The anti-pruritic effects of oyster extract

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Abstract

Intractable pruritus unresponsive to anti-histamine (anti-HS), common anti-pruritic drugs that are commercially available, is typically observed in patients with uremic pruritus who are undergoing maintenance hemodialysis. Many of these patients have decreased zinc concentrations in the blood and epidermis. This finding suggests that zinc replacement therapy may be effective for uremic pruritus. In the present study, the anti-pruritic effects on atopic dermatitis (AD) of oyster extract (OE), which is abundant in zinc, were examined. To investigate the action of OE on skin inflammation and pruritus in patients with AD associated with intractable pruritus, the anti-pruritic effects were first examined by a topical application test using a pruritus-induced guinea pig model, which showed that the quantitative measurable pruritic behavior related to both general pruritus, which is responsive to anti-HS, and intractable pruritus (Experiment 1). Then, inflammation and pruritus were examined by an internal use test using the IgE-miP-ICR mouse model of pruritus associated with IgE-mediated auricular skin inflammatory reactions (Experiments 2-4). In Experiment 1, immediately after intracutaneous administration of the pruritus-inducing substance, histamine (HS) or kallikrein (KK), 100 μl of normal saline containing 1% (w/v) OE or normal saline alone (control) was applied to the injection site. In Experiments 2-4, repeated doses of 200 mg/kg of OE in 0.3% CMC suspension or suspension alone (control) were given orally for 1 week before the start of the experiment. In Experiment 2, the cumulative duration of pruritus behavior within 2 hours was measured in the IgE-miP-ICR mouse model, and the anti-pruritic effects of the test substance were examined. Inflammation and pruritus were assessed at 1, 4, 24, and 48 hours after elicitation (Experiments 3-4). Experiment 1 showed that OE significantly inhibited pruritus induced by both HS and KK. Accordingly, the effects of the major components of OE, taurine (Tau), glycogen (Gly), and organic zinc (OZ) in normal saline containing 1% (w/v), on KK-induced intractable pruritus were examined to identify the major active ingredient in OE. As a result, only OZ showed a significant inhibitory action. Experiment 2 showed that both OE and OZ exhibited anti-pruritic effects and significantly reduced the cumulative duration of pruritic behaviors within 2 hours of DNFB application. Experiment 3 showed that OZ significantly inhibited inflammatory reactions in the IgE-miP-ICR mice, which showed biphasic skin inflammation at 1 and 24 hours after elicitation. Experiment 4 showed that OZ significantly inhibited the cumulative duration of pruritic behaviors within 1 hour in IgE-miP-ICR mice showing biphasic pruritus at 1 and 24 hours after elicitation.

Since OE and its active ingredient, OZ, significantly inhibited skin inflammation and pruritus in the AD animal model, they may be used as health food materials for treating inflammation and pruritus in AD patients as well as an effective medication for uremic pruritus in patients with chronic renal failure undergoing hemodialysis.

Keywords: Oyster extract, Zinc, Uremic pruritus, AD animal, Pruritus

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Introduction

In addition to pruritus in atopic dermatitis (AD), uremic pruritus in patients undergoing chronic hemodialysis due to chronic renal failure is well known as an intractable pruritus condition, which is unresponsive to commercially available anti-pruritic anti-histamine (anti-HS) drugs. Many uremic pruritus patients have decreased blood zinc concentrations and the amount and activity of Cu, Zn-superoxide dismutase (SOD), which is distributed in the basal cell layer of the epidermis, are significantly decreased compared with healthy subjects. Similarly, zinc concentrations in the blood and epidermis are also decreased in people with total parenteral nutrition. Izumi et al. confirmed that zinc-deficient rats have low zinc concentrations in the blood and epidermis, as observed in uremic pruritus patients, as well as a reduced threshold intensity of itch receptors located on free nerve endings of C-fibers at the dermal-epidermal junction, which provokes the itch sensation. These findings indicate that, when zinc becomes deficient in uremic pruritus patients and other organisms that suffer oxidative stress, in which decreased blood zinc concentrations decrease the zinc level in the basal cell layer of the epidermis, the number of Cu, Zn-SOD-positive cells present in the same cell layer further reduces. This appears to stimulate itch receptors located on free nerve endings of C-fibers at the junction between the adjacent epidermis and dermis, provoking itch sensation. Accordingly, we considered that pruritus in uremic pruritus patients could be suppressed by zinc supplementation. In the present study, we investigated ingestion of oyster extract (OE), a food abundant in zinc, and zinc supplementation on pruritus behavior in the lgE-mediated in vitro auricular skin inflammation model. After 1 week of preliminary rearing at room temperature (23 ± 2°C) and at a humidity of 55 ± 10%, the animals were divided into specific groups. Guinea pigs and mice were fed with RC4 (Oriental Yeast Co., Ltd., Tokyo, Japan) and CE-2 (CLEA Japan, Inc., Tokyo, Japan), respectively, and were provided with tap water ad libidum.

Materials and methods

Pruritus-inducing substances and other materials

In Experiment 1, HS hydrochloride produced by Wako Pure Chemical Industries, Ltd., (Osaka, Japan) and swine pancreas tissue KK (low molecular weight) produced by Merck Ltd., (Tokyo, Japan) were used to induce pruritus in guinea pigs. In Experiment 2, mouse monoclonal IgE (anti-DNP) from Seikagaku Corporation (Tokyo, Japan) was used to induce IgE-mediated auricular skin inflammatory reaction. Dinitrofluorobenzene (DNFB), acetone, and olive oil from Nakarai Chemicals Ltd., (Kyoto, Japan) were used. To measure auricular thickening, the Dial Thickness Gauge system from Mitsutoyo Corporation (Kanagawa, Japan) was used.

Laboratory animals

In Experiment 1, wild-type 8-week-old male Hartley guinea pigs (Hoshino Laboratory Animals, Saitama, Japan) were used. In Experiments 2-4, wild-type 4-week-old female ICR mice (CLEA Japan, Inc., Tokyo, Japan) were used to examine the inflammatory reactions and pruritic behavior in the IgE-mediated auricular skin inflammation model. After 1 week of preliminary rearing at room temperature (23 ± 2°C) and at a humidity of 55 ± 10%, the animals were divided into specific groups. Guinea pigs and mice were fed with RC4 (Oriental Yeast Co., Ltd., Tokyo, Japan) and CE-2 (CLEA Japan, Inc., Tokyo, Japan), respectively, and were provided with tap water ad libidum.

Experimental methods

Each experimental group consisted of 12 animals

a) HS or KK induced pruritus behavior in guinea pigs (Experiment 1)

Guinea pigs were intracutaneously given 50 μl of a pruritus-inducing substance, HS hydrochloride (0.3 mg/
ml) or swine pancreas KK (25 U/animal), in the midventral region. Animal behavior was recorded using an overhead video camera for 2 hours immediately after the injection. From the video recording, the cumulative duration of pruritic behaviors, including turning to the injection site to scratch it with their teeth and scratching it with their teeth, were measured (measurements were recorded in seconds within the 2-hour period). After intracutaneous administration of the pruritic–inducing substance, animals were assigned to receive 100 μl of normal saline containing 1% (w/v) OE, Tau, Gly or OZ, or saline alone (control) at the injection site.

b) Cumulative duration of pruritus behaviors in IgE–mlP–ICR mice within 2 hours (Experiment 2)\(^\text{15}\)

ICR mice were passively sensitized with 0.5 ml anti-DNP IgE Ab (×7,680 as PCA titer), and 100 μl 0.15% DNFB in acetone/olive oil (4:1) was applied to the auricle of the animals to elicit biphasic pruritus 1 hour after sensitization. After elicitation, pruritic behaviors against the DNFB application site were video-recorded within 2 hours as in Experiment 1. The cumulative duration of pruritic behaviors was measured. Animals received repeated oral doses of 200 mg/kg OZ in 0.3% CMC suspension or 0.3% CMC suspension alone (control) for 1 week before the start of the experiment.

c) Changes in auricular skin inflammatory reactions in IgE–mlP–ICR mice over 48 hours (Experiment 3)\(^\text{15}\)

DNFB solution was applied to the auricle of ICR mice sensitized with anti-DNP IgE Ab, as in Experiment 2, to elicit biphasic skin inflammation. At 1, 4, 24, and 48 hours after elicitation, auricular thickening (thickening based on auricular thickness before elicitation) at the DNFB application site was measured using a Dial Thickness Gauge. Animals received repeated oral doses of 200 mg/kg OE or OZ in 0.3% CMC suspension or 0.3% CMC suspension alone (control), as in Experiment 2.

d) Auricular pruritus behaviors in IgE–mlP–ICR mice over 48 hours (Experiment 4)\(^\text{15}\)

DNFB solution was applied to the auricle of ICR mice sensitized with anti-DNP IgE Ab, as in Experiment 2, to elicit biphasic skin pruritus. Pruritic behaviors at the DNFB application site of the auricle were video-recorded for 1 hour at 1, 4, 24, and 48 hours after elicitation, as in Experiment 1. Animals received repeated oral doses of 200 mg/kg OZ in 0.3% CMC suspension or 0.3% CMC suspension alone (control), as in Experiment 2.

Statistical analysis

Results are reported as means±standard deviations. Analysis of variance was performed for group comparisons, and Student’s t-test was performed for pairwise comparisons with the control group. A p-value less than 0.05 was considered to indicate a statistically significant difference.

Results

1. Pruritus behaviors in guinea pigs with pruritus induced by HS or KK (Experiment 1)

Figure 1 shows the total duration of pruritic behaviors induced by HS or KK in the OE group. Figure 2 shows the total duration of pruritic behaviors induced by KK in animals receiving Tau, Gly or OZ, the major components of OE. The total duration of pruritic behaviors induced by HS and KK was significantly lower in the OE group. The pruritic behavior lasted 11.4±5.4 s/2 h (p<0.05) with HS–induced pruritus.

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**Fig. 1** Effects of topical oyster extract (OE) on total pruritic behavior induced by histamine (HS) or kallikrein (KK) in guinea pigs. Each column represents mean with standard deviation. Each group consisted of 12 guinea pigs. *p<0.05 (Student’s t-test)

y-axis: Accumulated time of total pruritic behavior (s/2 h)

x-axis: left HS, right KK

open column: control group
solid column: OE group

**Fig. 2** Effects of topical taurine (Tau), glycogen (Gly) and organic zinc (OZ), major components containing into OE on total pruritic behavior induced by KK in guinea pigs. Each column represents mean with standard deviation. Each group consisted of 12 guinea pigs. *p<0.05 (Student’s t-test)

y-axis: Accumulated time of total pruritic behavior (s/2 h)

x-axis: left Tau, middle Gly, right OZ

open column: control group
solid column: Tau group (left)
Gly group (middle)
OZ group (right)
compared with 18.8±7.2 s/2 h in the control group, and 32.1±4.1 s/2 h (p<0.05) in KK-induced pruritus compared with 42.0±6.0 s/2 h in the control group. The total duration of pruritic behaviors in animals receiving Tau, Gly, and OZ was 38.6±5.7 (ns), 37.6±6.0 (ns), and 37.8±4.2 s/2 h (p<0.05), respectively, compared with 37.3±7.4, 35.9±7.4, and 42.2±4.5 s/2 h in the respective control groups.

2. Cumulative duration of pruritic behaviors in IgE-mIP-ICR mice within 2 hours (Experiment 2)

Figure 3 shows the cumulative duration of pruritic behaviors within 2 hours in IgE-mIP-ICR mice, which received either OE or OZ. The duration of pruritic behavior was significantly lower in the OE and OZ groups (286.0±35.3 s/2 h [p<0.01] and 290.5±33.0 s/2 h [p<0.01], respectively), compared with 383.0±20.2 s/2 h, 396.2±35.3 s/2 h in the respective control groups.

3. Changes in auricular skin inflammatory reactions in IgE-mIP-ICR mice over 48 hours (Experiment 3)

Figure 4 and 5 show the changes in auricular skin inflammatory reactions over 48 hours in IgE-mIP-ICR mice prepared in Experiment 2, which received OE or OZ. In the control group, a clear biphasic pattern of inflammation was observed, with auricular thickening of 61.8±8.4, 24.6±3.4, 41.6±5.1, and 24.8±4.4 μm at 1, 4, 24, and 48 hours after DNFB elicitation. On the other hand, inflammation was significantly suppressed in the OE group at 1, 24, and 48 hours after DNFB elicitation, with auricular thickening of 41.1±4.7 (p<0.01), 21.2±3.3, 32.2±4.0 (p<0.01), and 20.1±2.8 (p<0.05) μm at 1, 4, 24, and 48 hours (Fig. 4). In the OZ group,
inflammation was significantly suppressed at 1 and 24 hours after DNFB elicitation, with auricular thickening of $53.1 \pm 5.2$ (p < 0.01), 20.6 ± 2.5 (p < 0.05), 38.6 ± 4.1 (p < 0.01), and 21.9 ± 2.7 (p < 0.01) μm at 1, 4, 24, and 48 hours compared with 62.5 ± 3.6, 23.2 ± 2.2, 45.9 ± 4.6, and 28.3 ± 3.1 μm in the control group (Fig. 5).

4. Cumulative duration of pruritic behaviors in IgE-mlP-ICR mice over 48 hours (Experiment 4)

The cumulative duration of pruritic behaviors over 48 hours in the IgE-mlP-ICR mice were compared between the OZ group and the control group, and the pruritic behaviors are shown in Fig. 6. In the control group, a clear biphasic pruritus behavior pattern was observed, with duration of behavior of 204.7 ± 20.6, 85.2 ± 19.5, 94.3 ± 30.7, and 46.5 ± 19.1 s/1 h at 1, 4, 24, and 48 hours after DNFB elicitation. On the other hand, pruritus behaviors were significantly lower at 1 and 24 hours in the OZ group, with duration of behavior of $169.3 \pm 36.3$ (p < 0.01) and $69.6 \pm 25.6$ (p < 0.05) s/h, respectively.

Discussion

AD is an allergic disease that is not completely cured in adulthood, and the incidence of adult AD is increasing every year. In clinical practice, steroid and topical immunosuppressants, such as FK506, are used as standard therapy, while the use of anti-histamine with an anti-allergic action is recommended as combination therapy for pruritus. However, the flare of dermatitis and the associated recurrence of pruritus often fall into a vicious cycle, and dermatologists claim that, if pruritus can be suppressed, the disease will not worsen. To overcome this problem, it is critical to identify materials that can prevent intractable pruritus, which cannot be suppressed by anti-histamine. Meanwhile, uremic pruritus is well known as an intractable pruritus condition in patients undergoing hemodialysis as a result of chronic renal failure other than pruritus in AD. Uremic pruritus patients have decreased blood zinc concentrations, and the amount and activity of Cu, Zn-SOD distributed in the basal cell layer of the epidermis are significantly decreased compared with Cu, Zn-SOD-positive cells in healthy subjects. Izumi et al. showed that zinc-deficient rats, which were prepared by feeding a zinc-deficient diet, have decreased zinc concentrations in the blood and epidermis. As the result, a reduced threshold of the itch receptors located on free nerve endings of C-fibers at the dermal-epidermal junction, provoking the itch sensation. Therefore, it was considered that in patients undergoing hemodialysis as a result of uremic pruritus could be suppressed by zinc supplementation.

Accordingly, in the present study we investigated the effect of OE, a food abundant in zinc, and its major components, Tau, Gly, and OZ, on AD associated with intractable pruritus.

First, we confirmed the anti-pruritic effect using the pruritus-induced guinea pig model as an animal model that is highly reproducible because the conditions are similar (Experiment 1). This animal model can be used to quantitatively determine general pruritus, which responds to anti-HS, and intractable pruritus, which does not respond to it. So far, in this series of studies, we have explored health food materials, apple polyphenol and grape seed polyphenol, which also suppress intractable pruritus. Of these, clinical results with apple polyphenol showed improvements in skin symptoms and suppression of pruritus in patients with AD, representative intractable pruritus, and improvement of pruritus in hemodialysis patients. Therefore, we consider that this pruritus-induced guinea pig model used in Experiment 1 is a convenient and useful system, which can be used to quantitatively determine pruritus behavior and to predict clinical effects. Furthermore, since severe AD and blood IgE levels correlate well, and AD is predisposed to produce IgE antibody, the action on skin inflammation and pruritus in AD was investigated using the IgE-mediated inflammation ICR (IgE-mlP-ICR) mouse model, which was used in Experiments 2-4. This model was prepared by replacing the BALB/c mouse in the model of biphasic inflammation associated with IgE-mediated late phase reaction of Katayama et al., and Otoyama with the ICR mouse, which is optimal to observe pruritus behavior, and incorporating pruritus into dermatitis to obtain an animal model that is highly reproducible because conditions are similar.

The anti-pruritic effects of OE and its major components, Tau, Gly and OZ were first examined using the pruritus-induced guinea pig model (Experiment 1). As a result, OE significantly suppressed pruritus induced by both HS with behaviors lasting 11.4 ± 5.4 s/2 h (p < 0.05) compared with 18.8 ± 7.2 s/2 h in the control group and with KK-induced pruritus with behaviors lasting 32.1 ± 4.1 s/2 h (p < 0.05) compared with 42.0 ± 6.0 s/2 h in the control group (Fig. 1). We then examined the effect of Tau, Gly, and OZ on KK-induced pruritus. Only OZ significantly suppressed KK-induced pruritus, with behaviors lasting 37.8 ± 4.2 (p < 0.05) s/2 h compared with 42.2 ± 4.5 s/2 h in the control group (Fig. 2). We examined the anti-pruritic effects using the IgE-mlP-ICR mouse model (Experiment 2). The pruritic duration of behavior was significantly lower in both OE and OZ groups with values of 286.0 ± 35.3 s/2 h (p < 0.01), and 290.5 ± 33.0 s/2 h (p < 0.01). On the other hand, clear pruritus behavior was observed, with values of 383.0 ± 20.2 s/2 h, 369.2 ± 35.3 s/2 h in the respective control groups (Fig. 3).
Finally, the effect on dermatitis (Figs. 4, 5) in both the OE and OZ groups and cumulative pruritic behavior (Fig. 6) in the OZ group over 48 hours were examined using the IgE–mIP–ICR mouse model described above. The control group showed a clear biphasic inflammation pattern in skin inflammation, with auricular thickening of 61.8±8.4, 24.6±3.4, 41.6±5.1 and 24.8±4.4 μm at 1, 4, 24 and 48 hours after DNFB elicitation, respectively, whereas inflammation was significantly suppressed in the OE group at 1, 24, and 48 hours after DNFB elicitation, with auricular thickening of 41.1±4.7 (P<0.01), 21.2±3.3, 32.2±4.0 (P<0.01) and 20.1±2.8 (P<0.05) μm at 1, 4, 24, and 48 hours, respectively (Fig. 4). Inflammation was significantly suppressed at 1 and 24 hours after DNFB elicitation in the OZ group, with auricular thickening of 53.1±5.2 (P<0.01), 20.6±2.2 (P<0.05), 38.6±4.1 (P<0.01), and 21.9±2.7 (P<0.05) μm at 1, 4, 24 and 48 hours compared with 62.5±3.6, 23.2±2.2, 45.9±4.6 and 28.3±3.1 μm in the respective control groups. Both immediate pruritus (first peak) and late phase reaction (second peak) were suppressed in both the OE (Fig. 4) and the OZ groups (Fig. 5). In addition, cumulative pruritic behavior over 48 hours was examined in the OZ group, using the IgE–mIP–ICR mouse model10. Here, the control group showed a clear biphasic pattern in pruritus, with auricular thickening of 204.7±20.6, 85.2±19.5, 94.3±30.7 and 46.5±19.1 μm at 1, 4, 24 and 48 hours after DNFB elicitation, respectively, whereas cumulative pruritic behavior was significantly suppressed at 1, 24, and 48 hours after DNFB elicitation, with auricular thickening of 169.3±26.3 (P<0.01), 71.3±15.3, 69.6±25.6 (P<0.05) and 34.8±15.3 μm at 1, 4, 24, and 48 hours, respectively (Fig. 6). These results were consistent with the results in the pruritus–induced guinea pigs.

We previously reported successive condensation products, proanthocyanidone, apple polyphenol and grape seed polyphenol, which are health foods4), as materials that suppress intractable pruritus in the pruritus–induced guinea pig model as well as late phase reaction and intractable pruritus in evaluation of effectiveness on immediate inflammation, which is represented by the first peak and general pruritus as well as the second peak, which is represented by late phase reaction and intractable pruritus in the IgE–mIP–ICR mouse model10. Since uremic pruritus, an intractable pruritus condition, is improved by zinc supplementation9, OE, which is abundant in zinc, and its major components, Tau, Gly and OZ, were investigated in the pruritus–induced guinea pig model9 and the IgE–mIP–ICR mouse model10, which was prepared by incorporating pruritus in dermatitis in the present study as in previous reports. Both general pruritus and intractable pruritus were suppressed as with apple polyphenol and grape seed polyphenol, which are proanthocyanidine. Therefore, it is considered that, in chronic renal failure, the oxidative stress, which results in a decrease in blood zinc concentrations3) decreases zinc localized in the basal cell layer of the epidermis3, resulting in a lower level and activity of Cu, Zn–SOD distributed in this cell layer8. This process lowers the itch threshold of itch receptors present on free nerve endings of C–fibers at the junction between the adjacent epidermis and dermis, thus provoking an itch sensation8. Epidermis in the skin is designed to protect the body from oxidation stress such as UV radiation. Vitamins with antioxidation effects and radical scavengers such as Cu, Zn–SOD play a role in this defensive system10. Therefore, the proanthocyanidine apple polyphenol, is considered to suppress the peripheral itch receptors through potential antioxidation stress effect18, also appears to suppress peripheral pruritus by increasing of Cu, Zn–SOD activity in epidermis8.

References


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牡蠣肉エキスの鎮痒作用

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【要旨】代表的かつ市販鎮痒薬の抗ヒスタミン剤が効果しない難治性搔痒の疾患のひとつに、慢性腎不全による血液透析患者の皮膚搔痒症（uremic pruritus）があり、本症の多くは血中および表皮中の亜鉛濃度が低下している。このことから、血液透析患者の皮膚搔痒症には亜鉛補充療法が有効と考えられている。本研究では、亜鉛を多量に含む牡蠣肉エキス（OE：oyster extract）のアトピー性皮膚炎（AD）に対する鎮痒作用について検討した。まず、OEの発症モルモットモデルでの外用塗布試験による鎮痒作用（実験1）、次に、IgE介在性の耳介皮膚炎症反応を伴うICR搔痒（IgE-mIP-ICR）マウスマウスの模型での炎症と搔痒を内服試験で検討した（実験2-4）。実験1の発症モルモットモデル試験ではヒスタミン（HS）またはカリクリーン（KK）で発症したモルモットで鎮痒作用を検討した。次に、実験2-4では、OEは200 mg/kg（0.3% CMC懸濁）を塗布テントDinitrofluorobenzene（DNFB）塗布前に1週間連続経口投与し、対照には同懸濁液OE同様にDNFB塗布前に1週間連続経口投与した。また、実験2では、IgE-mIP-ICRマウスマウスで2時間累積搔痒行動を確認すると共に被験物質の鎮痒作用を検討した。実験3-4では、同モデルでの炎症及び搔痒に対する48時間経過変化および被験物質の作用を検討した。実験1では、OEは1%（w/v）OEの生理食塩液、対照には溶媒の生理食塩液を発症物質の皮内投与部位に投与直後に塗布（100 μl）した。実験2-4では、OEは200 mg/kg（0.3% CMC懸濁）をDNFB塗布前に1週間連続経口投与し、対照には同懸濁液OE同様にDNFB塗布前に1週間連続経口投与した。その結果、実験1では、OEはHSとKKの両発症に対して有意に抑制した。そこで、OE中の有効成分を探索する目的からOEの主成分であるタウリン（Tau：taurine）、グリコーダーゼ（Gly：glucogen）および亜鉛鉄（OS：organic zinc）の各1%（w/v）含有の生理食塩液について、難治性搔痒のKK発症に対して検討した結果、OZのみが有意な抑制を示した。実験2では、OEおよびOZはDNFB塗布後の2時間累積搔痒行動を共に有意に抑制し、鎮痒効果を示した。実験3では、OEおよびOZについて検討し、惹起1,24時間後に二酸化性の皮膚炎症を示すIgE-mIP-ICRマウスの炎症反応を有意に抑制した。実験4では、OZが惹起1,24時間後に二酸化性の皮膚炎症を示すIgE-mIP-ICRマウスの1時間累積搔痒行動を有意に抑制した。以上の結果より、OEおよびその有効成分のOZがAD動物モデルの皮膚の炎症及び搔痒のいずれも有意に抑制したことから、AD患者の炎症及び搔痒に有効な健康食品素材であると同時に、慢性腎不全の血液透析患者の皮膚搔痒症（uremic pruritus）に有効である可能性を示した。

＜キーワード＞牡蠣肉エキス、亜鉛、皮膚搔痒症、AD動物、搔痒