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Review Article

Efficacy of AMXs, Natural Filaggrin and TNF-alpha Modulators containing *V. amygdalina leaf Extracts,* on Inflammatory Skin Diseases

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Abstract: Environmental inflammatory skin diseases, such as atopic dermatitis (AD) and contact dermatitis (CD) are common skin disorders in both industrialized and developing countries. They are characterized by a defect of the skin barrier and increased inflammatory response. Worldwide, the prevalence of environmental and occupational dermatitis has increased exponentially during the COVID-19 pandemic due to the elevated utilization of disinfectants and personal protective equipment (PPE). Steroids have long been used as the first-line treatment for dermatitis; but consid ering their side effects and contraindications, there is a need of effective treatments with better safety profile. This mini-review and case report highlights the skin health benefits of African plant *V. amygdalina* leaf extracts (AMXs). Our research team was the first to explore the beneficial health effects of AMXs in animal models of atopic (AD) and contact dermatitis (CD). It was observed that the water (AMX1) and ethanolic (AMX2) leaf extracts were as effective as topical steroid preparation in preventing and alleviating AD and CD, as well as in relieving itch, skin erosion and excoriation. Another study (immuno-fluorescence assay) showed that AMX and AMX-contained *Vernodalin* both have significantly increased the production of filaggrin (FLG) in mouse skin and reduced plasma TNF-alpha (vs. steroid). In our clinical investigation in patients with moderate to severe AD and CD, AMX1 and AMX2 were as effective as steroid preparation; but relatively more effective in relieving itch and healing wounded skin. Four clinical cases of African and Japanese CD patients successfully treated with AMX2 are also presented. Research findings and observations from recent CD cases suggest that AMXs are effective and could be used as therapeutic alternative to steroids, with a better safety profile, in the management of inflammatory skin diseases, particularly AD and CD.

Keywords: Atopic dermatitis, Contact dermatitis, Eczema area severity index (EASI), *Vernonia amygdalina*

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1. Introduction

Inflammatory skin diseases caused by exposure to occupational and environmental factors, such as atopic dermatitis (AD) and contact dermatitis (CD), are common diseases in almost all countries. They are characterized by a defect in the skin barrier and an increased inflammatory response [1,2]. Their prevalence has increased over the last few decades due to rapid urbanization, increased use of disinfectants and personal protective equipment (PPE), especially during the COVID-19 pandemic [2]. Steroid-based drugs have long been used as the first line drugs or inflammatory skin diseases; however, given

their multiple side-effects and contraindications, there is a need to find new, safer and more effective treatments.

1.1. Atopic Dermatitis

AD is a common chronic infammatory skin disease that affects people of all ages, both children and adults, with a prevalence of up to 10% or more in most high income countries. In Asia-Pacific region, higher prevalence of AD in adult population has been reported. AD is the leading cause of the gobal burden of skin diseases that significantly impacts patients' quality of life. Additionally, AD which is manifested with symptoms such as xerosis or skin dryness, erythema, edema and pruritus, is associated with psychological issues such as depresssion, sleep disturbance and anxiety [3,4]. The etiology of AD is multifactorial, involving a complex interplay of skin barrier function impairment, immune dysregulation and environmental factors. There is no cure for AD; the treatment goals include the reduction of symptoms and disease flare prevention [3].

1.2. Contact Dermatitis

Contact dermatitis (CD) is an inflammatory sin disease caused by exposure to either irritants substances or contact allergens. There two major types of CD: allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD). Other CD types include photoinduced CD (photodermatitis), systemic contact dermatitis and non-eczematous contact dermatitis [5]. The well-known diagnostic approach for CD is the patch test. In the management of CD, it is important to restore the damaged skin barrier and reduce the inflammation. Corticosteroids and immunosuppressant drugs are most commonly used treatment, despite their numerous adverse effects [5].

1.3. Vernonia amygdalina: A African Plant with Numerous Health Benefits

Vernonia amygdalina, also known as bitter leaf in eastern Africa, has a variety uses in Africa both as source of nutrients and phytomedical compounds. Its leaves are rich in protein, crude fiber, minerals such as sodium, potassium, calcium, magnesium, zinc, and iron, making the plant an good source of food [6,7]. The plant has been studies in mainly western Africa for its beneficial health effects in traditional medicine. The extracts of the plant have been reported to have antioxidant, anticancer effects. Additionally, the leaves are used as appetite stimulant and indigenous treatment for the management of parasitic infections (malaria, leishmaniasis), diabetes and gastrointestinal disorders in some African countries [8-10].

The present report is a mini-review that highlights the effectiveness of AMXs on inflammatory skin disorders, enriched with three case reports.

2. Animal studies

2.1. Animal model of Allergic contact dermatitis (ACD)

This review of the literature includes experimental studies our team has conducted previously. Animal studies, three in total, included a preventive and a curative protocols using NC/Nga mice; dermatitis was induced by topically applying 15µl of 1% trinitrochlorobenzene (TNCB) on the skin.

2.2. Treatments and Approach used to assess the disease severity in animals

The concentration of the water (AMX1) and methanolic (AMX2) extracts of *V. amygdalina* was 7mg/m. Hydrocortisone ointment (steroid preparation) 0.1% was used a positive control, and vaseline as negative control. The severity of skin lesions was evaluated macroscopically using a scoring scale described previously, for each of the skin lesions (scaling/squamous lesion, erythema/hemorrhage, erosion/excoriation): 0, no symptom; 1, mild; 2, moderate; 3, severe) [6,7].

The effect of AMX on skin filaggrin (FLG) production was assessed on mice skin samples using immunofluorescence assay. The intensity of immunofluorescence of skin samples from mice treated with AMX, and AMX-derived terpenoid compound, *Vernodalin*, was compared to that of steroid-treated mice.

2.3. Main findings

The immunofluorescence assay of mouse skin samples showed that topical application of AMX and *Vernodalin* increased the FLG expression in a dose-response manner. This suggests that both *V. amygdalina* leaf extracts and their bioactive terpenoid compound, *Vernodalin,* have similar effect in regard to FLG production in the skin. On the other hand, the main findings on the effects of AMXs were as follows: allergic mice treated with AMX1 and AMX2 had significantly reduced severity score for scaling/xerosis ($p<0.01$; oneway ANOVA) as compared with the negative control mice; their anti-inflammatory activity was similar to that of the steroid preparation. Furthermore, for mice that had more severe skin lesions (wounded skin), AMX1 and AMX2 were as effetice as steroid drug for erythema/hemorrhage as well as skin erosion and excoriation. Compared to the negative control group, AMXs and steroid preparation had markedly reduced severity of wounded skin lesions ($p<0.01$) [11].

3. Clinical investigation

3.1. Treatments

The clinical investigation consisted in the treatment of AD and CD (both irritant and allergic CD) with the use of AMXs in comparison with a steroid drug (*Dexamethasone 0.2%*). The AMX ointments used in patients with either AD or CD (5 – 17 years of age) were at a concentration of 5 - 10%, mixed with either inactive cream or vaseline. Vaselin was used as negative control treatment.

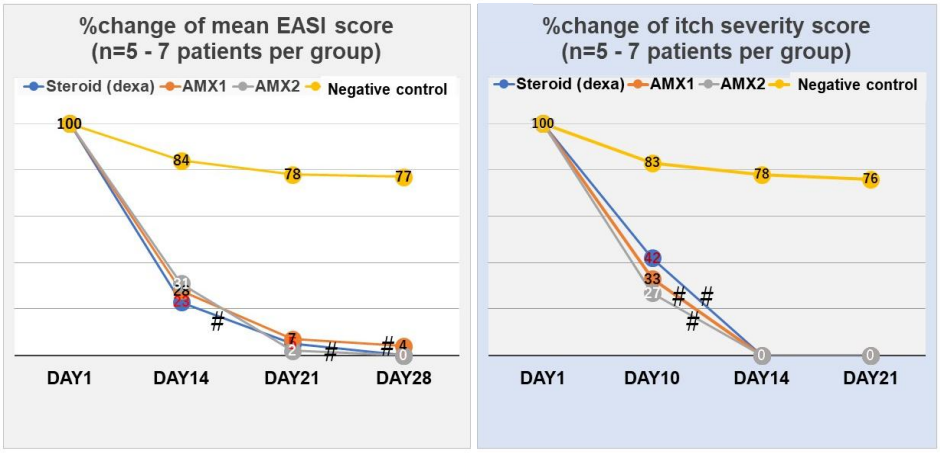
3.2. Assessment of the Severity of Skin Lesions in Patients

Treatment efficacy was assessed using the eczema area and severity index (EASI) score, estimating the total score for the following skin lesions: erythematous macule, scaling/xerosis, squamous lesion, erosion, excoriation and scratching lesion. The EASI assessment integrates body surface and the intensity of lesional skin into a composite score as described previously [12,13]. We observed that treatment with both AMX1 and AMX2 were as effective as steroid therapy in alleviating AD and CD skin symptoms, whereas AMXs had a better anti-itch effect as compared with the steroid drug (Fig. 1). All three treatmet groups had significantly lower EASI and itch scores ($p<0.01$) from day14 as compared with the negative control (vaseline) group. Furhermore, blood test showed decreased white cell count and serum CRP levels in AMXs and *dexamethasone* groups ($p<0.05$; vs. vaselin).

4. Case reports

4.1. Case 1: Allergic contact dermatitis in a female Japanese healthcare worker in Kagawa prefecture

As part of anti-COVID19 measures, the use of desinfectants and personal protective equipment (PPE) has increased considerably in medical setings in last five years. In 2022, the patient (a member of our research team) presented with itchy erythematous macules on her left upper limb following the use of a new stock of a desinfectant solution containing ethanol, glycerin, myristin, alantoin and other ingredients. In addition to severe itch, she presented erythema and scratch markings as main skin lesions whose severity increased day after day (Fig. 2). A week later, she started topical AMX2 treatment which relieved itch at day3. The following day, her skin health was recovered almost completely. At the first visit, blood test revealed increased eosinophil count; She was advised to refrain from using the new desinfectant; no patch test was performed.



(a) (b)

Figure 1. (a) Percent (%) change of mean eczema area severity index (EASI) and (b) itch severy scores by treatment group in atopic and contact dermatitis patients (Ngatu et al., 2014) [14]: Significantly reduced EASI (dermatitis) score and itch severity were observed in both AMX and steroid-treated patients' groups as compared to the negative control (vaselin) group; No significant difference was observed when comparing topical AMXs and dexamethasone.

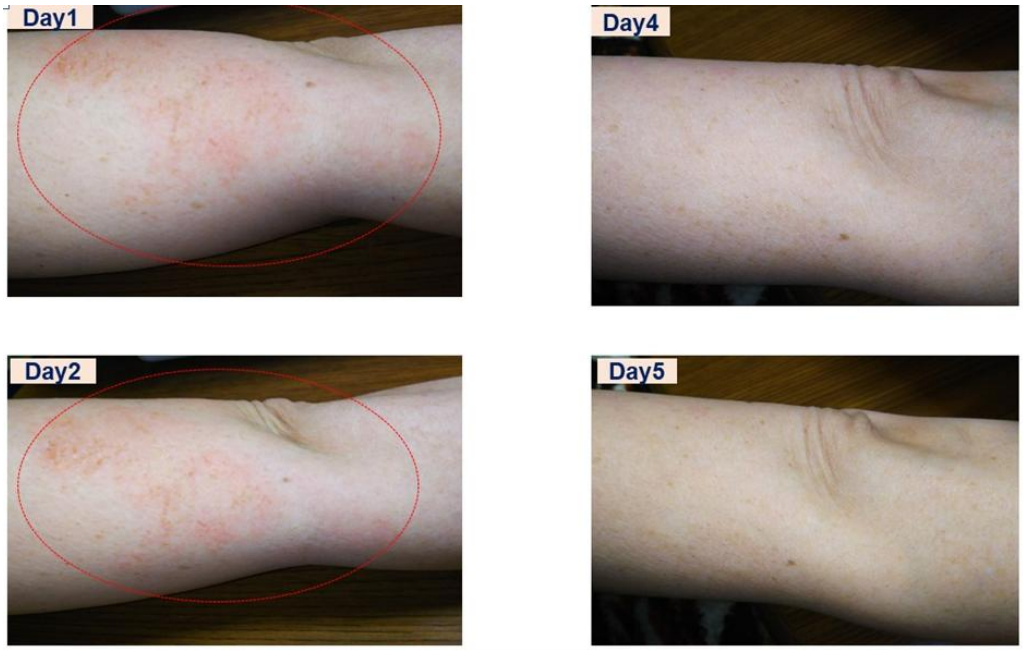


Figure 2. A female Japanese healthcare workers with allergic contact dermatitis caused by a contact with a detergent at her hospital: The patient presented itchy erythema mainly on her left forearm and elbow, which almost desappeared at day4 of topical AMX2; Eosinphilia was remarquable on blood test; however, no patch test wasperformed to confirm the diagnostic allergic contact dermatitis made by the caregiver.

4.2. Case 2: Rapidly evolving tumor-like dyschromic eczematous skin disorder in a male African doctor

In 2018, a male doctor from Democratic Republic of Congo presented with a circular itchy dyschromic lesion of his left upper limb. He did not remember having a contact with a chemical or other substance that might have caused the skin disorder. Two days later, he applied an antihistamine ointment that did not relieve the pruritus. However, the size of the dyschromic macula increased progressively reaching approximately two centimeters of diameter, with scaling lesion at the center. Given that he was allergic to a number of steroid drugs, he requested AMX ointment sample. Topical application of AMX2 significantly alleviated skin lesions and relieved itch after four weeks of treatment (Fig. 3).

Figure 3. A tumor-like dyschromic eczematous skin disorder in a male Congolese doctor successfully treated with topical AMX ointment: The figure shows a dyschromic eczematous with scratch markings, which was markedly reduced in size after 4 weeks of topical application of AMX2; A skin biopsy was requested but not performed due to patient's refusal to undergo invasive procedures at hospital.

4.3. Case 3: Pre-cancerous chronic and recalcitrant photodermatitis in a Congolese albino boy

A 17-year-old boy visited our research team member (N.R.N.) during a "free treatment campaign" at a rural health center in Mbanza-Ngungu town, Kongo central province, in Democratic Republic of Congo. He has been treated with different steroid preparations, including topical *betamethasone*, without any improvement. Actinic keratosis (popular plaques), erythema and squamous lesions were observed. We provided a sample of AMX2 ointment to be applied once a day at night. After 3 weeks of AMX treatment, his skin disorder was cured (Fig. 4).

5. Discussion and Conclusion

Topical steroids are most widely used drugs for AD and CD management; however, they are sometimes subject to poor adherence due the fear of adverse effects, including the destruction of the skin barrier, skin atrophy, hypopigmentation, telangiectasis, etc. Nonsteroidal therapies are thought to be good alternative treatments. Not long ago, the inhibitors of calcineurin and immunosuppressive therapies have been introduced particularly for AD [6, 7]. Their cost and side effects also make them less demanded in most regions of the world.

Almost a decade ago, we initiated a research project that used edible leaf extracts of *V. amygdalina*, an African plant used as remedy for chronic cough, diabetes and a number of cancers. In general, topical AMX was as effective as steroid drugs in alleviating AD and CD skin lesions, such as scaling lesion or xerosis, as well as erythematous and squamous lesions, whereas they had a relatively better effect on itch and wounded skin.

Figure 4. A 17-year-old school boy with a chronic and recalcitrant pre-cancerous skin disorder and a long history of steroid therapies failure: The patient had pre-cancerous lesions, which common in African albino population; He was introduced to our team after unsuccessful treatments based on steroid preparations; Skin lesions were markedly suppressed by a 3-week topical AMX2 treatment.

Additionally, no side effect has been observed in patients treated with AMX. Findings from this research on inflammatory skin disorders suggest that AMXs improve skin barrier, with good efficacy and safety profiles, and may serve as effective alternative therapeutic agents for AD and CD.

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