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Piceatannol enhances hyaluronic acid synthesis through SIRT1-Mediated HAS2 upregulation in human dermal fibroblasts

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ABSTRACT

Dermal fibroblasts play a crucial role in skin structure and function by producing hyaluronic acid. Piceatannol (PIC), a polyphenol abundant in passion fruit seeds, has been reported to activate sirtuin 1 (SIRT1). Clinical trials have demonstrated that PIC intake improves skin moisture and maintains skin elasticity, yet the underlying mechanism remains unclear. This study aimed to investigate the effects of PIC on hyaluronic acid biosynthesis and the involvement of SIRT1 in this process. Human dermal fibroblast Hs68 cells were stimulated with PIC, and the expression levels of *HAS2* and *HYAL2*, key enzymes in hyaluronic acid biosynthesis, as well as *SIRT1* expression, were assessed using quantitative real-time PCR. Additionally, the role of *SIRT1* in the hyaluronic acid biosynthesis pathway during PIC stimulation was examined using a SIRT1 inhibitor. The results demonstrated that PIC increased *HAS2* expression while decreasing *HYAL2* expression in human dermal fibroblasts. Furthermore, PIC enhanced *SIRT1* expression, and pre-treatment with a SIRT1 inhibitor mitigated PIC-induced upregulation of *HAS2*, suggesting that PIC promotes hyaluronic acid synthesis by inducing *SIRT1*. These findings suggest that PIC could serve as a beneficial food ingredient, enhancing skin structure and function by promoting hyaluronic acid biosynthesis via *SIRT1* induction.

1. Introduction

Skin fibroblasts, residing in the dermis, play a crucial role in skin structure maintenance by producing collagen, elastin, and hyaluronic acid. Collagen and elastin fibers impart elasticity to the skin, while hyaluronic acid, situated between these fibers, moisturizes the epidermis by retaining water [1]. Hyaluronic acid, a linear glycosaminoglycan composed of D-glucuronic acid and *N*-acetyl-D-glucosamine with a molecular weight exceeding 1 million, is regulated by a balance between synthesis and degradation [2,3]. There are three types of hyaluronic acid synthases (HAS1-3), contribute to its synthesis, and HAS2 is the predominant hyaluronic acid synthase isoform expressed in dermal fibroblasts [4,5]. Additionally, six hyaluronic acid-degrading enzyme (HYAL) genes, including HYAL1, 2, and 3, are universally expressed in somatic tissues [6,7]. HYAL2, in particular, plays a significant role in hyaluronic acid degradation, specifically hydrolyzing hyaluronic acid up to approximately 20 kDa [8]. In addition, it has been reported that transmembrane protein 2 (TMEM2) plays a role as a cell surface hyaluronidase in cleaving high-molecular weight hyaluronic acid into intermediate-sized fragments [9]. Maintaining and increasing hyaluronic acid levels is vital since its decline with aging leads to reduced skin water retention and elasticity [10].

Piceatannol (PIC), a polyphenol abundant in passion fruit seeds [11], possesses four hydroxyl groups. PIC exhibits robust antioxidant activity [12], and notably induce heme oxygenase-1 (HO-1), a potent antioxidant, more than other polyphenols such as epigallocatechin gallate (EGCG) and resveratrol [13]. Previous studies have highlighted PIC's positive effects on skin [14], including improvements in moisture and elasticity with continuous intake [15–17]. Passion Fruit seeds extract containing PIC has been shown to exhibit antibacterial activity against *Propionibacterium acnes* [18]. Moreover, PIC suppresses UV-induced reactive oxygen species production in human epidermal keratinocytes [19] and enhances collagen synthesis in human fibroblasts [11], contributing to its role in skin function enhancement. However, its impact on hyaluronic acid production in human dermal fibroblasts remains unclear.

PIC's functionality includes activating sirtuin 1 (SIRT1) [20,21], a member of the sirtuin family, which are NAD^+-dependent enzymes regulating energy metabolism. SIRT1, among seven isoforms (SIRT1-7) in mammals, deacetylates target proteins, initiating mRNA transcription

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and regulating enzyme activity [22,23]. In skin fibroblasts, SIRT1 governs collagen biosynthesis by modulating collagen production and degradation [24–28]. Nonetheless, the influence of SIRT1 on hyaluronic acid biosynthesis in the skin remains elusive.

This study aims to elucidate PIC's effects on hyaluronic acid biosynthesis in human fibroblasts. Additionally, with a focus on *SIRT1*, we investigate PIC's impact on *SIRT1* expression in fibroblasts and its involvement in hyaluronic acid biosynthesis.

2. Materials and methods

2.1. Cell culture

Human dermal fibroblast Hs68 cells (JCRB Cell Bank, Japan) were cultured in Dulbecco's modified Eagle's medium (DMEM, Gibco, USA) supplemented with 10 % fetal bovine serum (FBS, Global Life Sciences Technologies Japan K·K., Japan) and 1 % penicillin-streptomycin (Gibco, USA) at 37 °C in a 5 % CO_2 environment. Prior to stimulation with test compounds, the medium was replaced with DMEM containing 0.5 % FBS, and the cells were cultured for 24 h. Test compounds, dissolved in dimethyl sulfoxide (DMSO), were diluted in 0.5 % FBS-DMEM to the desired concentrations and added to the cells. The final concentration of DMSO in the medium was 0.1 % under all conditions, and no cytotoxicity was observed under these study conditions.

2.2. RNA isolation and quantitative real-time PCRs

Hs68 cells were seeded in 12-well plates and incubated for 3 d until confluence was reached. Subsequently, cells were treated with PIC for either 6 or 16 h. When Ex-527 (Merck, USA), a SIRT1 inhibitor, was utilized, cells were pretreated for 6 h before PIC treatment. Total RNA was extracted and reverse-transcribed as described previously [13]. During RNA extraction, DNase treatment was performed to avoid DNA contamination. mRNA levels were analyzed by quantitative real-time PCR employing a Light Cycler® 96 (Roche, Switzerland) and the KAPA SYBR Fast qPCR Kit (Kapa Biosystems, Inc., USA), following the recommended protocol of the reagents. The amplification conditions were as follows: 95 °C for 3 min; and 45 cycles each of 95 °C for 10 s, 60 °C for 20 s and 72 °C for 1 s. The primer sequences utilized in this study are detailed in Table 1. Target gene expressions were normalized to *GAPDH* mRNA expression levels.

2.3. Statistical analysis

Each experiment was conducted independently a minimum of three times. Results are expressed as mean ± standard deviation (SD). Group comparisons were assessed using the unpaired Student's t-test for two groups. For three or more groups, Dunnett's or Tukey's tests were employed. Statistical significance was defined as $p < 0.05$. All statistical analyses were conducted using SPSS software version 26 (IBM, USA).

3. Results

3.1. Effect of PIC on gene expression in human dermal fibroblasts

Preliminary cytotoxicity assays using the WST-8 showed that PIC concentrations above 50 μM greatly reduce cell viability, leading to a maximum treatment concentration set at 20 μM in this study. PIC treatment for 16 h resulted in a significant increase in *HAS2* mRNA expression (Fig. 1A) and a significant decrease in *HYAL2* mRNA expression (Fig. 1B), indicating that PIC affects the expression of these key enzymes involved in hyaluronic acid biosynthesis. However, *HAS1* and *HAS3* mRNA expressions were not significantly changed under these conditions (data not shown).

3.2. Impact of PIC on SIRT1 expression

Given the observed alterations in hyaluronic acid-related gene expression (Fig. 1), particularly *HAS2* and *HYAL2*, we investigated the potential involvement of SIRT1. PIC treatment notably increased the mRNA level of *SIRT1* in human dermal fibroblasts (Fig. 2).

3.3. Involvement of SIRT1 in PIC-mediated regulation of HAS2

To ascertain the involvement of SIRT1 in the stimulatory effect of PIC on *HAS2* and *HYAL2* expression, we conducted experiments using a SIRT1 inhibitor, Ex527. Pre-treatment with Ex527 attenuated the PIC-induced increase in *HAS2* mRNA expression (Fig. 3A), indicating that the induction of *HAS2* by PIC is mediated by SIRT1. However, the downregulation of *HYAL2* by PIC was unaffected by the addition of a SIRT1 inhibitor under these conditions (Fig. 3B), suggesting that the role of SIRT1 in the regulation of *HYAL2* by PIC remains unclear.

4. Discussion

In this study, we observed that PIC stimulated hyaluronic acid biosynthesis in human skin fibroblasts by upregulating *HAS2* expression and downregulating *HYAL2* expression. Furthermore, the induction of *HAS2* by PIC was impeded by a SIRT inhibitor, suggesting that PIC enhances *HAS2* expression via increased *SIRT1* expression. Previous clinical trials have demonstrated that PIC intake enhances skin moisture and elasticity [15–17], and our findings suggest that the upregulation of hyaluronic acid biosynthesis by PIC contributes to these improvements in skin function. Notably, PIC has been reported to induce *HAS2* mRNA expression in mouse fibroblasts [29], and our study reveals that PIC also suppresses hyaluronic acid degradation, shedding light on the mechanisms underlying its effects on human skin. While there are limited reports on the effects of polyphenols on hyaluronic acid synthesis, green tea extract containing polyphenols such as EGCG has been shown to induce *HAS2* expression in fibroblasts [30]. Conversely, certain polyphenols like plumbagin, pongapin, and karanjin have been found to decrease hyaluronic acid levels in human cervical cancer HeLa cells [31]. Although the relative potency of PIC compared to other polyphenols, such as green tea extract, in influencing hyaluronic acid remains uncertain, compounds that promote hyaluronic acid production are relatively rare. Consequently, PIC stands out as a promising food ingredient capable of enhancing hyaluronic acid production and thus potentially benefiting skin health.

PIC has been demonstrated to enhance SIRT1 activity [20] and elevate SIRT1 levels in human monocytic leukemia cell lines [32]. In an *in vivo* study, mice fed a high-fat diet and orally administered PIC (10 mg/kg/day) for four weeks exhibited increased expression of *SIRT1*, *SIRT3*, and *SIRT6* in the liver than the high-fat diet group [21]. While there have been no previous reports on the effects of PIC on SIRT1 in

Table 1
Sequences of PCR primers employed for quantitative real-time PCR.

Gene	Forward sequence (5′-3′)	Reverse sequence (5′-3′)
HAS2	GTGGATTATGTACAGGTTTGTGA	TCCAACCATGGGATCTTCTT
HYAL2	CTAATGAGGGTTTTGTGAACCAGAATAT	GCAGAATCGAAGCGTGGATAC
SIRT1	TGCTGGCCTAATAGAGTGGCA	CTCAGCGCCATGGAAAATGT
GAPDH	GCACCGTCAAGGCTGAGAAC	TGGTGAAGACGCCAGTGGA

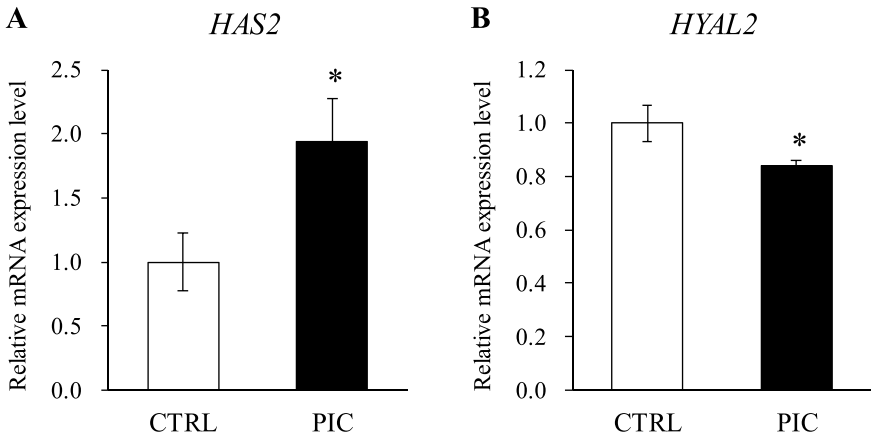

Fig. 1. Effects of PIC on *HAS2* and *HYAL2* Expression in Human Dermal Fibroblasts
Hs68 cells were subjected to treatment with either DMSO control (CTRL) or 20 μM piceatannol (PIC) for 16 h. Subsequently, mRNA expression levels of (A) *HAS2* and (B) *HYAL2* were assessed via quantitative real-time PCR and normalized to *GAPDH* expression. Data are presented as the mean ± standard deviation (n = 3). *$p <$ 0.05 vs CTRL (Student's t-test).

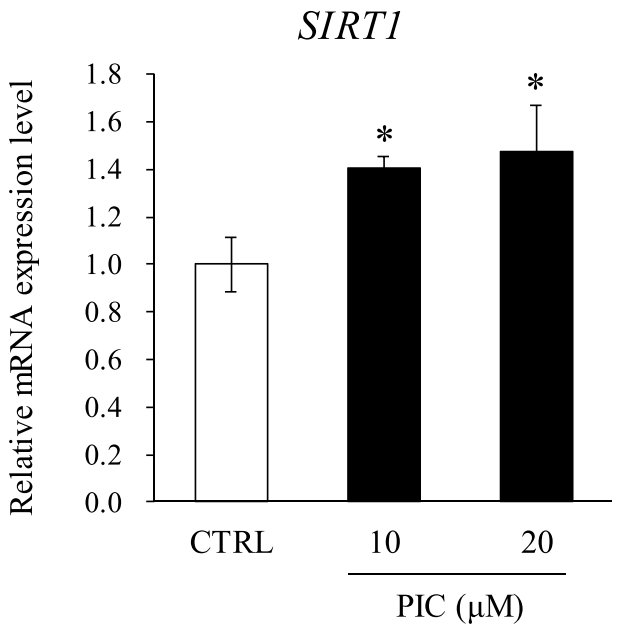

Fig. 2. Effect of PIC on *SIRT1* Expression in Human Dermal Fibroblasts
Cells were treated with either DMSO control (CTRL) or piceatannol (PIC) at concentrations of 10 μM and 20 μM for 6 h. Subsequently, mRNA expression levels of *SIRT1* were determined via quantitative real-time PCR and normalized to *GAPDH* expression. Data are presented as the mean ± standard deviation (n = 4). *$p <$ 0.05 vs CTRL (Dunnett's test).

skin fibroblasts, our study revealed that PIC also induces *SIRT1* in human skin fibroblasts. This induction suggests that PIC may exert beneficial effects on skin through the upregulation of SIRT1. Nicotinamide mononucleotide (NMN), a compound that enhances NAD^+, a coenzyme of SIRT1, has garnered attention for its ability to activate SIRT1. Studies have shown that NMN administration in mice reduces UVB-induced damage, suppresses the UVB-induced decrease in *SIRT1* expression, and preserves the skin's collagen structure [33]. Combining NMN with PIC may potentially produce an additive effect on maintaining skin function.

The effects of SIRT1 in the skin have been studied, with findings indicating that upregulation of SIRT1 increases the expression of collagen synthesis enzymes COL1A1 and COL1A2 [24,25], while simultaneously decreasing the expression of matrix metalloproteinase (MMP)-9, an enzyme responsible for collagen degradation, in skin fibroblasts [27]. Conversely, downregulation of SIRT1 has been associated with elevated MMP-1 and MMP-3 expression [26], implying that SIRT1 plays a crucial role in regulating collagen biosynthesis and enhancing collagen production in the skin. However, limited research has focused on the relationship between SIRT1 and hyaluronic acid synthesis. While Matsuoka et al. reported that oxidative stress in skin fibroblasts leads to decreased *SIRT1* and hyaluronic acid levels [34], the specific connection between SIRT1 and hyaluronic acid production remains unclear. In our study, we found that the induction of *HAS2* by PIC was attenuated by a SIRT1 inhibitor, suggesting that SIRT1 partially contributes to hyaluronic acid synthesis. This indicates that components capable of activating SIRT1, such as PIC, hold promise for promoting hyaluronic acid synthesis and thereby improving skin function. Additionally, the reduction in *HYAL2* expression induced by PIC was not reversed by SIRT1 inhibition, suggesting that SIRT1 may not be directly involved in hyaluronic acid degradation. Recently, the involvement of a long noncoding RNA, HA synthase 2 antisense 1 (HAS2-AS1), has been shown as a new mechanism of action for the regulation of HAS2 gene expression [35]. HAS2-AS1 is thought to regulate chromatin structure around the HAS2 promoter in the nucleus and increase HAS2 transcription, and the involvement of SIRT1 in the HAS2-AS1/HAS2 axis has also been suggested [35]. It is possible that PIC may exert its effects through modulation of HAS2-AS1 via SIRT1. However, further studies on the mechanism of action of PIC are needed. In a separate experiment involving rabbit synovial membrane cells, the decline in *HAS2* expression and hyaluronic acid levels caused by D-galactose were restored by the addition of melatonin [36]. Interestingly, a SIRT1 inhibitor suppressed melatonin-mediated hyaluronic acid and *HAS2* expression, aligning with the findings of our study and strongly suggesting the involvement of SIRT1 in hyaluronic acid synthesis. Conversely, in smooth muscle cells, treatment with SIRT1 activators is reported to inhibit HAS2 expression [37]. The effect of PIC on HAS2 expression in smooth muscle cells has not been verified, suggesting a potential tissue-specific effect. Further studies across various tissue types will provide a deeper understanding of the effects of PIC.

Okawa et al. reported that stimulating dermal fibroblasts with collagen tripeptides increases hyaluronic acid levels [38], suggesting a potential interaction between collagen and hyaluronic acid. This finding implies that collagen and hyaluronic acid may synergistically stimulate

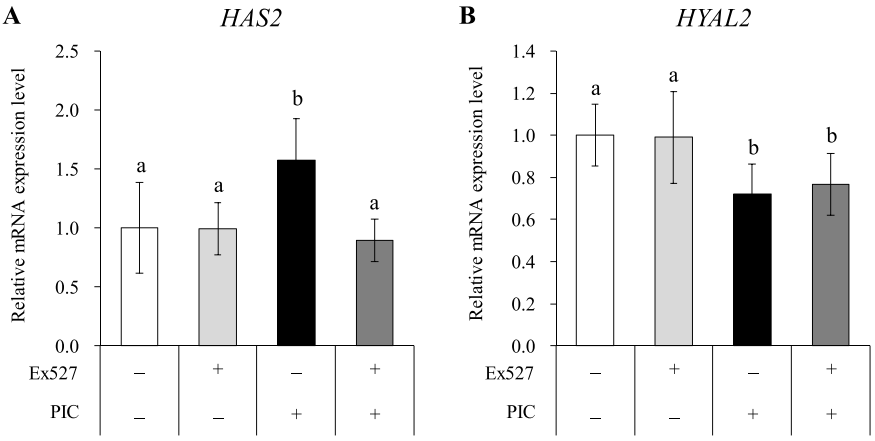

Fig. 3. Effects of SIRT1 Inhibitor on PIC-Induced Hyaluronic Acid Biosynthesis-Related Gene Expression
Hs68 cells were subjected to treatment with or without 10 μM Ex527 for 6 h, followed by treatment with 20 μM PIC and incubation for 16 h. Subsequently, gene expression levels of (A) *HAS2* and (B) *HYAL2* were assessed via quantitative real-time PCR and normalized to *GAPDH* expression. Data are presented as mean ± standard deviation (n = 6). Different letters indicate significance ($p < 0.05$, Tukey's test).

collagen production, contributing to the maintenance of skin structure. Previous studies have demonstrated that PIC promotes collagen production in dermal fibroblasts [11], and our study further reveals that PIC facilitates the hyaluronic acid biosynthesis pathway. Thus, the concurrent promotion of collagen and hyaluronic acid biosynthesis by PIC may effectively synergize to uphold skin structure and function by mutually influencing each other.

External factors such as UV irradiation and aging lead to reductions in hyaluronic acid and collagen levels, resulting in deteriorating skin structure and function [10,39–42]. PIC has been shown to mitigate UV-induced ROS generation in epidermal keratinocytes, suggesting its potential in attenuating skin aging caused by oxidative stress [19]. Future investigations to assess whether PIC can mitigate skin aging induced by UV and oxidative stress in dermal fibroblasts will provide deeper insights into its effects on the skin. Moreover, PIC has demonstrated the ability to increase SIRT1 levels in various cells and tissues. Further exploration of its effects on other bodily systems beyond skin function will heighten expectations for PIC as a beneficial food ingredient capable of positively impacting diverse bodily functions.

5. Conclusion

Our study unveiled that PIC enhances *HAS2* gene expression through *SIRT1* induction in human fibroblasts. Consequently, PIC emerges as a promising food ingredient capable of enhancing skin moisture and elasticity by stimulating hyaluronic acid synthesis.

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CRediT authorship contribution statement

Mizuki Yoshihara: Writing – original draft, Investigation, Formal analysis. **Shinpei Kawakami:** Writing – original draft, Investigation, Conceptualization. **Yuko Matsui:** Writing – review & editing, Conceptualization. **Toshihiro Kawama:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Mizuki Yoshihara reports a relationship with Morinaga & Co., Ltd. That includes: employment. Shinpei Kawakami reports a relationship with Morinaga & Co., Ltd. That includes: employment. Yuko Matsui reports a relationship with Morinaga & Co., Ltd. That includes: employment. Toshihiro Kawama reports a relationship with Morinaga & Co., Ltd. That includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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