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The effect of levofloxacin ointment against imiquimod induced–psoriasis in mice model

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Abstract

The goal of this study was to prepare levofloxacin as a topical ointment for evaluating its anti-psoriatic activity in imiquimod-induced psoriasis in mice. Sixty mice 24 – 30 grams were randomly divided into six groups of 10 mice each. The first group was a control group, in which the baseline ointment was application to the shaved back. The second group received imiquimod (5%) cream for 6 days on back in the same way as the remaining four groups to induce psoriasis of skin inflammation. The 3rd, 4th, 5th and 6th groups were treated with application of imiquimod daily clobetasol, levofloxacin 10, 20 and 40% ointment. At the end of the experiment, blood was obtained to prepare serum for measuring inflammatory biomarkers, while skin samples were used to study histopathological changes. Levofloxacin ointment dramatically reduced the scores of erythematous, scaling, and epidermal thickenings, as well as the inflammatory cytokines TNF-α, IL-8, IL-17, and IL-37. Levofloxacin ointment has strong anti-psoriatic and anti-inflammatory activities.

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Introduction

Psoriasis is a chronic, immuno-mediated inflammatory dermatosis that often has a relapsing-remitting course and is defined by the development of erythematous plaques that are covered in white scales, occasionally pruritogenic, and concentrated primarily on the extensor areas (1). One of the most prevalent chronic dermatological illnesses, its prevalence and incidence vary greatly depending on the location, age, and gender globally. Its prevalence, for instance, ranges from 0.91 to 8.5% in adults to 0.1% to 2.1% in children, while its incidence is 40.8 cases in 100,000 people in the former and 78.9–230 cases in 100,000 in the latter (2). In psoriasis therapy, cytokines' roles in psoriasis etiology have spurred the development of specific interleukin modulators that restore homeostatic keratinocyte proliferation and function. (3). Imiquimod antiviral effect was mediated through the activation of Toll-like receptors (TLR) 7 and TLR8, making it a strong immune stimulant. It is used for topical treatment of genital and perianal warts caused by human papilloma virus (4). The clinical indications have additionally been expanded to include treatment of other virus-associated skin abnormalities as well as skin lesions such as actinic keratosis and superficial basal cell carcinomas (5,6). Imiquimod can exacerbate psoriasis in patients with well-controlled psoriasis during topical treatment of actinic keratosis and superficial basal cell carcinomas (7). Important hallmarks of imiquimod-induced psoriasis are the infiltration of dendritic cells (pDC) nd type I IFN activity (8,9). Accordingly, the application of imiquimod on mouse skin leads to a rapid influx of pDC (10). Levofloxacin, as a third-generation fluoroquinolone antibiotic (11,12), has been widely used in the treatment of humans for affecting the growth of bacteria by inhibiting the

DNA replication process of Gram-negative bacteria (13). A third-generation fluoroquinolone antibiotic with a broad spectrum of activity, levofloxacin is used to treat bacterial infections. In the WHO's list of necessary medications, levofloxacin is a safe and efficient drug. It was granted a patent in 1987 and later approved by the FDA for use in medicine in the US in 1996 (14). Levofloxacin has been given FDA approval for the treatment of a number of infectious conditions (15). The mechanism of action of levofloxacin was directly preventing bacterial DNA synthesis (16,17). Levofloxacin encouraged DNA strand breaks by preventing DNA-gyrase in organisms that are vulnerable to it from relaxing supercoiled DNA. Levofloxacin had the most improved activity of the fluoroquinolone class against gram-positive, penicillin-sensitive, and resistant pathogens, particularly Streptococcus pneumonia (18). The anti-inflammatory and anti-proliferative effects of levofloxacin are mediated by inhibiting inflammatory cytokines (19). Levofloxacin hydrochloride showed universal anti-proliferation activity in cancer cell lines in our previous study (20,21). Clobetasol is typically prescribed for moderate to severe cases of psoriasis. It can provide relief from psoriasis symptoms that may associated with potential side effects, such as skin thinning, discoloration, or increased risk of infection (22,23).

The present study aimed to evaluate the effects of different concentrations of topical levofloxacin on induced psoriasis by measuring their potential anti-psoriatic activity and anti-inflammatory effects besides physical and histopathological evaluations.

Materials and methods

Animals

obtain sixty adult male mice, whose weights ranged between 24-33 g and their ages ranged between 11-15 weeks. Healthy male adult albino mice obtained from the animal house. Mice were housed in polypropylene cages and fed on a standard pellet diet and water ad libitum. All animals were maintained under standard management conditions at 22±3°C, 50-60% relative humidity, and 12 hours' light-dark cycles. Animals were allowed to acclimatize for 7 days prior to experiments being carried out. The animals were housed in plastic cages in a convenient environment for the aspect of heat, ventilation, and nutrition materials. The animals were allowed to acclimate for two weeks in the College of Pharmacy-University of Karbala. The study protocols were conducted according to the Ethical approval of the Ethics Committee (14/1/2022, UE/5/20), University of Al-Ameed.

Preparation of levofloxacin ointment

Levofloxacin (Auro-Bindo, India) was dissolved in an amount of 10 g, 20 g and 40 g concentrated ethanol (Auro-Bindo, India) to prepare with the addition of 5 ml of glycerol (Auro-Bindo, India), then the mixture was supplemented with Vaseline for a final weight of 100 g in a beaker and was mixed at 70 C using a water bath (APC, China) to ensure melting all components (24). The mixture was slowly cooled and further stirred for 30 minutes until solidified using a motor at 500 revolutions per minute. The prepared ointment was filtered using filter paper to remove any impurities. The rheological evaluations using a viscometer and microbiological tests were done (24).

Experiment design

Sixty mice were taken, after which an area of 2 x 2cm was shaved from the back of each mouse (Figure 1) (25). They were divided randomly into six groups within the imiquimod -induced psoriasis. The control group was treated daily for six days with 0.5 mg of vaseline ointment which was applied on the skin from which the hair was removed. imiquimod induction group in which psoriasis was developed by applying 62.5 mg of imiquimod cream 5% on the hair removed area daily for 6 days (25). Group 0.05% (25) clobetasol propionate ointment was applied after applying 62.5 mg of clobetasol 5% on the area from which hair was removed daily for 6 days. Finally, levofloxacin ointment groups at doses 10, 20, and 40%, these concentrations were selected based on previous pilot study, applied after applying 62.5 mg of imiquimod 5% on the area from which the hair was removed daily for 6 days among three different groups respectively. The observed changes that occur on the skin in terms of redness and scaling are recorded from the first to the sixth day. On day seven, all animals were anesthetized by ketamine 0.08 ml and xylazine 0.16 ml, and blood was drawn by using a syringe 1 mL inserted inside the heart for measuring cytokines levels of TNF-a, IL-8, IL-17and IL-37 by ELISA technique, and the skin from the treated area was taken. The taken skin was preserved in formalin 10% (Fluka, Switzerland), and then the tissue was sliced and stained with eosin and hematoxylin to study histological changes, then separated by cold centrifuge (China) at a speed of 5000 rpm for 10 minutes (25). Serum was collected and frozen at -80°C to measure biomarkers to examine the levels of TNF-alpha, IL-8, IL-17 and IL-37 (Sunlong, China).

Clinical symptoms follow-up

The clinical symptoms were monitored daily throughout the experimental period with the help of the indicator of the severity of the psoriasis area. The follow-up of the redness and scaling intensity on the mouse skin independently on a scale from 0 to 4 as follows (0): no symptoms, (1) minor symptoms, (2): symptoms moderate, 3: obvious symptoms, 4: severe symptoms) (25), and score the level of erythema using a standardized Figure 1. The skin Histopathological texture was examined using a light microscope and the thickness of the histological cortex layer was measured.

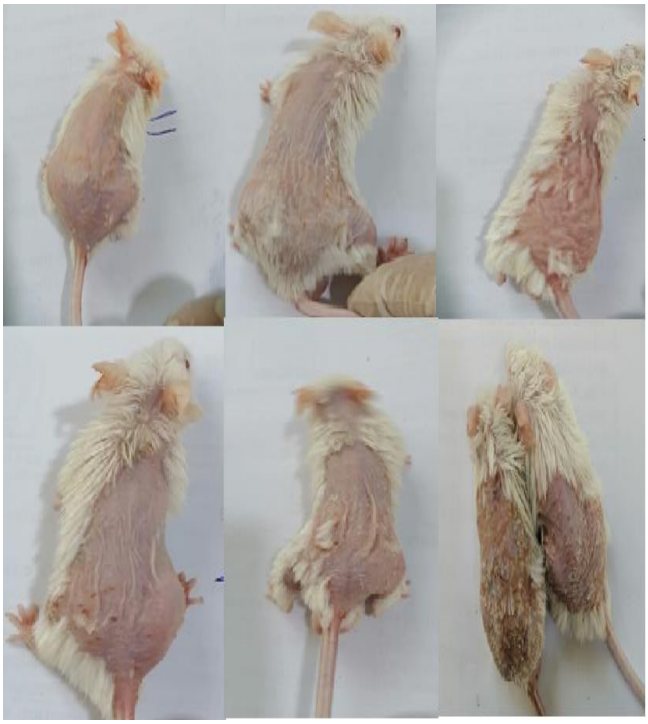

Figure 1: shows the shaved from the back of each mouse for treated groups.

Statistical analysis

The data are analyzed by using the Statistical Package for the Social Sciences (SPSS 22). The means and the standard error of the means (mean ±S.E.M) are the two components of descriptive statistics for numerical data. A one-way analysis of variance or an independent t-test was used to assess numerical data (ANOVA). *P*-values less than 0.05 were regarded as statistically significant.

Results

All descriptive properties of levofloxacin compound ointment namely color, liquefaction, viscosity, and skin irritation test were evaluated. The results indicated that the three prepared concentrations 10, 20, and 40% of levofloxacin showed good physical stability due to the absence of liquefaction, change in color, or phase separation over a period of three months from the time of ointment formulation. There was no skin irritation or erythema on the skin of volunteers during the test after levofloxacin ointment application at different concentrations in certain area.

The psoriasis induction group in compared to the control group showed a statistically significant rise in the erythema, and crusting grade of psoriasis (Figure 2). The Clobetasol group significantly reduced the severity of psoriasis symptoms, erythema and crusting in imiquimod group. When levofloxacin 10, 20, and 40% ointment groups compared with induction group showed gradually improving and ameliorating effect in visual changes (Figure 3). As demonstrated in figures 2 and 3, there were no statistically significant changes in the severity of the psoriatic lesion between levofloxacin ointment 10, 20, and 40% and clobetasol ointment 0.05%.

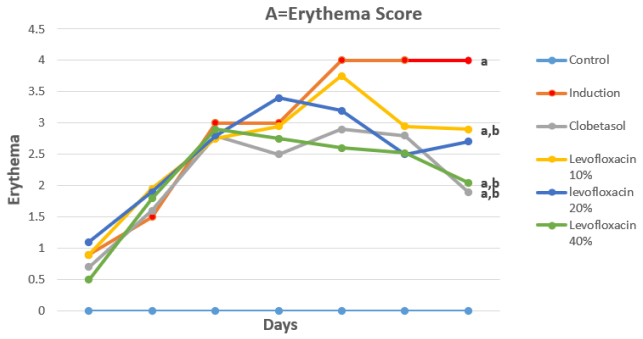

Figure 2: Shows the changing in erythema in levofloxacin treated groups.

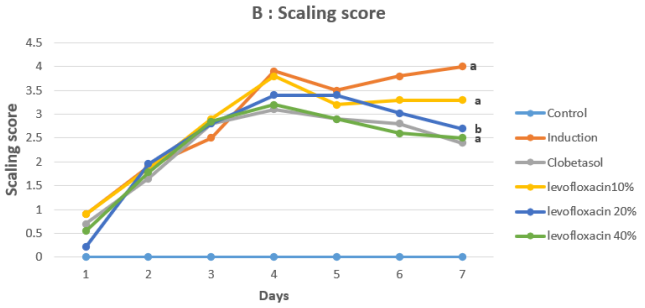

Figure 3: Shows the changing in scaling score in levofloxacin treated groups.

Imiquimod 5% significantly increased the concentration of cytokines in serum (TNF-α, IL8, IL17 and IL37) compared to the control group, as indicated in the Table 1, while Clobetasol ointment was able to significantly reduce the levels of these serum biomarkers compared with the inducted group in which psoriasis developed as shown in the table 1. The levels of biomarkers in the serum compared to the group in which psoriasis developed, as a decrease and significant differences were observed between Levofloxacin ointment and clobetasol ointment 0.05%, in addition to the three concentrations of Levofloxacin ointment 10, 20 and 40% were able to restore some cytokines to their normal level compared to the control group (Table 1).

The control group's histological features included keratin layer proliferation without Munro's inflammation and a lack of modifications to the epidermal layer's structure thickness as presented in figure 3. Imiquimod 5% generated severe histological alterations characterized by Munro's inflammation with extension of epidermal layers toward the dermis in comparison to the control group. While the

histological characteristics of the clobetasol ointment group 0.05% caused a weakening of the epidermal thickness and reduced the inflammation signs. Furthermore, the histopathological features of the levofloxacin ointment group 10 and 20% were characterized by normal proliferation of keratin and survival of the epidermal thickness, but it was lessening the imiquimod group (Figure 4). The study data showed the obvious effect of the levofloxacin ointment group 40% by normalizing the epidermal shape, thickness, and keratin layer compared to the imiquimod group.

Table 1: The effect of imiquimod, clobetasol and levofloxacin ointment groups on inflammatory biomarkers

Groups	TNF alpha	IL 8	IL 17	IL37
Control	48.50±1.83	22.65± 0.78	31.92± 1.74	29.63±0.98
Imiquimod	269.38±6.38 [a]	86.35± 2.76 [a]	113.46± 3.76 [a]	74.03± 2.12 [a]
Clobetasol	142.80± 3.26 [ab]	57.56± 1.82 [ab]	69.19± 2.67 [ab]	53.45± 1.48 [ab]
Levofloxacin 10%	94.06± 7.24 [abc]	52.74± 1.76[abc]	61.42± 1.81 [abc]	50.07±1.38 [ab]
Levofloxacin 20%	95.79± 6.25 [abc]	42.15± 2.31 [abc]	56.63± 2.50 [abc]	45.93±1.36 [ab]
Levofloxacin 40%	98.20± 5.75[abc]	35.40± 2.20 [abc]	50.21± 3.64 [abc]	40.28±1.20 [abc]

a: means P≤0.05 when being compared to group control; b: means P≤0.05 when being compared to imiquimod group II; c: means P≤0.05 when being compared to clobetasol group.

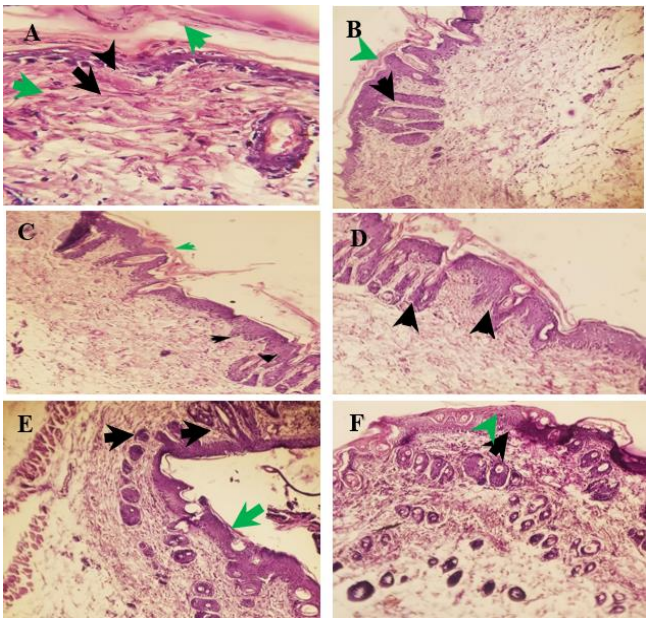

Figure 4: Histopathological effects of levofloxacin against imiquimod among study groups. a=control group; b =induction group; c = clobetasol group; d = levofloxacin 10% group; e = levofloxacin 20% group; f = levofloxacin 40% group. The epidermal layer (black arrow), keratin in the superficial most of the epidermal layer (green arrow) (A), thickening of epidermal layer which reveal extension of the epidermis deeply in the dermal layer (black arrow), thick keratin layer with parakeratosis (green arrow) (B),skin of clobetasol treated group show marked thickening of epidermal layer which reveal extension of the epidermis deeply in the dermal layer(black arrow) (D), thickening of epidermal layer with deep extensions of the epidermis in to the dermal layer (black arrow), thick keratin layer with parakeratosis (green arrow)(C), thickening of epidermal layer (blue arrow) with deep extensions of the epidermis in to the dermal layer (black arrow), thick keratin layer with parakeratosis (green arrow) (E), mid thickening of epidermal layer (black arrow), parakeratosis (green arrow) (F).

Discussion

In the present study, the inflammation induced by imiquimod may be mediated through the elevation of cytokines levels that include TNF alpha, IL8, IL17 and IL37. TNF-α (tumor necrosis factor alpha) and IL-17 (interleukin-17) are pro-inflammatory cytokines, which means they promote inflammation in the body (26). On the other hand, IL-37 (interleukin-37) is an anti-inflammatory cytokine, which means it reduces inflammation in the body (27). Studies have shown that TNF-α and IL-17 can induce the expression of other pro-inflammatory cytokines, such as IL-6 and IL-8 (28,29). They can also activate immune cells and cause tissue damage, leading to various inflammatory diseases, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease (30). In contrast, IL-37 has been shown to have potent anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (31). It Inflammatory cells, such as neutrophils, can release pro-angiogenic factors such as VEGF and bFGF in response to IL-8 and other pro-inflammatory cytokines (32,33) IL-8 is a pro-inflammatory cytokine that can promote angiogenesis, and its effects on both inflammation and angiogenesis are interrelated (34). can also suppress the activation of immune cells and reduce tissue damage, thereby preventing or alleviating inflammatory diseases (35). Thus, the levels of TNF-α, IL-17, and IL-37 can serve as biomarkers of inflammation and anti-inflammatory status in various diseases (36,37). Monitoring these cytokines can help in understanding the underlying mechanisms of inflammation and developing

new therapeutic approaches for treating inflammatory diseases. IL-8 (Interleukin-8) is a pro-inflammatory cytokine that has been shown to play a role in angiogenesis, the formation of new blood vessels from pre-existing ones. Angiogenesis is a complex process that involves the activation, proliferation, and migration of endothelial cells, which form the lining of blood vessels (38). IL-8 can promote angiogenesis by stimulating the production of other angiogenic factors such as VEGF (vascular endothelial growth factor) and basic fibroblast growth factor (bFGF). IL-8 can also directly promote the migration and proliferation of endothelial cells, leading to the formation of new blood vessels (39). In addition, IL-8 can also promote inflammation, which can in turn promote angiogenesis. The imiquimod-induced psoriasis-like skin inflammation model has attracted much attention over the past few years, due to its many similarities with human psoriasis (40). Imiquimod may produce erythema because it directly and/or indirectly degranulates mast cells via IgE-linked pathways (41). Mice were treated with imiquimod also developed a scaling rash on their backs. Scaling may have been caused by imiquimod-induced psoriasis-like skin inflammation, which mimics the pathogenesis of human psoriasis by activating IL17 axis (42). These phenotypical features, as measured by the scoring of the erythema and the scaled intensity that were influenced by imiquimod in this investigation and compatible with another study (43). Bowman and his colleagues found that clobetasol reduced erythema and scaling scores study that agreed with our findings (44). It is unclear how clobetasol, a powerful vasoconstrictor with a blanching effect, works to reduce erythema (45). Possible vasoconstriction results from the inhibition of vasodilators such as histamine and bradykinin, which in turn reduces erythema. The vasoconstrictive impact may have a role in the anti-inflammatory and immunosuppressive effects (46). Clobetasol's anti-inflammatory and anti-proliferative properties may explain why it reduced scaling via inhibiting the production of inflammatory cytokines and reducing immune cell activity (47). The dermis also showed signs of atrophy due to inhibition of fibroblast proliferation, migration, chemotaxis, and protein synthesis (48,49). In the present study, clobetasol found to be suppress the TNF alpha and IL6 levels and this effect was agreed with other study involved used of clobetasol on imiquimod-induced psoriasis (50). Regarding the effectiveness of clobetasol in the present study, it showed a more pronounced effect; clobetasol was able to impact the IL17 axis in the pathogenesis of psoriasis-like inflammation in mice such as decreasing TNF alpha, IL8, IL17, and IL37. It seemed to be compatible with another study on the effect of clobetasol against imiquimod (50).

In the current study, levofloxacin topical effect showed a reduction of erythema and scaling scores that induced by imiquimod. Topical levofloxacin concentration (10%, 20% and 40%) exerted therapeutic effects. It showed significant reduction effects on levels of TNF alpha, IL8, IL17 and IL37, through which it exerted anti-inflammatory effects and immunomodulation which may lead to amelioration of psoriatic lesion and the reduction of inflammatory signs of the skin. The current study data showed that topical application of it improved imiquimod-induced skin inflammation in mice. Levofloxacin treatment led to reduction in inflammatory markers and cytokines including TNF alpha such as IL-17 (51). Levofloxacin decreased the neovascularization area and reduced levels of inflammatory and angiogenic cytokines, showing that such a strategy is more efficient in treating neovascularization (52). The immune responses of quinolones may be indirectly by suppressing pro-inflammatory cytokines such as TNF-α and affecting both the growth and activity of T and B lymphocytes. Furthermore, their effect could be summarized by modulating the cytokines expression (53). In addition to what was mentioned above, the histopathological features improvement effect also clearly observed but there are no, or fewer studies are involved in the anti-psoriatic effects of a topical formulation of levofloxacin.

Conclusion

This study suggested that levofloxacin ointment when applied topically displays significant anti-psoriatic and anti-inflammatory activities in mouse model imiquimod-induced psoriasiform skin inflammation in mice.

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Conflicts of interest

The authors declare no conflict of interest.

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تأثير مرهم الليفوفلوكساسين ضد الصدفية المستحدثة بالايميكويمود في نموذج الفئران

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الخلاصة

إن الهدف من هذا الدراسة هو تحضير الليفوفلوكساسين كمرهم موضعي لتقييم فعاليته المضاد للصدفية المستحدثة بالإيميكويمود في الفئران. قسمت الستون فأرا، يتراوح معدل أوزانها بين ٢٤-٣٠ غم، إلى ست مجموعات وفي كل مجموعة عشر فئران بشكل عشوائي. إن المجموعة الأولى هي مجموعة السيطرة عوملت بوضع المرهم الأساس على منطقة الظهر بعد إزالة الشعر منها. وان المجموعة الثانية قد أعطيت كريم إلايميكويمود ٥٪ على منطقة محددة من الظهر لمدة ستة أيام كما تم إعطائها للمجموعات الأربع الأخر المتبقية بالطريقة ذاتها لاستحداث الصدفية المشابهة لالتهاب الجلد. بعد إعطاء كريم الإيميكويمود، عوملت المجموعات الثالثة والرابعة والخامسة والسادسة بوضع مرهم الكلوبيتازول ومرهم الليفوفلوكساسين ١٠، ٢٠ و ٤٠% على اظهر الفئران و حسب الترتيب شكل يومي. بانتهاء التجربة، استحصل الدم لتحضير المصل لغرض قياس المؤشرات الحيوية الالتهابية. بينما تستخدم عينات الجلد لدراسة التغيرات المرضية النسجية. أظهرت النتائج أن مرهم الليفوفلوكساسين مع التركيزات المذكورة قلل بشكل كبير من درجة الحُمامِيٌّ والتقَشُّر وتحجيم السمك البَشْرَويّ بالإضافة الى تقليل مستويات السيتوكينات الالتهابية وهي كل من عامل النخر الورمي الفا والانترلوكين الثامن والانترلوكين السابع عشر والانترلوكين السابع والثلاثون. إن مرهم الليفوفلوكساسين له فعالية قوية ومضادة للصدفية ومضادة للالتهاب.

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