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Azelaic Acid: Mechanisms of Action and Clinical Applications

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Abstract: AZA is a non-phenolic, saturated dicarboxylic acid with nine carbon atoms, naturally produced by the yeast Malassezia. It has diverse physiological activities, including antibacterial, anti-keratinizing, antimelanogenic, antioxidant and anti-inflammatory effects. AZA is widely used in dermatology and is FDA-approved for treating papulopustular rosacea. It also shows significant efficacy in acne vulgaris and melasma. This review summarizes the mechanisms of action and clinical applications of AZA, aiming to provide theoretical support for its clinical and cosmetic use and to facilitate further research.

Keywords: azelaic acid, mechanism, rosacea, acne, melasma, safety

Introduction

Azelaic acid (AZA), also known as azalea acid, is a beautiful mistake. Upon investigation, it was found that it has little to do with azaleas, as the similarity in their English names led to its early translation as azalea acid. AZA is widely present in nature, found in grains such as rye, wheat, and barley.[1] In the human body, it exists in small amounts in the urine of healthy individuals as a physiological component, synthesized from fatty acids via ω-oxidation.[2] Additionally, on the human skin surface, Pityrosporum ovale synthesizes and secretes AZA.[3]

The discovery of AZA in dermatology dates back to the 1970s, significant depigmentation was found in the lesions of pityriasis versicolor by a dermatologist in Rome. Further research revealed that the yeast Malassezia furfur, a normal skin commensal, could degrade unsaturated fatty acids into C8-C12 dicarboxylic acids, including AZA, which inhibit melanocytes.[4] AZA was first applied in combination with surgical treatment for malignant melanoma patients in 1980, achieving good results.[5] Subsequently, extensive research on AZA revealed its remarkable efficacy not only in inhibiting melanogenesis but also in exhibiting multiple physiological activities such as antibacterial, anti-keratinization, antimelanogenic, antioxidant and anti-inflammatory effects. It is extensively used in the treatment of various conditions, including rosacea, acne vulgaris, and melasma. In recent years, its popularity in cosmetics has been steadily increasing, indicating a broad application prospect.

Therefore, we systematically review the various mechanisms of action and clinical applications of AZA to provide theoretical support for its use in clinical and cosmetic fields and to lay the foundation for further research.

Molecular Characteristics

AZA is a straight-chain saturated dicarboxylic acid with the molecular formula $C_9H_{16}O_4$ and a molecular weight of 188.22. Due to its two carboxyl groups, it dissociates as a weak acid in aqueous solutions, with two pKa values, pKa1 at 4.5 and pKa2 at 5.3. The absorption of AZA strongly depends on the pH value and degree of dissociation in the topical formulation. Unlike other substances, increased dissociation enhances the absorption rate of AZA in the skin.[6] This is

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likely because higher dissociation improves the solubility of AZA in the formulation, thereby increasing the total skin permeation.

Mechanism of Action of AZA

We systematically elucidated and refined the potential mechanisms underlying AZA's effects on antibacterial activity, keratinization inhibition, melanogenesis suppression, antioxidant and anti-inflammatory responses through a comprehensive analysis of AZA's structure and properties, as illustrated in Figure 1.

Bacteriostatic

AZA exhibits bacteriostatic activity against bacteria such as *Propionibacterium acnes, Staphylococcus epidermidis, Staphylococcus aureus*, and *Pseudomonas aeruginosa*, as demonstrated by in vitro studies. Its bacteriostatic efficacy is concentration and pH-dependent, with more pronounced effects at low pH and high concentrations.[7,8] Unlike antibiotics, AZA does not induce bacterial resistance. It effectively targets antibiotic-resistant strains of *Propionibacterium acnes* and *Staphylococcus aureus*, closely related to its mechanism of action.[9–11] AZA can non-specifically traverse the bacterial cell membrane via ion transporters, subsequently lowering intracellular pH and disrupting membrane pH homeostasis. To maintain this balance, bacteria increase energy consumption, ultimately leading to decreased vitality or even death.[2] Additionally, AZA inhibits bacterial thioredoxin reductase activity, thereby suppressing protein and DNA synthesis.[12] This broad-spectrum antibacterial mechanism makes AZA less prone to inducing bacterial resistance.

One study evaluated the effects of AZA on the skin microbiota of individuals with acne vulgaris. Over a 28-day period of daily application of 15% AZA gel by 55 acne patients, microbial diversity at acne sites improved, with slight reductions in bacterial and staphylococcal populations, and a significant increase in lactobacilli. Long-term use brought the levels of *Propionibacterium* and *Staphylococcus* closer to those found in normal skin.[13] Another study, using a *Propionibacterium acnes* model, assessed the antibacterial effects of AZA micro-nanocrystals in vitro and explored their anti-acne efficacy in vivo. The findings demonstrated that AZA micro-nanocrystals inhibit *Propionibacterium acnes* and have a superior therapeutic effect on acne compared to standard AZA formulations.[14]

Antikeratin

AZA is a mild anti-keratinizing agent that exhibits reversible inhibitory effects on the proliferation of keratinocytes, with its action being dose- and time-dependent.[15] Studies indicate that the inhibitory effect of AZA is primarily achieved by inducing mitochondrial swelling and rough endoplasmic reticulum dilation in keratinocytes, thereby affecting

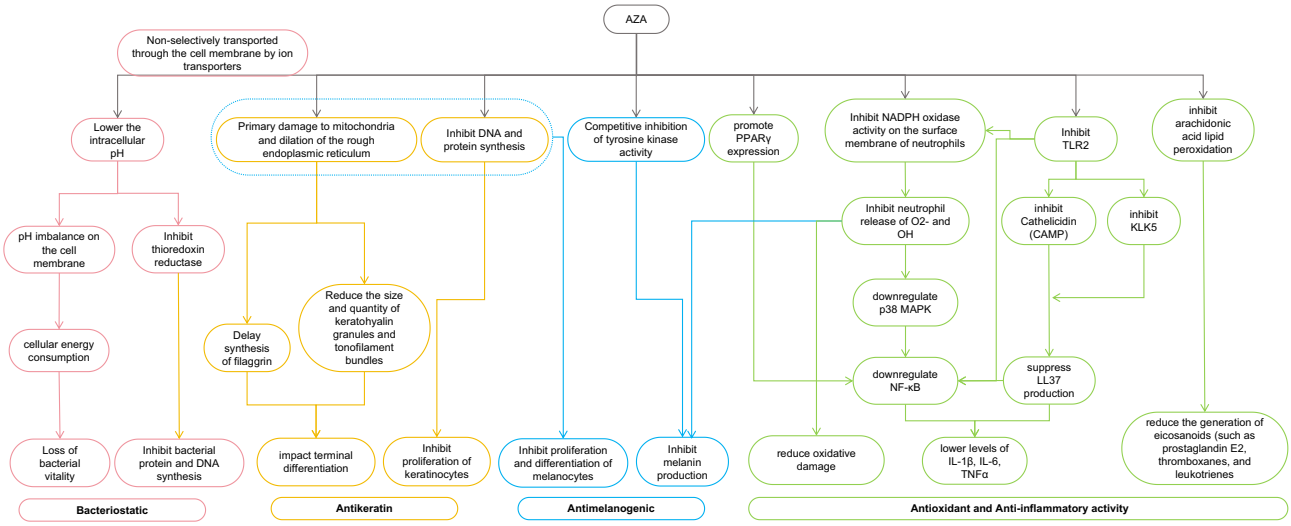

Figure 1 Mechanism of Action of AZA. This figure illustrates the mechanisms of action of AZA using different line colors: pink for the antibacterial mechanism, yellow for the anti-keratinization mechanism, blue for the antimelanogenic mechanism, and green for the antioxidant and anti-inflammatory mechanisms. AZA, Azelaic acid.

keratinocyte differentiation, particularly terminal differentiation[12,16,17] Keratohyalin granules and filaggrin are key markers of terminal differentiation in keratinocytes, with mature filaggrin aiding in the aggregation of keratin filaments to form tonofilament bundles, serving as the primary structural scaffold in keratinocytes.[18] Studies have demonstrated that AZA can delay the synthesis of filaggrin, reducing the size and quantity of keratohyalin granules and tonofilament bundles.[17] Additionally, AZA reversibly inhibits the synthesis of DNA, RNA, and proteins in keratinocytes, affecting their proliferation.[12,17]

A study demonstrated that 8–12 weeks of twice-daily application of 20% AZA cream to acne-affected skin led to significant reduction or normalization of intra- and interfollicular hyperkeratosis. Additionally, there was a notable decrease in both the number and size of keratohyalin granules in follicular and epidermal keratinocytes.[19] Another study evaluated the effects of 20% AZA cream, 0.05% retinoic acid (RA) cream, and a placebo cream on acne, focusing on anti-keratinization indicators. With 30 subjects randomly allocated into three equally sized groups, participants received either twice-daily application of 20% AZA cream, once-daily application of RA cream, or a placebo cream. Results showed that both AZA and RA significantly reduced the number of comedones compared to the placebo group, and the reduction in follicular hyperkeratinization induced by AZA was similar to that induced by RA.[20]

Antimelanogenic

AZA selectively targets hyperactive and malignant melanocytes without affecting normal cells. This may be related to the increased permeability of the membrane of abnormal melanocytes to AZA.[21] In vitro studies have shown that AZA can penetrate the cell membrane, disrupt mitochondrial respiration, induce rough endoplasmic reticulum expansion, and inhibit DNA synthesis, thereby suppressing the proliferation and differentiation of melanocytes.[15,22] Additionally, AZA competitively inhibits tyrosinase activity, a key enzyme in melanin production that promotes the conversion of tyrosine to dopa and dopaquinone, effectively inhibiting melanogenesis.[23] These multifaceted mechanisms contribute to AZA's efficacy in treating abnormal pigmentation disorders, while its selective action enhances safety. Numerous studies have reported the clinical application of AZA in treating conditions such as melasma, post-inflammatory hyperpigmentation.[24,25]

Antioxidant and Anti-Inflammatory Activity

AZA is a competitive inhibitor of various redox enzymes in vitro, including the aforementioned tyrosinase and thioredoxin reductase involved in DNA synthesis.[23] Additionally, AZA exhibits significant anti-inflammatory activity. The antioxidant and anti-inflammatory activities of AZA are interconnected and mutually influential.

Neutrophils are a significant source of ROS in the early stages of the inflammatory process.[26] Studies have shown that AZA can dose-dependently inhibit the release of ROS from neutrophils, such as hydroxyl radicals (OH·) and superoxide anions (O_2-). Further research indicates that this inhibition may be related to the suppression of Nicotinamide Adenine Dinucleotide Phosphate oxidase (NOXs) activity on the surface membrane of neutrophils.[27] It is well-known that ROS are crucial mediators of inflammatory responses, activating a series of inflammatory signaling pathways and triggering inflammation. Several articles have reported that AZA can interfere with the NF-κB/MAPK inflammatory signaling pathway. AZA inhibits MAPK p38 phosphorylation and impairs the translocation of NF-κB to the nucleus.[12] Additionally, AZA can modulate the inflammatory response by activating peroxisome proliferator-activated receptor gamma (PPARγ), inhibiting the transactivation of NF-κB, and reducing the production of pro-inflammatory cytokines.[28] Studies have shown that AZA can inhibit the mRNA expression of IL-1β, IL-6, and TNFα induced by UVB.[29] Furthermore, AZA can inhibit lipid peroxidation of arachidonic acid, potentially reducing the production of its peroxidation products, such as prostaglandin E2, thromboxane, and leukotrienes, which play significant roles in the development of inflammation.[30,31]

Additionally, AZA can inhibit the expression of toll-like receptor 2 (TLR2), a key molecule in recognizing various pathogens such as bacteria, viruses, fungi, and parasites, and playing a significant role in many diseases.[32] In rosacea, TLR2 expression increases, stimulating keratinocytes to produce more serine proteases, such as KLK5.[33] The upregulation of KLK5 leads to the aberrant accumulation of active LL37, which can promote inflammation through various pathways and induce the upregulation of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8. Additionally, LL37

bind to TLR2 on keratinocytes, creating a positive feedback loop that amplifies and sustains inflammation. LL37 also activates the NF-κB signaling pathway.[34] Studies have shown that AZA not only inhibits TLR2 but also effectively suppresses KLK5 and LL-37, providing a theoretical basis for its use in rosacea treatment.[35] AZA was approved by the FDA for the treatment of papulopustular rosacea (PPR) in 2002. Additionally, the overactivity of TLR2 also plays a crucial role in the pathogenesis of acne. *Propionibacterium acnes* can stimulate TLR2 activity, inducing skin inflammation.[36,37] Similar to its mechanism in treating rosacea, the inhibition of TLR2 activity by AZA helps explain its efficacy in the treatment of acne vulgaris.[38]

Clinical Applications of AZA

AZA, as a natural dicarboxylic acid, exhibits broad-spectrum antibacterial effects, mild anti-keratinizing actions, selectively targets hyperactive melanocytes and excellent antioxidant and anti-inflammatory properties. These characteristics confer soothing, whitening, and spot-fading benefits. Therefore, AZA is frequently used clinically for skin beautification and the treatment of skin diseases.

Rosacea

Rosacea is a chronic inflammatory skin condition primarily affecting the central face, characterized by recurrent flushing and erythema. 15% AZA was approved by the FDA in 2002 for the topical treatment of PPR, and it has been in use for over 20 years. AZA was included in the standard management options for rosacea by the Rosacea guidelines of the National Rosacea Society Expert Committee in 2019.[39] AZA is rated as Grade A evidence for the treatment of PPR and is also recommended in the Chinese guidelines for the diagnosis and treatment of rosacea.[40] There are an increasing number of clinical reports on the application of AZA in the treatment of PPR.

A large randomized, double-blind study compared the efficacy of AZA foam with vehicle foam in patients with PPR. The study included 961 subjects, who were randomly assigned in equal proportions to either the AZA group or the vehicle group. The single treatment dose of AZA was 0.5g, administered twice daily for a total of 12 weeks. The results indicated that the 15% AZA group showed significant improvement in IGA scores compared to the vehicle foam group (32.0% vs 23.5%; $P<0.001$), with a significant reduction in the mean percentage of inflammatory lesion counts (61.6% vs 50.8%; $P<0.001$) and a notable improvement in erythema scores (61.5% vs 51.3%; $P<0.001$). Although the incidence of drug-related adverse reactions was higher in the AZA group than in the control group, the tolerance was good, and the rate of discontinuation due to adverse events was low.[41] Another study also supported that AZA gel was more effective than vehicle gel in reducing erythema and inflammation in PPR subjects, with good tolerability and no unexpected adverse events.[42]

Another randomized, double-blind study evaluated the efficacy of 15% AZA gel versus 0.75% metronidazole gel in treating PPR. In this study, a total of 251 subjects were randomly assigned to receive either AZA gel or metronidazole gel, with both treatments administered twice daily for 15 weeks. The results indicated that AZA demonstrated a significant therapeutic advantage in both investigator-assessed and patient-assessed efficacy.[43] Another trial comparing the efficacy of 15% AZA gel with 1% metronidazole gel also supported this view. The study demonstrated that the AZA regimen acted more quickly and effectively.[44]

A clinical study was conducted in two phases, involving a total of 172 participants. In the initial phase, patients with moderate to severe PPR were treated with a combination of 15% AZA gel and 100mg oral doxycycline, administered twice daily for 12 weeks. In the second phase, subjects who showed good clinical outcomes in the first phase were randomly assigned to apply either 15% AZA gel or a vehicle gel for maintenance treatment, twice daily for 24 weeks. The results showed that at the end of the first phase, 81.4% of the subjects had a reduction in inflammatory lesions by 75% or more, and 64% of the patients achieved treatment success. During the maintenance phase, 15% AZA gel provided better maintenance effects.[45]

Additionally, we conducted a detailed review of several clinical reports on the application of AZA for rosacea over the past 10 years, as summarized in Table 1. Extensive clinical studies on AZA for the treatment of PPR have demonstrated its excellent efficacy and good tolerability, providing valuable treatment guidance for clinicians.[46–50] However, additional clinical reports are needed to offer more options and further benefit patients.

Table 1 Clinical Applications of AZA in Dermatology

Authors, Year	Skin Condition	Study Design	Research Method	Concentration and Dosage Form	Results	Side Effect
Dall'Oglio et al, 2021[46]	Mild to moderate inflammatory rosacea	A multicentre, prospective, open-label trial	Forty-five adult patients applied a cream containing 15% azelaic (AZA) and 1% dihydroavenanthramide D twice daily for 8 weeks	Cream containing 15% AZA	Forty-four patients completed the study. By week 8, significant reductions were observed in the Investigator Global Assessment (IGA) score [median from 3 (T0) to 1 (T1)], inflammatory lesion count [median from 8 (T0) to 1 (T1)], and erythema score [median from 2 (T0) to 1 (T1)]	Only one case of severe erythema as a local side effect was recorded, and 90% of patients assessed the product's tolerability as excellent
Draelos et al, 2015[47]	Moderate to severe PPR	A Phase 3 randomized, double blind, vehicle-controlled, parallel-group, multicenter study	A total of 1156 patients were randomly divided into two groups: one group used 15% AZA foam, and the other used a placebo, both applied twice daily for 12 weeks	15% AZA foam	A total of 961 patients completed the trial. At the end of treatment, the AZA group had a significantly lower IGA score and a greater reduction in inflammatory lesion count (ILC) compared to the vehicle group (P<0.001 for both)	Drug-related adverse events (as assessed by investigators) were slightly higher in the AZA foam group (7.6%) compared to the vehicle group (4.6%). These events, mainly skin-related and occurring at the application site, were more common in the AZA group (7.0%) and included pain, itching, and dryness. They peaked in the first 4 weeks and decreased thereafter, with over 96% resolving by the end of the study
Tyring et al, 2016[48]	Moderate or severe PPR	A randomized, double-blind, vehicle-controlled, parallel-group, multicenter, phase 3 study	A total of 961 patients were randomly assigned to either the AZA foam group or the vehicle group, with application to the entire face twice daily for a total of 12 weeks	15% AZA foam	The AZA foam group had higher treatment response scores (excellent 17.2%; good 40.0%) compared to the vehicle group (excellent 9.7%; good 35.0%) with a statistically significant difference. Dermatology Life Quality Index (DLQI) scores improved more in the AZA group (2.6 vs 2.1; P=0.018), and 24.6% of AZA patients had a DLQI improvement of over 5 points, versus 19.0% in the vehicle group (P=0.047)	Tolerability was rated as excellent or good for 67.8% of the AZA foam group versus 78.2% of the vehicle group. The AZA group had a higher incidence of drug-related adverse events (7.7% vs 4.8%), including pain (3.5% vs 1.3%), itching (1.4% vs 0.4%), and dryness (1.0% vs 0.6%). The vehicle group had one case of serious adverse event (application site dermatitis), with other events being mild or moderate
Williamson et al, 2019[49]	Erythematotelangiectatic and PPR (74.1% each)	A non-interventional, prospective, observational design	Fifty-four patients with confirmed rosacea, enrolled via the Rosacea Concierge Program and using azelaic acid foam as monotherapy, were screened. Participants were required to be 18 years or older and willing to participate	15% AZA foam	Most patients (74.1%) had no concerns about the treatment. Cost was the primary concern (11.1%), with an average importance score of 9.3 (on a 10-point scale). Overall satisfaction averaged 79.0, and treatment efficacy scored 70.8. The impact of rosacea on quality of life was minimal (mean DLQI: 2.35).	The majority (77.8%) of patients reported no side effects. Reported side effects included dryness (13%; importance score (IS): 5.3), stinging (7.4%; IS: 2.5), itching (5.6%; IS: 4.7), or burning (3.7%; IS: 7.0)
Dall'Oglio et al, 2021[50]	Mild to moderate PPR	A pilot, prospective, two-center, assessor-blinded, instrumental evaluation study	Thirty patients applied the cream twice daily, morning and evening, for 8 weeks.	A cream containing modified glutathione (0.1%), β-glycerol (0.5%), and azelaic acid (10%).	Twenty-six (87%) completed the study, while four dropped out due to low skin tolerance (n=3) or being lost to follow-up (n=1). At baseline, the mean IGA score was 2.6 (0.9). At week 8, the score significantly dropped to 1.2 (1) (p=0.0001). The inflammatory lesion count reduced by 63% from baseline (5.1) to week 8 (1.9), confirmed by VISIA images. Hemoglobin content also dropped significantly by 24% on ANTERA 3D images.	Not reported

(*Continued*)

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Table 1 (Continued).

Authors, Year	Skin Condition	Study Design	Research Method	Concentration and Dosage Form	Results	Side Effect
Tomić et al, 2021[51]	Mild to moderate Acne vulgaris	A double-blind, randomized controlled trial	Sixty patients were randomly assigned to two groups, receiving either 10% AZA nanocrystals (AZA-NC) hydrogel or 20% AZA cream, applied 1 gram twice daily for 8 weeks	Treatment group: 10% AZA-NC hydrogelControl group: 20% AZA cream	By the 8th week of treatment, the success rate of the 10% AZA-NC hydrogel reached 36.51% ($p < 0.001$), while the AZA cream achieved 30.37% ($p < 0.001$). The AZA-NC hydrogel reduced inflammatory lesions by 39.15% ($p < 0.001$) and non-inflammatory lesions by 34.58% ($p < 0.001$), compared to 33.76% and 27.96% for the AZA cream. The effectiveness of the 10% AZA-NC hydrogel was comparable to the 20% AZA cream	The 10% AZA-NC demonstrated better safety compared to the 20% AZA cream, with a lower incidence of adverse events, most of which were mild
Szymańska et al, 2021[52]	Mild to severe acne	A self-comparison trail	Thirty-five women with facial acne received 30% AZA peels every two weeks, for a total of six treatments	30% AZA, pH 2.4	After treatment, there was a significant reduction in sebum secretion, and both the total number of acne lesions and the severity of the condition showed marked improvement	All participants tolerated the treatment well, with no dropouts due to side effects. Reported effects included burning, stinging, mild itching, and redness lasting up to one hour post-treatment
Chilicka K et al, 2020[53,54]	Mild to moderate Acne vulgaris	A prospective parallel randomized clinical trial	120 women were randomly divided into two groups: one received AZA, and the other received pyruvic acid (PA), with treatments given every 2 weeks for 6 sessions	AZA group: Exfoliant 1 (16% AZA, 10% mandelic acid, 2% salicylic acid); Exfoliant 2 (16% AZA) PA group: Peeling agent (50% PA, pH 0.8)	Both AZA and PA groups showed significant improvements in acne severity and skin oiliness, with PA being more effective in reducing oiliness. The PA group had slightly higher quality-of-life scores than the azelaic acid group	AZA's side effects mainly included itching, burning, irritation, and abnormal sensations
Abdel Hay et al, 2019[55]	Mild to moderate Acne vulgaris	Single-blinded randomized clinical trial	A total of 34 patients were included, receiving 4 treatments every 2 weeks. A 20% AZA and 20% salicylic acid (SA-AZA) mixture was applied to one side of the face, while 25% tricarboxylic acid (TCA) was applied to the other side	SA-AZA group: 20% AZA and 20% salicylic acid TCA group: 25% TCA	After two treatments, non-inflammatory lesions improved significantly on the TCA side, and inflammatory lesions improved on the SA-AZA side. Both treatments showed similar overall improvements, with no significant difference. Redness improved on both sides, and patients were more satisfied with the SA-AZA treatment	Most patients had a burning sensation and mild redness that resolved within a week, with no difference between treatments. In the TCA group, 30% (10 patients) had persistent redness and severe peeling for over a week, and 15% (5 patients) developed excess pigmentation after 2 weeks and needed bleaching treatment
Shucheng et al, 2024[25]	Acne-related PIE and PIH	A randomized, double-blind, placebo-controlled trial	72 patients were divided into two groups: one group used 15% AZA gel, and the other used a placebo gel, both applied twice daily for 12 weeks	15% AZA gel	Among the 60 patients who completed the trial, the AZA group showed significant reductions in PIE, PIH, hemoglobin, and melanin levels after 12 weeks. They also had greater DLQI improvement and higher satisfaction, all with statistical significance ($P < 0.05$)	Mild skin reactions, such as erythema and stinging, occurred in 66.67% of patients in the AZA group. A pause in treatment for 3–5 days, along with enhanced moisturizing and sun protection, was recommended. Symptoms usually resolved within 7 days, and patients developed tolerance. No side effects persisted by week 8 or 12
Sobhan et al, 2023[56]	Acne-related PIH	Single-blinded randomized clinical trial	Sixty participants diagnosed with acne-related PIH were randomly assigned to the AZA group or the tranexamic acid (TXA) group. Both groups applied their respective treatments twice daily for 12 weeks	AZA group: 20% AZA cream TXA group: 5% TXA solution	acne-related PIH scores improved in both the AZA and TXA groups ($P_{time} < 0.001$), with no significant difference between them ($P_{group} = 0.05$). There was also no significant interaction between time and treatment ($P_{time \times group} = 0.66$)	At week 4, the AZA group experienced significantly more side effects, such as redness and stinging, compared to the TXA group ($P < 0.05$). By weeks 8 and 12, side effect rates were similar ($P > 0.05$)

Akl et al, 2021[57]	Bilateral melasma	Randomized controlled study	Fifty women with melasma were split into two groups: one used 20% azelaic acid liposome cream and the other 4% HQ. Both applied their creams at bedtime, starting with 15 minutes and increasing based on tolerance, for three months. All participants also took 250 mg of TXA daily	AZA group: 20% azelaic acid liposomes creamHQ group: 4% HQ cream	Women using 20% azelaic acid liposome cream had greater improvement in melasma and quality of life compared to those using 4% HQ. The 20% azelaic acid cream also showed better tolerance	20% azelaic acid liposome cream had significantly better tolerance than 4% HQ
Malik et al, 2019[58]	Bilateral melasma	An interventional comparative study	One hundred patients were divided into two groups: one used 3% TXA topically twice daily, and the other used 20% AZA topically once daily at night. Both groups took 250 mg of TXA orally twice daily for 6 months	TXA group: 3% TXA solution AZA group: 20% AZA	At 6 months, the average melasma area severity index (MASI) score in TXA group was significantly lower than in group B (6.06 ± 5.06 vs 10.62 ± 7.43, p = 0.001). The TXA group had 14 participants (28%) with excellent responses, compared to 11 participants (22%) in AZA group	Not reported
Rohullah et al, 2023[59]	Centrofacial melasma	A single blind-randomized clinical trial study	Fifty patients with central facial melasma were randomly selected and equally divided into two groups. One group received HQ treatment, while the other received azelaic acid treatment, applied once nightly for 10 weeks	AZA group: 20% AZA cream HQ group: 4% HQ cream	HQ users had better skin color improvement than azelaic acid users. 61% of HQ users saw good or excellent results, with 31% reporting side effects. For azelaic acid, 34% had good improvement, and 21% experienced side effects	Patients using azelaic acid experienced fewer adverse effects and better tolerance compared to those using HQ
Komal et al, 2021[60]	Melasma	Comparative prospective study	116 female patients were randomly assigned to two groups: Group A received intradermal TXA injections (20 mg in 0.8 mL normal saline) every two weeks, with 1 to 3 mL (20–60 mg) per visit, for a total of three treatments over six weeks. Group B applied 20% azelaic acid once daily for six weeks.	Group A: TXA solution Group B: 20% AZA cream	The MASI scores before and at 6 weeks of treatment were 7.10±2.94 and 5.27±2.44 in Group A, and 7.56±2.57 and 5.76±2.89 in Group B. The effective rates for poor, good, and excellent responses were 27.6%, 41.4%, and 31% for TXA injection, and 62.1%, 20.7%, and 17.2% for azelaic acid. The differences were statistically significant (p=0.001)	Not reported

Abbreviations: AZA, azelaic Acid; IGA, Investigator Global Assessment; PPR, papulopustular rosacea; ILC, inflammatory lesion count; DLQI, Dermatology Life Quality Index; IS, importance score; AZA-NC, AZA nanocrystals; PA, pyruvic acid; SA, salicylic acid; SA-AZA, combination of salicylic acid and azelaic acid; TCA, tricarboxylic acid; TXA, tranexamic acid; HQ, hydroquinone; MASI, melasma area severity index.

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Acne Vulgaris

Acne is a chronic inflammatory skin disease that commonly affects the pilosebaceous units of the face, particularly during adolescence. Its clinical manifestations include comedones, papules, pustules, nodules, and cysts. AZA is an effective anti-acne medication with good therapeutic effects on both non-inflammatory and inflammatory acne, especially the latter, commonly used in concentrations of 15% and 20%.[61] It is now recommended by most physicians as a second-line treatment option.[62] Studies have shown that AZA can be used for maintenance therapy in acne, extending the period without relapse, with effectiveness comparable to adapalene.[63,64] With sufficient evidence supporting its use and high safety, the European evidence-based guidelines also recommend AZA with medium strength for the treatment of acne.[65] Currently, there are increasing cases of AZA being used to treat acne.

AZA can inhibit sebum secretion, although its exact mechanism remains unclear. This has a positive effect on the treatment of acne. One study evaluated the effects of a 30% AZA peel on sebum secretion and acne in patients with acne vulgaris. A total of thirty-five acne patients received facial applications of a 30% AZA solution (pH 2.4) for 10 minutes, biweekly, for six treatments. The measured outcomes were sebum secretion and improvement of acne.The results showed that after AZA treatment, sebum secretion was significantly reduced, and the total number and severity of acne lesions also significantly improved.[52] Another study evaluated the effect of a 20% AZA solution on sebaceous gland activity in patients with acne vulgaris. Similar conclusions were reached, and the study found that sebaceous gland activity remained reduced 12 weeks after the final treatment, with scores lower than those recorded 2 weeks after the final treatment. This indicates that AZA peeling has a long-term inhibitory effect on sebaceous gland activity and improves acne treatment outcomes.[66]

AZA can improve post-inflammatory erythema (PIE) and post-inflammatory hyperpigmentation(PIH).[67] A study evaluated the efficacy and safety of a 15% AZA gel in treating acne-induced PIE and PIH. A total of 72 patients with mild to moderate acne were enrolled and randomly assigned to two groups: the AZA group and the control group. The AZA group applied 15% AZA gel twice daily for 12 weeks, while the control group used a blank vehicle. Key indicators included the post-acne hyperpigmentation index, melanin content, hemoglobin levels, and adverse reactions. Results showed that, compared to the control group, the AZA group had significantly lower post-acne hyperpigmentation index, melanin content in the lesions, and hemoglobin levels, with fewer adverse reactions.[25]

AZA can improve patients' Dermatology Life Quality Index (DLQI). One study assessed the impact of a 20% AZA cream on quality of life and disease severity in adult female acne patients. A total of 251 participants with mild to moderate acne were included, and they applied the cream twice daily for 12 weeks. The median DLQI decreased from 9 at baseline to 5, with 90% of doctors and patients rating the treatment tolerance as very good or good.[68] In two comparative studies, AZA has consistently shown significant improvement in patients' DLQI. Although AZA treatment is less effective compared to treatments with 1% benzoyl peroxide/1% clindamycin and combined oral contraceptives, it still significantly improves acne therapy outcomes.[69,70]

In recent years, the use of AZA in acne treatment has increased significantly. We compiled clinical reports with a high number of studies from the past 5 years, as shown in Table 1. These studies have shown that AZA is effective and safe for the treatment of acne, providing an effective treatment option for acne patients.[25,51–56]

Melasma

Melasma is a chronic, acquired hyperpigmentation disorder of the facial skin, clinically manifested as light to dark brown patches with unclear boundaries, symmetrically distributed on the cheeks, forehead, and jaw. Hydroquinone (HQ) is the gold standard for melasma treatment; however, its repeated use can lead to permanent discoloration and ochronosis. Therefore, safer alternative topical treatments for melasma are needed. AZA is considered an effective and safer alternative to HQ, commonly used at concentrations of 15–25%.[71]

A study compared the therapeutic effects of 20% AZA and 4% HQ on melasma. It included 329 participants with epidermal or mixed epidermo-dermal type of melasma who were not pregnant or breastfeeding. Participants were randomly assigned to two groups: one using 20% AZA cream and the other using 4% hydroquinone cream, applied twice daily along with broad-spectrum sunscreen, for 24 months. At the end of the treatment period, there were no

significant differences between the groups in overall improvement scores (64.8% for AZA and 72.5% for HQ), the time course and magnitude of median lesion size reduction (71% for AZA and 78% for HQ), and improvement in pigment intensity (84.2% for AZA and 89.2% for HQ). AZA did not show severe adverse reactions such as allergic sensitization.[72] Subsequently, several studies also compared the therapeutic effects of 20% AZA and 4% HQ on melasma, yielding similar results.[73–75]

Several studies have also investigated the combined effects of AZA. One study examined the therapeutic effects of 20% AZA combined with 5% HQ compared to 5% HQ alone in melasma, applied nightly for 16 weeks. The results showed significant efficacy in both treatments, with better outcomes observed with the combination, albeit with increased side effects.[76] Another study observed the therapeutic effects of 20% AZA combined with 0.05% tretinoin cream, applied nightly for 12 weeks. The findings indicated some effectiveness in treating melasma, accompanied by notable adverse reactions.[77] Additionally, research compared three AZA-containing cosmetics for reducing female melasma using objective skin measurement parameters. The results demonstrated significant melanin reduction with all three products, most pronounced within the first three months of use. A combination containing 20% AZA, 10% mandelic acid, 5% phytic acid, 5% 4-n-butylresorcinol, and 5% arbutin proved most effective.[78] Lastly, a recent study evaluated the efficacy of locally applied 20% AZA and its combination with 755 nm picosecond laser in treating facial melasma. The findings showed significant improvement in melasma with 20% AZA alone or combined with picosecond laser treatment, without significant differences between the two approaches. Combination therapy exhibited better improvement in immune cells and dendritic cells.[79]

In addition, AZA is preferred in pregnancy with FDA category B. A study evaluated the efficacy and safety of AZA in treating melasma in pregnant women, involving 28 participants. They applied 15% AZA gel topically twice daily for four months. The results showed that 92.9% to 96.4% of cases experienced either disappearance or lightening of pigmented lesions. Compared to healthy skin, there was a reduction in size and contrast of the lesions, along with improvements in skin texture and quality of life. This suggests that topical application of 15% AZA gel twice daily is an effective and safe method for treating melasma in pregnant women.[80]

We further listed several clinical applications of AZA in the treatment of melasma over the past 5 years, as detailed in Table 1. Numerous studies have confirmed the efficacy and safety of AZA in treating melasma.[57–60] However, clinical practice requires further research to explore optimal treatment strategies. Only through simultaneous assessment of effectiveness and safety can we truly address patient concerns.

Other Skin Disorders

Psoriasis is an immune-related chronic inflammatory skin condition characterized by scaly red patches. Research suggests that AZA can improve symptoms of psoriasis. In a single-blind randomized clinical trial, patients had lesions on their left and right sides randomly assigned to receive either 15% AZA gel or placebo treatment twice daily for one month. The results showed that compared to placebo, AZA treatment significantly improved symptoms, effectively reducing the pruritus, scaling, and hyperkeratosis of psoriasis plaques.[81]

Alopecia areata is an autoimmune condition marked by temporary, non-scarring hair loss. A study assessed the efficacy of 20% AZA cream in treating patients with alopecia areata. The control group used topical 0.05% clobetasol propionate cream, applied nightly for 12 weeks with monthly follow-ups. The results indicated that topical 20% AZA showed acceptable efficacy compared to 0.05% topical clobetasol propionate. This suggests that 20% AZA is an effective topical treatment for patients with alopecia areata. Another study comparing 20% AZA with 0.5% anthralin in treating alopecia areata also supported this conclusion.[82]

Folliculitis is a skin condition that often recurs, presenting with inflammatory papules and pustules in multiple body areas. Research indicates that applying 15% AZA foam twice daily to affected areas for 4 weeks resulted in a 78% reduction in overall folliculitis. This suggests that 15% AZA foam may be an effective treatment or adjunct therapy for folliculitis.[83]

Studies have also reported clinical applications of AZA in conditions such as melasma, female pattern hair loss, perioral dermatitis, and keratosis.[84–87] AZA exhibits diverse mechanisms, and its therapeutic effects in various skin conditions warrant further exploration.

Concentration and Dosage Form

In clinical applications, the most commonly used concentrations of AZA are 15% and 20%. In certain cases, such as for acne treatment, higher concentrations of AZA, such as 30%, are also utilized. In contrast, the concentration of AZA used in cosmetic products is typically lower and often combined with other ingredients, although 15% and 20% AZA skincare products are also available on the market.[24,52,88,89]

The percutaneous absorption of AZA is relatively poor and is influenced by concentration and dosage form. While higher concentrations can enhance skin absorption, they also increase the risk of side effects. To improve the percutaneous absorption of AZA, researchers have proposed various dosage forms, including gels, foams, microemulsions, liposomes, ethosomes, and liquid crystal formulations. These dosage forms are designed to enhance the solubility and permeability of AZA in the skin while reducing the required dosage.[90] Studies have shown that after the application of a single dose of topical AZA cream, approximately 3–5% of the drug is retained in the stratum corneum. However, when using a gel formulation, the percutaneous absorption rate can increase to 8%.[91,92] These findings provide valuable insights into improving the percutaneous absorption of AZA.

Safety

AZA is classified as pregnancy category B for topical use and is suitable for individuals aged 12 and above. Local application of 15% or 20% AZA is well tolerated in humans, with main adverse effects being mild and transient sensations of stinging, burning, or itching. There are no significant systemic adverse reactions or photosensitivity reported.[92,93] Overall, AZA appears to be highly tolerated with high patient satisfaction rates.

Conclusion

This review summarizes the mechanisms of action and research progress of AZA in various diseases. AZA acts through multiple mechanisms, including inhibiting neutrophil ROS release, interfering with inflammatory cytokine expression, reducing bacterial intracellular pH, damaging mitochondria and endoplasmic reticulum, and inhibiting DNA, protein, and tyrosinase synthesis. These actions contribute to its antibacterial, keratolytic, depigmenting, antioxidant, and anti-inflammatory effects. AZA is FDA-approved for treating PPR, and research supports its use in melasma and as a second-line treatment for acne vulgaris. However, its application in conditions like psoriasis, alopecia areata, and folliculitis is less explored, indicating a need for further studies.

Abbreviations

AZA, azelaic acid; RA, retinoic acid; OH, hydroxyl radicals; O2-, superoxide anions; NOXs, Nicotinamide Adenine Dinucleotide Phosphate oxidase; PPARγ, peroxisome proliferator-activated receptor gamma; TLR2, toll-like receptor 2; PPR, papulopustular rosacea; IGA, Investigator Global Assessment; PIE, post-inflammatory erythema; PIH, post-inflammatory hyperpigmentation; HQ, Hydroquinone; ILC, inflammatory lesion count; DLQI, Dermatology Life Quality Index; IS, importance score; AZA-NC, AZA nanocrystals; PA, pyruvic acid; SA, salicylic acid; SA-AZA, combination of salicylic acid and azelaic acid; TCA, tricarboxylic acid; TXA, tranexamic acid; MASI, melasma area severity index.

Disclosure

The authors report no conflicts of interest in this work.

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