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Immunomodulatory Therapies of Curcumin on Induced Dermatitis

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Abstract

The aim of this study was to Evaluating the therapeutics and immunomodulatory effect of the curcumin on induced dermatitis, Comparison of therapeutic efficacy between different concertation of curcumin on induced atopic dermatitis in female Albino rats, pure acetone 99.9% in female rats, this study has been carried out at the department of physiology and pharmacology, faculty of veterinary medicine, University of Kufa, Iraq, The study was performed from September to December by evaluating hematological analysis, IL-4, IL33, histopathology, and. This research was conducted in the animal house, Faculty of Science at the University of Kufa in Iraq, thirty 12-weeks old female Albino rats weighing (150-200g) were supplied from Veterinary Medicine Laboratories (College of Veterinary Medicine, University of Takrit). Rats were placed in plastic cages (six rats per cage) with woods shared for bedding. kept in well-ventilated under controlled temperature (between 23 ºC and 25 C), animals were fed with commercial food from the manufacturer green world company. Rats were assigned randomly one weeks before the experimental period for adaptation.

Keywords: *curcumin, IL33, IL4, Histopathology, Atopic dermatitis*

Introduction: dermatitis is the most common atopic disease [1]. Symptoms of atopic dermatitis include erythema, diffuse pruritic skin lesions, and occasional flares. An atopic immune response involves T cells and antigenpresenting cells (APCs) such as B cells and neu- trophils. The APCs bind and present epitopes of allergens to the T cells to evoke cell-mediated responses and maintain immune responses. atopic dermatitis is a Th2-mediated hyper-immune response. In atopic dermatitis, T cells excessively differentiate to Th2 cells and induce both IgE synthesis and mediate mast cell differentiation through Th2 cytokines such as IL-4, IL- 5, and IL-13 [2].Atopic dermatitis (AD) is a Th2-dominant skin inflammatory disorder. It is a result of skin barrier disruption and dysregulated immune system, Allergen exposure to the impaired skin induces itching and scratching, resulting into the formation of eczematous skin lesions which are the hallmarks of AD, It further leads to the production of epithelial cell-derived cytokines, mainly, thymic

stromal lymphopoietin (TSLP) and IL-33 [3].TSLP activates the skin laden dendritic cells, which further stimulates the differentiation and proliferation of 8 T cells toward Th2 phenotype. IL-33 is another cytokine which is known to promote the expression of Th2 cytokines such as IL-4, IL-5, IL-13, and IL-31 [4]. Innate lymphoid cells (ILCs) are a unique family of immune effector cells that functionally resemble T cells, but they lack clonal antigen receptors. ILCs stimulate the production of cytokines and affect immune and non-immune cells in the local tissue environment. Innate lymphoid cells type 2 (ILC2) are known for their ability to secrete proallergic cytokines, including IL-4, IL-5, IL-9 and IL-13 [5].

Material and Methods

The study was performed from September to December, thirty 12-weeks old female Albino rats weighing (150-200g) were supplied from Veterinary Medicine Laboratories (College of Veterinary Medicine, University of Takrit). Rats were placed in plastic cages (six rats per cage) with woods shared for bedding. kept in well-ventilated under controlled temperature (between 23 ºC and 25 C), animals were fed with commercial food from the manufacturer green world company. Rats were assigned randomly one weeks before the experimental period for adaptation[6]. Induced atopic dermatitis Squad the cotton in container (3.5cc) with 99.9% pure acetone was used and it was put on skin for 5 minute for six days consequently to induce atopic dermatitis, acetone has been used due to its desiccating effect (increasing transcutaneous water loss) on the skin and due to the principle of acetone action, the effect on the skin is to alter the cutaneous barrier of the skin causing the destruction of the filaggrin protein and skin tissue [7]. A skin biopsy was taken by making circular cuts and using forceps to lift the skin in the middle and cut it with sterile scissors. Samples were placed in 10% buffered formalin for 12 hours, then formalin was replaced to confirm sample stability. These samples were taken for histopathological technique, blood collected directly from heart, it was placed in test tubes containing gel The serum was separated by centrifugation at 3000 rpm for 15 minutes before being stored at -20 C° in Eppendorf tubes for ELISA Test [8]. The assay was 42 conducted according to the manufacturing company (Bioassay Technology Laboratory-China) for measure IL4and IL33.

Result and Discussion

Interleukin 4 level result (ng/ml)

Determination the level of Interleukin-4 serum samples results that used in this study show a significant increase ($P<0.05$) in control positive compared with all experimental groups except pure gel group. When comparing the treated groups with the negative group there is a significant different ($P<0.05$) except for the (curcumin 5%).

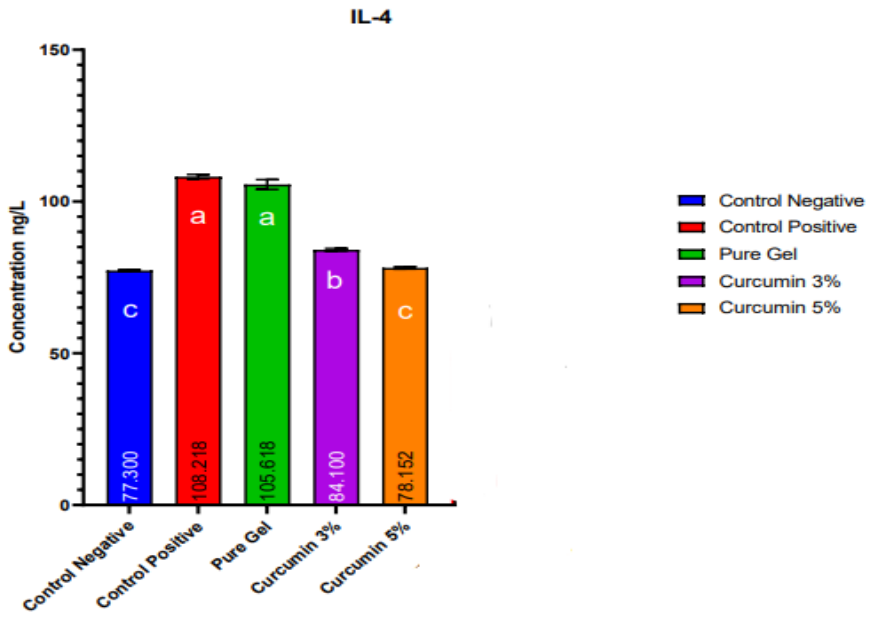

Figure (1) The serum of Interleukin 4 concertation (ng/ ml) in female rats
(The different small letters denoted significance between groups, P<0.05.)

Interleukin 33 level result(ng/ml)

Determination the level of Interleukin-33(ng/L) serum samples results that used in this study show a significant increase (P<0.05) in control positive compared with all experimental groups. When comparing the treated groups with the negative group there is a significant different (P<0.05) except for the (curcumin 5%).

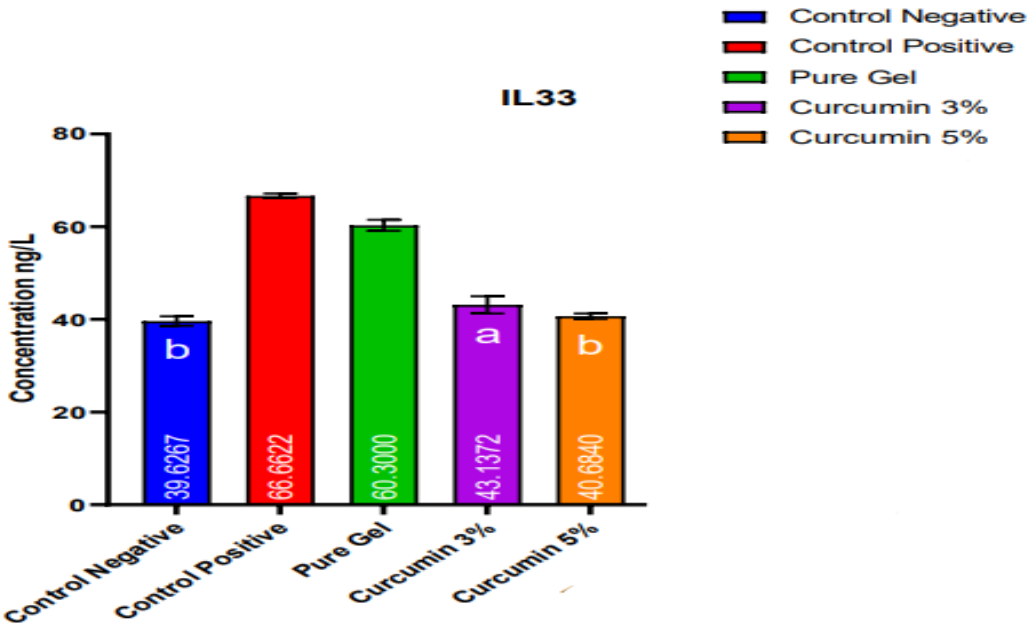

Figure (2) The serum of Interleukin 33 concertation (ng/ ml) in female rats
(The different small letters denoted significance between groups, P<0.05.)

Histological change

The histology of the skin rats from control negative groups showed normal morphological appearance epidermis layer of skin, and a fibroblastic connective tissue layer (dermis), The blue-staining keratohyalin granule also showed up in this section illustrated in the figure (3) by use Mason tri chrome stain[9].

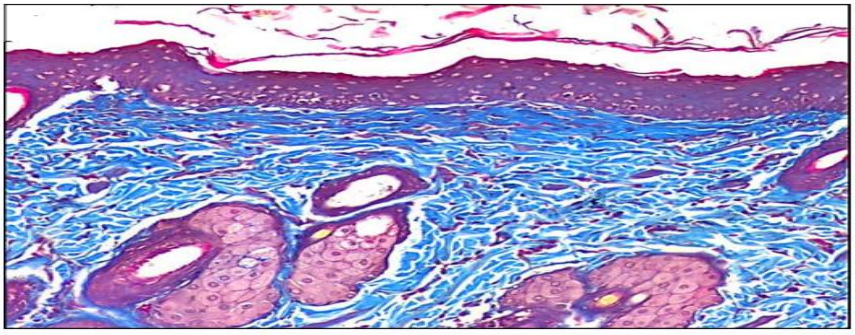

Figure 3: Photomicrograph of skin of control negative group in rat. A&B Normal histological architecture of skin, Mason tri chrome(100x)

The histopathological results of atopic dermatitis induction in rats by pure acetone 99.9%, show the Severe infiltration of inflammatory cells (black arrow) . Note disappearing of epidermis layer due to severe necrosis of epithelial cells of epidermis layer, illustrated in the figure (4)

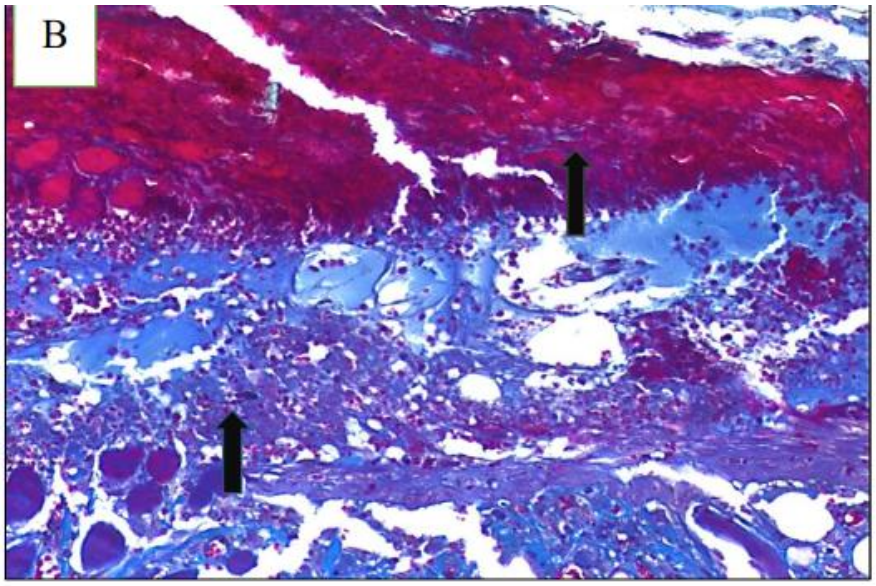

Figure (4): Photomicrograph section of skin in rat induced atopic dermatitis by 99.9% pure acetone for 6 days (atopic dermatitis group) MTC stain. B (400x).

The histopathological results of atopic dermatitis treatment by pure gel, show Severe inflitration of inflammatory cells (black arrow) were observed in affected area.

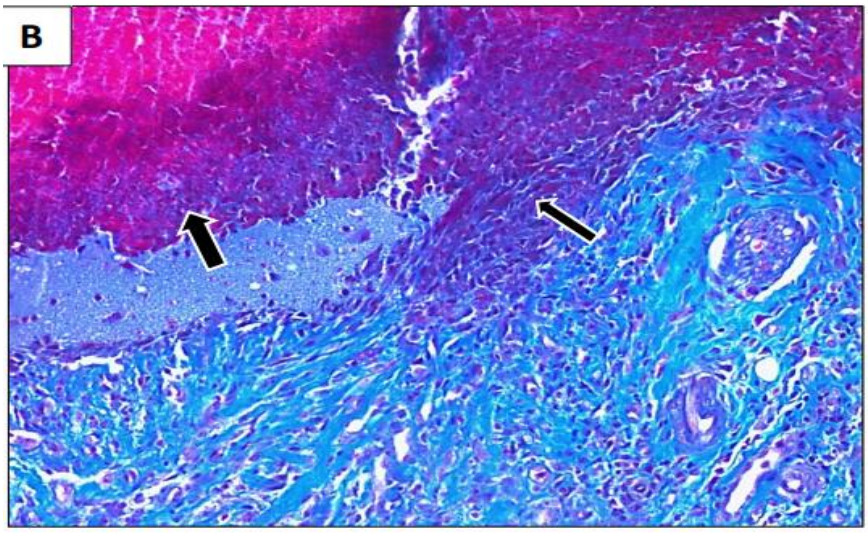

Figure 5. The histopathological section of atopic dermatitis skin in rat that treated with pure gel. Mason tri chrome (X100).

The histopathological results of atopic dermatitis treatment by Curcumin 3%, show Thin epidermis layer (black arrow) was observed, where one to two layer of epithelial cells of epidermis with presence of debris of sloughing epithelial cells (yellow arrow), illustrated in the figure 6

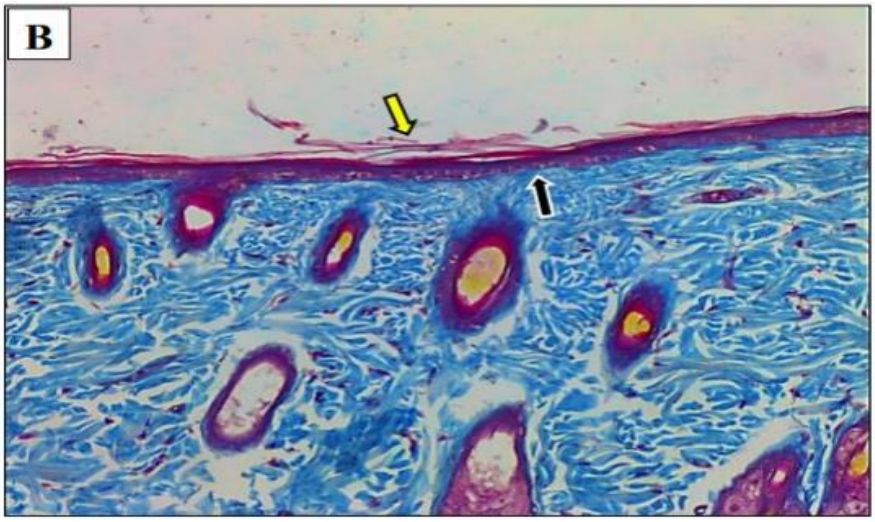

Figure (6) Photomicrograph section of atopic dermatitis skin in rat that treated with Curcumin 3% of atopic dermatitis. (B)Mason tri chrome (X100).

The histopathological results of atopic dermatitis treatment by Curcumin 5%, show re-epithelialization activity maintained the epidermis layer (black arrow), which showed normal thickness, illustrated in the figure (7)

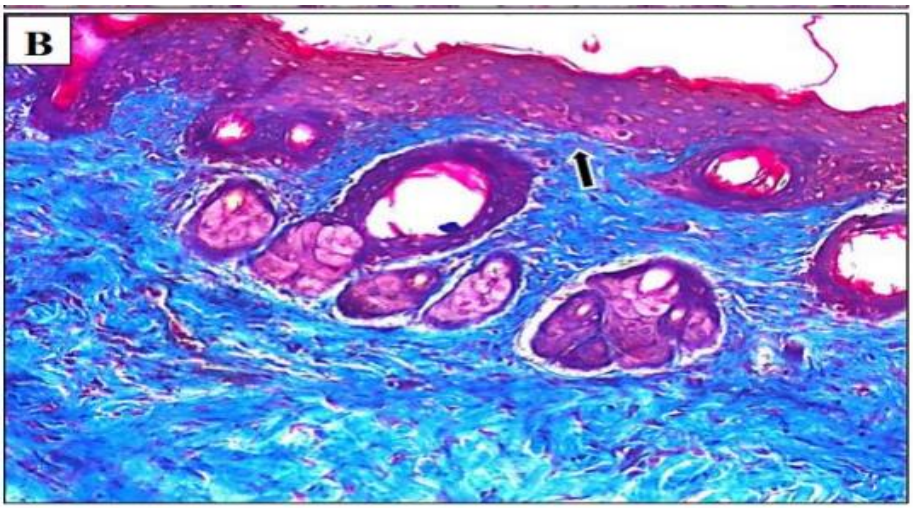

Figure 7. Photomicrograph section of atopic dermatitis skin in rat that treated with Curcumin 5% of atopic dermatitis. (B) Mason tri chrome (X100)

Discussion

At the curcumin gel 5% group of the experiment the result showed significant decrease ($P<0.05$) interleukin 4 level than untreated group (+) also there were decrease in other treated groups when compared to the untreated but slight, curcumin is a promising therapeutic agent due to its natural antioxidant properties and strong anti-inflammatory and antimicrobial functions and the reduce water loss from wound [10]. Curcumin gel 5% decrease in IL-4 level as compared with untreated group because of damage repair by the action of Curcumin has been reported to induce apoptosis in damaged cells, the process may allow more rapid replacement of the injured cells by normal healthy cells, this may be the mechanism for our clinical observations of improved healing of dermatitis due to Curcumin-induced apoptosis may improvement observed with the application of curcumin gel on damaged skin, The removal of damaged premalignant cells by apoptosis allows the space for replacement by new, healthy cells without the potential of malignant transformation. By blocking phosphorylation, curcumin may block the DNA Damage Repair (DDR) pathway through histone-mediated DNA repair [11]. curcumin 3% is also treated atopic dermatitis and decrease interleukin 4. At the curcumin gel 5% group of the experiment the result showed significant decrease ($P<0.05$) interleukin 33 level than untreated group (+) also there were decrease in other treated groups when compared to the untreated but slight pharmacological activity of curcumin is potent immunomodulatory property, which arises from its strong interactions with various types of immune cells such as epithelial cells, basophils, mast cells, neutrophils, eosinophils, and also T cells, leading to the regulation of pathologic immune responses, These finding were agreement with [12]. Interestingly, the evidence clearly showed that curcumin as a pleiotropic molecule is capable of interacting with various signaling molecules and transcription factors, including MAPKs, NF-κB, and Janus kinases/Signal transducer and activator of transcriptions (JAKs/STATs), by which mediates its

immunomodulatory actions [13]. Histopathological examination shows normal skin appearance with typical squamous epithelial cells as well as a fibroelastic type of connective layer was seen in the control (-) group , The eczematous skin indicates acetone-induced damage Show The atopic dermatitis skin was an index of damage caused by acetone. Shows the obvious density and lengthening of skin's external layer due to acetone action, that destroys the proteins like *pro filaggrin*, resulting in a destruction in the barrier of skin and raising trans epidermal water lack, in the end leading to skin dehydration, as well as infiltration of inflammatory cells[14]. There were also fissures and breaks in the epidermal layer as a result of skin dryness, which allows dust, pollutants and microbes to enter. In addition, there is edema under the dermal layer and keratinization of the epithelial layer. Moreover, the skin's changes to a brownish color, In chemotherapy, curcumin has positive effects and is a chemosensitizer and also reduces toxic and adverse effects of chemotherapeutic ,they have a variety of mechanisms of action that contribute to their efficacy in treating AD, which include anti-inflammatory, antiproliferative, and immunosuppressive effects[15]. More specifically, they suppress the quantity and activity of many inflammatory cell types and cytokines, including neutrophils, monocytes, lymphocytes, Langerhans cells, interleukins (ILs, including IL-1α, IL-1ß, IL-2), and granulocyte-monocyte colony stimulating factor (GM-CSF). They also induce anti-inflammatory proteins, such as lipocortin, vasocortin, and vasoregulin, topical corticosteroids can effectively prevent AD flares, as compared to proactive use of nonmedicated vehicle [16].

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