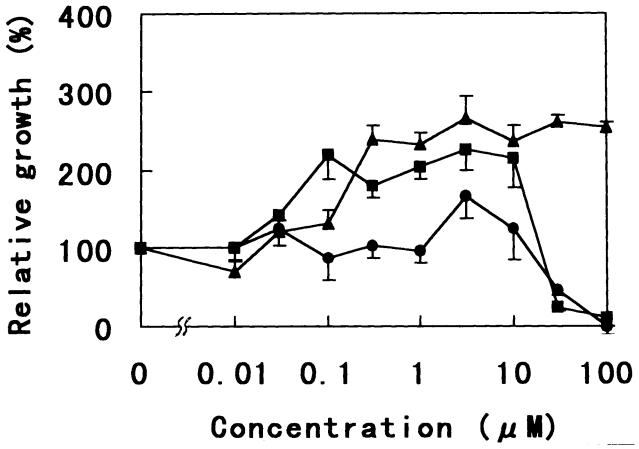

Figure 7. Procyanidin dimer and trimer intensively promote the growth of mouse keratinocytes to a greater extent than the procyanidin monomer. Growth-promoting activities for keratinocytes relative to controls (=100%) are shown. Procyanidins were added to the culture during the last 6 d. For the control, a medium without procyanidins was used. ●, (–)-Epicatechin; ▲, procyanidin B-2; ■, procyanidin C-1. Results are represented as the mean ± SD (n = 6) carried out with primary cultures prepared from 50 neonatal mice.

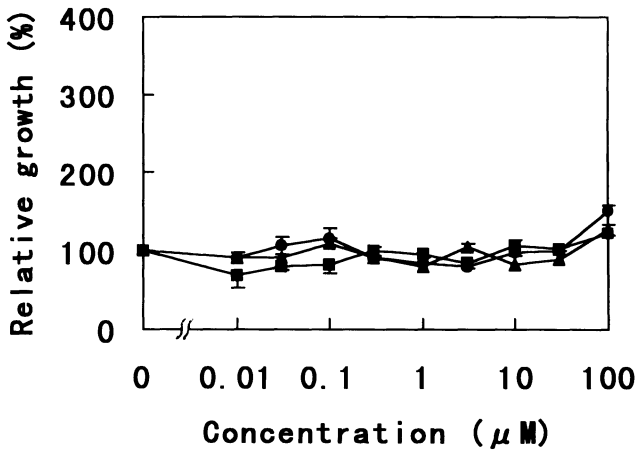

Figure 8. Dermal fibroblasts did not respond when exposed to procyanidins with different degrees of polymerization. Growth-promoting activities for dermal fibroblasts relative to controls (=100%) are shown. Procyanidins were added to the culture during the last 4 d. For the control, a medium without procyanidins was used. ●, (–)-Epicatechin; ▲, procyanidin B-2; ■, procyanidin C-1. Results are represented as the mean ± SD (n = 6) carried out with primary cultures prepared from 50 neonatal mice.

In this assay system, minoxidil gave a positive response. After a 19 d application of 1% minoxidil-containing agent, about 80% (81.2% ± 10.5%, average ± SD) of the shaven area was covered with hair. The control group to which vehicle was applied, on the other hand, showed little hair growth: only about 40% (41.7% ± 16.3%) of the shaven area was covered with hair on day 19. The groups to which 1% procyanidin oligomers had been applied showed an extensive growth area [procyanidin B-2, 69.6% ± 21.8% (average ± SD); procyanidin B-3, 80.9% ± 13.0%; procyanidin C-1, 78.3% ± 7.6%] on day 19 (**Fig 9**).

These results demonstrate that procyanidin oligomers, such as procyanidin B-2, procyanidin B-3, or procyanidin C-1, possess marked hair-growing activity to induce anagen phase *in vivo*. On the other hand, neither (+)-catechin nor (–)-epicatechin, a flavan-3-ol unit of procyanidins, stimulated anagen induction *in vivo* (data not shown).

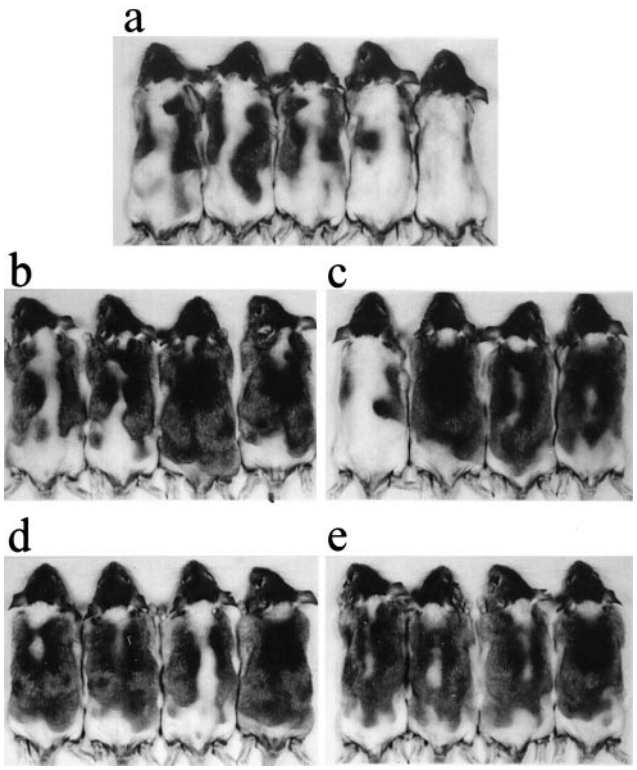

Figure 9. Procyanidin oligomers are able to induce anagen phase efficiently in hair cycle progression in the murine model to the same degree as minoxidil. Photographs were taken after the topical application of test agents for 19 d. Test agents were applied to 8 wk old C3H telogen mice (♂), 200 μl per d per mouse. (*a*) Vehicle; (*b*) 1% minoxidil; (*c*) 1% procyanidin B-2; (*d*) 1% procyanidin B-3; (*e*) 1% procyanidin C-1.

DISCUSSION

Proanthocyanidins Proanthocyanidins have been used as medications aimed at protecting the capillary vessels (Dartenuc *et al*, 1980), as cosmetics to protect the skin (Wayne *et al*, 1996), and as antioxidants in foods and beverages; however, there has been very little information gathered on the correlation between their degree of polymerization and properties. Barnard *et al* (1993) report that proanthocyanidin polymers possess anti-viral activities against the herpes virus. Ariga *et al* (1988) report that its anti-oxidant properties increase in proportion to the degree of polymerization. The profile of the proanthocyanidins from grape seeds in which we first discovered their hair-growing activity is as follows: the constitutive monomers were catechin and epicatechin, the degree of polymerization was 3.5, and the galloylation rate was 25% at the molar ratio per constitutive flavan-3-ol unit (Takahashi *et al*, 1998). Here, we investigated which proanthocyanidin molecules possess the highest hair-growing activity. It was revealed that among the monomer, dimer, and trimer of procyanidins, procyanidin dimer possesses the highest growth-promoting activity. The order of optimum concentration showing the maximum proliferative activity was trimer < dimer < monomer. In *in vivo* hair-growing activity to induce anagen phase, the intensity of dimers and trimers was almost equal; however, neither (–)-epicatechin nor (+)-catechin, monomers of proanthocyanidins, stimulated anagen induction. In *in vitro* and *in vivo* assays, we could find no difference between dimeric isomers composed of different monomers: procyanidin B-1, procyanidin B-2, and procyanidin B-3. The excision of gallate using tannase from proanthocyanidins purified from grape seeds raises the activity *in vitro* and *in vivo* (data not shown). Our *in vitro* studies led to the discovery of no other active flavonoid compounds. The procyanidin compounds we examined were built only of flavan-3-ol, so hair-growing activity may be associated with this structure.