Evaluation of Anti-Psoriatic Effects of Ellagic Acid on Imiquimod Induced Psoriatic-Like Dermatitis in Mice

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Abstract
Ellagic acid is polyphenolic compound which is present in many fruits. Many pharmacological properties of Ellagic acid have been reviewed and described for many years. Some properties study in animals, while the other have been evaluated in humans including anti-inflammatory, neuroprotective, and Hepatoprotective effects, as well as the protection it provides against diabetes, cardiovascular disease, and cancer. In this study we investigated the effect of Ellagic acid on induced psoriatic-like dermatitis in mice. In this study, 50 mice were involved, divided into 5 groups (10 group of each). Except Group I (healthy), all group received Imiquimod for psoriasis induction during all days of experiment. Group II Induced and without treatment and the other groups III, IV and V were induced and treated twice daily with wool fat, 0.05% Clobetasol propionate, 5% Ellagic acid respectively, from day 7 until the end of experiment. The result showed that Ellagic acid has anti-psoriatic effect by significant decreasing the PASI score and ameliorating the histological changes that induced by IMQ and by significant decreasing the concentration of skin TNF-alpha as compared to induced group (II), and also significant decreasing the concentration of skin VEGF and pJAK3 as compared to induced group II and vehicle group III. In conclusion, the therapeutic effect of Ellagic acid against Imiquimod-induced psoriasis probably through mechanistic pathway involved anti-inflammatory, anti-proliferative and anti-angiogenesis effect.

Keywords: Ellagic acid, Psoriasis, Imiquimod, Keratinocyte, pJAK3, IL-17A, VEGF, TNF-a, Inflammation, Mice

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Introduction
Psoriasis is a chronic inflammatory, immune-mediated, polygenic skin disorder with different periods of relapses and remission, affecting approximately 2–3% of the world population. The complexity of the disease doesn't only in the hardship of the symptoms but also in its psychological, social and emotional impact on the patients additional to increase the risk of developing cardio-metabolic and rheumatologic comorbidities (Hashim et al., 2018).Psoriasis can divide into five subtypes according to clinical presentation of lesion: plaque, guttate, pustular, inverse, and erythrodermic. The most common is chronic plaque type that occurs in (85 – 90%) of cases (Griffiths and Barker, 2007). A thickened epidermis (acanthosis) arising from rapid Keratinocyte proliferation, a reduced or absent granular layer (hypogranulosis) due to the reduce keratinocytes differentiation, distinct inflammatory cell infiltrates, and an
increased number of tortuous and blood vessels in the dermis lead to erythema (Nickoloff et al., 2007). Psoriasis can result from imbalanced interactions of the innate and acquired (adaptive) immune system in the layers of skin that lead to uncontrolled Keratinocyte proliferation and impair differentiation (Griffiths and Barker, 2007). The innate immune system plays primary role in antigen detection through many immune cells including dermal dendritic cells, natural killer [NK] T lymphocytes, and Neutrophils. Adaptive (acquired) immunity mediates its action by mature CD4+ and CD8+ T lymphocytes in the skin. Activated mDCs move into lymph nodes and interact with T lymphocyte via histocompatibility complex (MHC). The secretion of pro-inflammatory cytokines by myeloid dendritic cells promotes differentiation and proliferation of CD4+ T lymphocytes into Th17 and Th1 cell subsets. These cytokines are including IL-23, IL-12 and tumor necrosis factor alpha (Hänsel et al., 2011). The activation of the adaptive immune is important to keep the maintenance phase of psoriatic inflammation. Th17 cells secret cytokines namely IL-17, IL-21, and IL-22 that stimulate Keratinocyte for proliferation in the epidermis via activation JAK/STAT pathway. In this activation results phosphorylation and modulation of pro-inflammatory gene transcription (Bachelez et al., 2015). The STAT3 is consider as downstream signaling pathway of IL-23 action, and is essential in T cell proliferation and Th17 polarization. The proliferation of keratinocytes also occurs via stimulation by TNF-alpha, IL-17, and IFN-gamma. The TNF-α – IL-23 – Th17 inflammatory pathway plays primary role in signaling pathways that develop plaque-type psoriasis (Van der Fits et al., 2009). Vascular endothelial growth factor” (VEGF) is function of angiogenic factor that mediates the angiogenesis of blood vessels and is highly expressed in thepsoriatic skin lesions. VEGF promotes microvascular changes in the dermal papillae, which facilitate the development and insistance of the psoriatic lesions. Finally, the increase vascularity and permeability is an important to provide nutrition to the hyper-proliferating keratinocytes and assist the migration of inflammatory cells (Xia et al., 2003). Ellagic acid is polyphenolic compound which is present in many fruits including: nut galls and plant extracts in the forms of hydrolysable tannins called ellagitannins or in free form such a pomegranate, raspberries, strawberries, grapes, mango, guava, walnuts, black currants, almonds, green tea and longan seeds. Ellagic acid exists in plant either in free form or ellagitannins. Later compound resist gastric acidity and hydrolyze in small intestine by enzyme called ellagitannins while ellagic acid in small proportion absorbed from stomach and the rest amount absorbed in small intestine (Lei et al., 2003). In case of a skin many studies have been performed to enhance pharmacokinetic profile some of them used polyethylene glycol ointment (Moe et al., 2014), nanoemulsion and niosomes (Junyaprasert et al., 2012) in order to deliver ellagic acid deeper into skin layers. Many pharmacological properties of ellagic acid have been reviewed and described for many years. Some properties study in animals, while the other has been evaluated in humans. These include its anti-inflammatory, neuroprotective, and Hepatoprotective effects, as well as the protection it provides against diabetes, cardiovascular disease, and cancer (García and Zazueta, 2015). Ellagic acid is one of a major antioxidant, like the well-known vitamins C and α-tocopherol. Because of containing two lactones and four hydroxyls functional groups aid ellagic acid scavenger activity that enable it to scavenger wide range of ROS and reactive nitrogen species, additional to the role in free radical scavenger, ellagic acid report to be effective in prevention of lipid peroxidation (Uzaret et al., 2012). As Ellagic acid has antioxidant effect also it has potent anti-inflammatory effect and many studies emphasized role of Ellagic acid to candidate for treatment of chronic inflammatory conditions (Mishra and Vinayak, 2014). Furthermore, Ellagic acid exert a protection effect on hepatocytes by different molecular mechanisms such as inhibit generation of nitric oxide, NF-kP activity and by antioxidant system (García-Niño and Zazueta, 2015).
Methods and Materials

Preparation of topical Emulsion (Water-in-oil) of Ellagic acid

The wool fat (70 g) was melted in a water bath at 75°C until the material become liquid. Ellagic acid (5 g) added into different baker contained up to 30 ml distilled water and stir until the solutions were achieved. Then the last solutions added into the melted wool fat baker and the final mixture was cooled while being stirred until it congealed (Chauhan and Gupta, 2020).

Experimental design and Animals Models

The protocol of the present study was approved by Iraqi Board Review (IBR) of the College of Medicine / Al-Nahrain University, the Period of present study from September 2019 to September 2020. Healthy male adult albino mice (18-25 g in weight, 8-12 weeks in age) obtained from the animal house of College of Pharmacy / Baghdad University and National Center for Drug Control and Research. Mice were housed in polypropylene cages and in an environmentally controlled condition (22 ± 2 °C, relative humidity of 50 ± 5%) with a 12 h light/dark cycle and allowed free access to water and food. All efforts were made to minimize animal suffering and to decrease the number of animals used in the experiments.

Study design

After shaving of back mice hair with depilatory cream (Veet), the day after day application of 62.5mg Imiquimod (IMQ) on the skin of mouse back induced a scaly inflamed lesion in the skin similar to plaque type of psoriasis. These lesions show a typical differentiation and an increase in the epidermal proliferation.

An application of the IMQ for a 6 uninterrupted days on the skin of the mouse results in the influx of different cells of the immune system, in addition to epidermal hyperplasia (Van der Fits et al., 2009). In semi-therapeutic model, the animals divided into 5 groups as followings:

Group I: 10 apparently healthy mice (without any treatment) used as a control
Group II: 10 mice in which psoriatic lesion was induced by Imiquimod without treatment used
Group III: 10 mice in which psoriatic lesion was induced by Imiquimod and treated topically with wool fat twice daily from day 7 to day 14 with continue of application of IMQ to day 14
**Group IV**: 10 mice in which psoriatic lesion was induced by Imiquimod and treated topically with 0.05% Clobetasol propionate ointment twice daily from day 7 today 14 with continue of application of IMQ to day 14.

**Group V**: 10 mice in which psoriatic lesion was induced by Imiquimod and treated topically with 5% Ellagic acid mixed with sterile wool fat twice daily from day 7 to day 14 with continue of application of IMQ to day 14. Except Group I, rest all the groups were Imiquimod induced psoriatic was continued for 14 days and the treatment was given twice daily (2 hours after topical application of IMQ cream) and from day 7 to day 14 (Parmar et al., 2017; Nadeem et al., 2015). After 14 days, the mice were sacrificed by diethyl ether, while skin lesions collected and weighed and added Buffer phosphate saline (1:10 parts) and homogenized on ice using Electrical Tissue Homogenizer (IKA, Germany) and then were centrifuged at 12,000 rpm at 4 °C for 10 min and store at -80°C for the other assays.

**Psoriasis Area and Severity Index (PASI)**
PASI is modified human scoring system Psoriasis Area Severity Index (PASI) to measure the severity of skin inflammation during the procedure of application, except that for the mouse model the affected skin area is not taken into account in the overall score. It consists of erythema, thickness and scaling and scored independently from 0 to 4 where 0 = no signs; 1 = slight signs; 2 = moderate signs; 3 = marked signs; and 4 = very marked clinical signs (Chen et al., 2017), Psoriasis Area and Severity Index (PASI), which used for measurements of these parameters during the period of experiment (Baek et al., 2012).

**Histopathological study**
A histological study of all tissues was carried out in histopathology department / Bagdad College of medicine/ Bagdad Government to observe the changes in tissues. The skin samples of mice were kept in 10% formalin and embedded in paraffin. The Paraffin-embedded sections were then cut to a thickness of 5 μm and stained with hematoxylin and eosin (H & E) for histological evaluation (Bancroft and Gamble, 2008).

**Measurement of interleukin-17 (IL-17), tumor necrosis factor alpha (TNF-α), vascular endothelial growth factor (VEGF), and pJAK-3 protein**
To evaluate the levels of pro-inflammatory cytokines (IL-17A, TNF-α, VEGF) (Harper EG et al, 2009; Caldarola G et al, 2009; Bhushan et al, 1999) and intracellular protein (pJAK3) (Alves et al., 2016) in the skin, enzyme-linked immunosorbent assay (ELISA) kits were used according to the manufacturer's instructions. The absorbance was read at 450 nm with a micro plate spectrophotometer.

**Statistical analysis**
All data were collected, tabulated, and entered using the program statistical package for social sciences (SPSS) version 14 under windows 7. Descriptive data were summarized by using mean and standard deviation. The one-way analysis of variance (ANOVA) was used to determine the statistical significance of differences of laboratory parameters between healthy and treated groups. The P values ≤ 0.05 were considered statistically significant (Daniel, 2018).

**Results**
**Morphological Evaluation**
On day 2-4 after the application of IMQ treatment, the signs of erythema, thickness and scaling were beginning on the skin of the IMQ treated mice and continued in the severity until reached today 6, figure (2). After that, mice that treated
with Clobetasol (group IV) and Ellagic acid (group V) significantly decreased their total PASI score as compared to induced (group II) and vehicle (group III). While induced II and vehicle III groups continued with the increasing of severity (Fig.3).

Figure (2): Representative photographs of back skin on day 15

![Representative photographs of back skin on day 15](image-url)

Figure (3): Effects of Ellagic acid on PASI scores of the skin tissue in IMQ-induced psoriasis-like mice. (A) The Erythema of the back skin was scored on the indicated days with a scale from 0 to 4; (B) the thickness of the back skin was scored on the indicated days with a scale from 0 to 4; (C) the scaling of the back skin was scored on the indicated days with a scale from 0 to 4; (D) The total PASI scores of the skin tissue. All values in figure are shown as Mean ± Standard Deviation. When * P-value is < 0.05 is considered significantly difference compared to the induced group and # P < 0.05 vs. vehicle group III.

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Histopathological evaluation

Skin treated with IMQ demonstrated pathological changes of the epidermal tissue, including significant hyperkeratosis, acanthosis, increase in rate-ridges and perivascular infiltration of inflammatory cells in the upper dermis, a phenotype typical of human psoriatic skin, these changes obviously seen in induced (II) and vehicle (III) groups. Clobetasol (IV) and Ellagic acid (V) treated groups significantly reduced the thickness of the epidermis by decreasing the hyperkeratosis and rate-ridges and less infiltration of inflammatory cells that produced by IMQ treatment. While healthy group (I) exhibited look - like normal thickness of stratified epithelium dermis and epidermis, figure (4).

Figure(4): Histological evaluation of the back skin of IMQ-induced psoriasis-like mice, (H & E staining; magnification X40). Group I: healthy group, Group II: Positive control group, red arrows and red arrows indicate hyperkeratosis, acanthosis, and elongation of rate-like ridges, Group III: vehicle group, Group IV: Clobetasol treated group and Group V: 5% Ellagic acid treated group

Tissue Biomarkers evaluation by ELISA

The results of statistical analysis of ELISA assays for the levels of IL-17A, TNF-α, VEGF and pJAK3 (M± SD Pg/ml) in skin tissue homogenate were exhibited in Fig.5. As compared with control group I, the level of IL-17A and TNF-α were clearly increased and the level of VEGF and pJAK3 were significantly increased in the skin of induced II and vehicle III groups. Regarding Clobetasol treated group IV the levels of IL-17A, VEGF and pJAK3 significantly decreased as compared to induced group II and vehicle group III. While Ellagic acid (5%) treated group V showed the clearly reduction in the level of IL-17A and significant decreasing in the level of TNF-α as compared to induce group II. Related to the levels of VEGF and pJAK3 in Ellagic acid (5%) treated group V, it exhibited significant reduction as compared to induced group II and vehicle group III.
Discussion

Psoriasis induction by Imiquimod

Imiquimod is specific toll like receptors TLR7/8 agonist (Chen et al., 2017). It can stimulate innate immune system by activation of dendritic cells, monocytes and macrophage leading to promote signaling of cytokines cascade by expression of IL-8, IL-1, IL-6, IL-12, INF-yR, TNF-α, INF-α and others cytokine in the body. Therefore, it raises Th-1 mediated immune response to yield anti-tumor and anti-viral effects (Hemmi et al., 2002). IMQ is approved for treatment of general wart caused by human papilloma virus, basal cell carcinoma and keratosis. IMQ induces psoriasis like lesions in skin when applied by dose 62.5mg/cm² on shaved area of mice skin. This reaction is mediated through IL-23/IL-17 axis. The mouse developed lesion is closely resembled to human plaque-type psoriasis with respect to inflammatory cells infiltration, thickness, scaling and redness (Van der Fits et al., 2009). Related to molecular mechanism, IMQ bind with TLR7 on plasmodium dendritic cells (pDC) and activated them. This causes massive release the inflammatory factors such as INF-α, TNF-α and IL-6. These chemical mediators promote the expression of IL-23/IL-17 axis (Chen et al., 2017) leading to excessive keratinocytes proliferation by increase the expression of intercellular transgenetic pathway such as JAK/STAT and NF-kB pathways (Rodríguez et al., 2017). Although IMQ model produces characteristics are clearly like psoriatic symptoms but these symptoms lead to spontaneously decline after 6 days of application. These findings reported that mice are not genetically compromised that able to revert the inflammatory process due to instability of adoptive reaction to IMQ stimulation (Sun et al., 2013; Na Takuathung et al., 2018). For this reason, we applied IMQ in dorsal shaved skin of mice for 14 consecutive days. In the present study, the
application of IMQ produced obvious and higher histological change including hyperkeratosis, acanthodians, increase the rate-ridges and inflammatory cell infiltration in group II and group III as compared to group I. PASI score is significantly higher in IMQ induced group II and group III as compared with healthy group. Imiquimod causes Erythema since it may be acting as a direct mast cell degranulation through IgE-linked mechanisms. Another possible theory is that Imiquimod may also activate mast cells by IgE-independent mechanisms (Redegeld et al., 2018). The ELISA results of skin cytokines exhibited the levels of TNF-α and IL-17 were accentuated in IMQ-induced group II and group III as compared to healthy group I. While the levels of VEGF and pJAK3 are significantly higher in IMQ-induced group II and group III relative to healthy group I. However, there were no significant differences between group II and group III in the parameters used in this study. Finally, these findings are consistent with previous studies (Chen et al., 2017; Van der Fits et al., 2009) that suggested IMQ can induce and exacerbate psoriasis in the mice.

Clobetasol effect on psoriasis induced by Imiquimod

Clobetasol is super potent corticosteroid approved by FDA for treatment of inflammatory disorders including psoriasis due to anti-inflammatory anti-proliferating and immunosuppressive effects (Castela et al., 2012). Although, topical Clobetasol is powerful part in the psoriasis treatment, it reported to have well known side effects like, striae, atrophy, telangiectases and additional to systemic side effects (Schoepe et al., 2006). This limitation makes steroidal drug not favor to use for long period. The mechanism behind the actions of Clobetasol divided into genomic and no genomic pathways. The genomic pathway referred to Glucocorticoids receptors in the plasma membrane. When steroid binds with its receptors, the complex subsequently migrate into nucleus and express the Glucocorticoids response elements, transcription genes with anti-inflammatory effect (Adcock and Lane, 2003). In general, the Glucocorticoids enhance the transcription of anti-inflammatory gene and reduce the genes with inflammatory actions.

The various studies showed Glucocorticoids can induce the expression of MAPK Phosphatase 1 that has anti-inflammatory properties (Rhen and Cidlowski, 2005) and also it reported to have a negative effect on the expression of NF-kB. The non-genomic pathway is rapidly effect of Glucocorticoids. The Glucocorticoids reported to induce the expression of Annexin A1 that bind to phospholipids and reduce the formation of inflammatory prostanoids. It also reported to reduce the expression and activation of pro-inflammatory cytokines, decrease the expression of nitric oxide and modulates the mast cells (Goldsmith et al., 1996).

In this study, Clobetasol exhibited powerful effect in the reduction of inflammatory response induced by IMQ. The optimum reduction in PASI that seen clearly by decreasing the erythema due to Clobetasol vasoconstrictor action, achieved by blocking of action of vasodilators like histamine and bradykinine, and decreasing the thickness and scale due to Clobetasol anti-inflammatory and anti-proliferating actions (Kwatra and Mukhopadhyay, 2018). The attenuation of severity score is supporting by the ameliorating of histological change of inflammatory features, it showed with Clobetasol group (IV). This occurred by decreasing the hyperkeratosis, inflammatory cells infiltration and rate-ridges. Additionally, the pro-inflammatory cytokines, IL-17A, VEGF and pJAK3 were significantly reduced when treated with Clobetasol as compared with induced group II and group III. Unfortunately, psoriasis requires the long term therapy for treatment psoriasis by available medicines, including Clobetasol, that have unwanted side effect, makes phytochemical substances are good alternative option to find out a new agents have the same effect with few adverse effects.
Effect of Ellagic acid 5% on Imiquimod induced psoriasis

Ellagic acid is a major component of pomegranate tannins that demonstrated the good antioxidant, anti-inflammatory and anti-proliferating activities. Due to anti-cancer properties, Ellagic acid is being investigated for use in follicular lymphoma, brain injury in intrauterine growth restricted babies, solar lentigines and obese adolescents (Alfei et al., 2019). The two lactones and four hydroxyl groups make Ellagic acid a good antioxidant and potent anti-inflammatory agent. Additional to scavenger activity of free radical, it can prevent the generation of reactive oxygen species (ROS) by inhibiting lipid peroxidation (Salem et al., 2016). In this study, we investigated the effect of Ellagic acid on mouse model of psoriasis. It established IMQ induced psoriasis and found Ellagic acid significant ameliorated the histopathological changes, inflammatory infiltration and Keratinocyte hyper-proliferation. The results obtained from IMQ induced psoriasis is showed significant reduction of total PASI score of mice after treatment with 5% Ellagic acid topical preparation as compared with induced group II and vehicle group III, this achieved by reduction in epidermal thickness, redness and scaling. In addition, for histological result, Ellagic acid improved skin conditions such as smoother epidermis, less hyperkeratosis with obvious decline of inflammatory cells and rate-ridge that caused by IMQ. The findings are directly in line with previous findings showed topical application of Ellagic acid alleviated skin inflammation and wrinkle caused by UV-B. These achieved by decreasing epidermal thickness and roughness and mitigating the inflammatory cells infiltration and pro-inflammatory cytokines (Bae et al., 2010). Regarding to histochemical assay by ELISA, there is strong evidence that shown IL-23/IL-17 play important role in IMQ induced psoriasis in mice. After the activation of dermal DCs, they release IL-23 that promote the activation and differentiation of T-17 helper cells, the later secret the pro-inflammatory cytokines including IL-22, IL-17A, IL-17F and IL-26 that induced the activation and mobilization of other immune cells and symptoms proliferation of keratinocytes (Hugh and Weinberg, 2018). IL-17 cytokine is a family cytokines consist of six that vary homology and functions: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. The previous study showed IL-17A and IL-17F are greater expressed in IMQ induced psoriasis model (Russell et al., 2014). Although IL-17F reported to has greater expression than IL-17A in psoriatic plaque produced by IMQ, and the later has important role in localized skin lesion through the activation of NF-kB and JAK3/STAT3 signaling pathway (Sun et al., 2013). In the present study, we found that Ellagic acid is markedly decreased IL-17A level as compared to induced group II and vehicle group III. This result is consistent with previous studies that reported the ability of Ellagic acid to decrease the pro-inflammatory cytokines such as IL-1β, IL-17, IL-1 and IL-10 and can used for chronic inflammatory conditions (Cornéllo et al., 2013; Ding et al., 2017). Among the cytokines that are responsible for psoriatic inflammation, TNF-α has been considered as a master pro-inflammatory cytokine of innate immune system due to wide spread sources and targets. TNF-α is produced by activated T cells, macrophages, monocytes, keratinocytes, natural killer cells (NK) and antigen presenting cells, it responsible for keratinocytes proliferation, angiogenesis via VEGF and pro inflammatory cytokines synthesis (Hugh and Weinberg, 2018). In this research, Ellagic acid showed significant decreasing in TNF-α level compared to the level of TNF-α in the induced group II. This supported by previous evidence that reported Ellagic acid has ability to reduce the level of TNF-α level and activity (Bae et al., 2010). VEGF is signal protein that highly expressed in psoriatic lesion and has crucial role in mediating blood vessels angiogenesis. It increased the vasculature and permeability to provide the nutrition to hyper-proliferated keratinocytes and promote inflammatory cell migration (Xia et al., 2003; Rodríguez et al., 2017). In the current study, Ellagic acid showed a significant reduction in the level of VEGF as compared with the induced group.
II and vehicle group III. This result is consistent with previous research that reported Ellagic acid has anti-angiogenic activity by inhibiting the level of VEGF and the expression of its receptors (Kowshik et al., 2014). The JAK/STAT signaling pathway is a recently discovered that had crucial role in the development and maintenance of psoriasis pathogenesis. It opened a new way to find approach for the treatment of inflammatory diseases (Wohlmann et al., 2010). JAK is tyrosine kinase protein that belong Janus kinase family including JAK1, 2, 3, and TYK2. JAK protein binds with cytokine receptors in immune cells, keratinocytes and has catalytic activity that can induce the phosphorylation of another protein called STST. pSTST transmit from cytoplasm to nucleus and promote genetic transcription. pJAK3 is reported as mainly JAK over expressed in B, T lymphocytes and keratinocytes of psoriatic tissue (Palanivel et al., 2014). Due to kinase domain of JAKs, make them an easier pharmacological target compared to STAT that lack of the catalytic activity (Villarino et al., 2015). In the present study, Ellagic acid significantly reduced the level of pJAK3 as compared to induced group II and vehicle group III. This consistent with previous study that reported the anti-proliferative effect of Ellagic acid through inhibiting of different cellular signaling pathways such as STAT3, AKT and pERK1/2 (Eskandari et al., 2016). It is also suggested that Ellagic acid has anti-inflammatory effect through dropping the pro-inflammatory cytokines by direct inhibition of intracellular NF-kB pathway (Eskandari et al., 2016).

**Conclusion**

The results of the present study amply demonstrated that Ellagic acid had anti-psoriasis effects in IMQ-induced mice through the mechanistic pathway involved anti-inflammatory, anti-proliferative and anti-angiogenesis effects. Ellagic acid, naturally occurring tannin with potent anti-psoriatic effects, had the potential to be a promising alternative therapeutic drug for the treatment of local inflammation in psoriasis.

**References**


