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Evaluation of Anti-Inflammatory Potential of Morin Anhydrous using Acute and Chronic Dermatitis Mice Models

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A B S T R A C T

A complicated biological process, inflammation is triggered by exposure to toxins, chemicals, infections, ad injury. Consumption of several non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids, commercially available, provide the treatment for inflammation results in various side effects like itching, rash, photosensitivity and angioedema. This highlights requirement for developing the novel anti-inflammatory agent that can help to cure inflammation with fewer adverse effects. Flavonoids and other natural substances have shown positive effects on dermatitis. Natural bioflavonoid Morin (3,5,7,2′,4′-pentahydroxyflavone), which is a key ingredient in medicinal herbs, was first isolated from plants in the Moraceae family, including figs (*Chlorophora tinctoria*) and almonds (*Prunus dulcis*). Morin possesses anti-inflammatory and antioxidant properties but its connection to dermatitis has'nt yet been investigated. Goal of this study was to examine *in vitro* antioxidant and *in vivo* anti-inflammatory properties of Morin using different models. Morin's antioxidant activity was assessed using *in vitro* assays, namely 2, 2-diphenyl-1-picrylhydrazyl (DPPH), 2, 2-azino-bis-3-3-thylbenzthiazoline-6-sulphonic acid (ABTS), and lipid peroxidation (LPO). The findings demonstrated that Morin is the potent antioxidant agent, depending on the dose and its significance. DPPH (23.6 µM), ABTS (13.86 µM), and LPO (91.81 µM) are the IC^{50} values. Additionally, acute skin inflammatory mice model induced by TPA and chronic skin inflammatory mice model induced by oxazolone were used to investigate Morin's *in vivo* anti-inflammatory properties. Two criteria, namely edema weight and edema volume, were used to assess the degree of edema. According to the findings, edema weight and volume were reduced by 50% and 80%, respectively, in acute inflammatory model of TPA, whereas both were reduced by 60% in the chronic inflammatory model of oxazolone. In summary, this study illustrates Morin's anti-inflammatory and antioxidant properties. Consequently, it is possibly referred to be a novel therapeutic approach for treating variety of inflammatory skin conditions.

Keywords: Flavonoid, Morin, Anti-inflammatory, Antioxidant, Edema, NSAIDs.

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INTRODUCTION

Immune responses are essential in order to protect the skin from a variety of harmful stimuli. Atopic dermatitis, allergic/irritant contact dermatitis, and psoriasis are among various disorders of the skin, that can arise as a result of compromised immunological responses, including excessive inflammation (Pasparakis et al., 2014). Reddishness of skin, swelling, chaffing, epidermal hyperproliferation and abscesses are some of the symptoms of inflammation that define these chronic relapsing illnesses (Tamura et al., 2004). Medications which are used to suppress immune system like

glucocorticosteroids are currently the first line of treatment for various skin conditions in order to reduce inflammatory symptoms. But such treatments are usually linked to serious side effects like Cushing-like changes and repression of the HPA-axis which highlights the need for a novel anti-inflammatory agent for treating dermatitis.

Skin inflammation is induced by the releasing the mediators, include Nitric oxide (NO), prostaglandin E2 (PGE2), interleukin (IL)-1β, IL-6, and tumour necrosis factor-α (TNF-α). Activating cellular pathways is responsible for regulating nuclear factor κB (NF-κB) and mitogen-activated protein kinases (MAPKs) (De Benedetto et al., 2009). Apart from Pro-inflammatory mechanisms, anti-inflammatory signals like nuclear erythroid 2-related factor/hemeoxygenase-1 (Nrf2/HO-1) are also essential for controlling skin inflammation (Beyer et al., 2007; Chun et al., 2014; Martin, 2015). Potential medications that target these biological triggers as well as alter the way pro-inflammatory mediators are released which is possibly crucial for treating dermatitis.

Special attention is being paid to natural substances for the treating diseases related to inflammation. Numerous flavonoids have got discovered to exhibit advantageous properties in skin inflammatory model, as topical anti-inflammatory drug (Giangaspero et al., 2009). Natural products may contain unique chemicals and are not always the final medicinal entity (Newman and Cragg, 2012). Although it is a potential approach to medication development to extract natural chemicals to increase their bioactivity, as there is limited research on the antioxidant and anti-inflammatory characteristics of natural flavonoids like Morin to treat skin inflammation. A naturally occurring flavanol, Morin is derived from *Psidium guajava*, *Lotus ucrainicus*, and other species. It belongs to family Moreaceae. It has been observed that many pharmacological actions like antioxidant, antihypertensivity, hepatoprotectivity, neuroprotectivity, anti-inflammatory, antineoplastic and antibacterial are present in it. In our present study the antioxidant activity of Morin was examined by performing ABTS, DPPH and LPO assays whereas acute dermatitis model induced by TPA and chronic dermatitis model induced by oxazolone determined anti-inflammatory property of Morin, indicating its capability as a novel treatment option for the extreme inflammatory conditions. Hence, the goal of current research was to analyse the anti-inflammatory and antioxidant characteristic of Morin anhydrous to discover its efficacy for treating skin inflammatory diseases.

MATERIAL AND METHODS

ABTS (3,6-azinobis-3-ethylbenzothiazoline), silymarin, 2, 2-DPPH (1,1-diphenyl-1 picrylhydrazl), methanol, diclofenac sodium, potassium dihydrogen phosphate, trichloroacetic acid, and Morin (3, 5, 7, 2, 4-Pentahydroxyflavone) were the subsequent compounds purchased from Sigma Aldrich in Germany. The American Bio-M Laboratories provided L-ascorbic acid and ferrous sulfate (FeSO4). Perchloric acid (HClO4), sodium hydrogen phosphate, and sulfanilamide were bought from Daejung, Korea. thiobarbituric acid (TBA) and sodium nitroprusside were bought from Merck in the United States. The potassium chloride (KCl), ethylenediamine tetraacetic acid (EDTA), and disodium hydrogen phosphate were bought from the Spanish corporation Scharlau. Merck supplied Indomethacin (Indo) and Trolox in Germany. The sodium chloride was bought from the BDH Laboratory in England, whereas the potassium persulfate (K2S2O8) was bought from Lab chem in Malaysia.

Evaluation of free radical scavenging activity

ABTS discolourisation analysis of radical cations

A method from (Syed et al., 2016) was used to assess ABTS radical's scavenging ability. Both potassium 45 persulfate (2.45mM) and ABTS (7mM) were combined in an equal volume of 1/1 in stock solutions of water to produce free radicals of ABTS. Later, incubation of mixed material was done at room temperature and in fully dark area for round 14 to 16 hours. Then ABTS mixture was combined with solvent till an absorbance 0.7± 0.05 at 735nm was achieved. After that, 2.7 ml of the ABTS+ free radical solution was mixed with 300 µl of multiple doses of control or Morin. After 15 minutes, measure the absorbance at 735nm by UV-Visible spectrophotometer. The scavenging capacity of Morin was calculated using the following formula.

Morin's Scavenging ability (%) = [(Ablank - Asample) / Ablank] × 100

A sample indicates Morin or control absorbance, while a blank indicates control absorbance. To analyse data, Graph Pad Prism V8 was utilized and a p value of less than 0.05 was deemed significant in statistic. For calculating amount of a drug needed to control up to 50% of free radicals, an inhibition graph against concentration (IC_{50}) was employed.

DPPH radicals scavenging assay

The Morin's ability to scavenge free radicals was evaluated using the DPPH test. This test was done following protocol explained in (Talaz et al., 2009). In short, 2 ml of various doses of Morin were combined with 1 ml of 300 µM DPPH. Then mixture was taken for incubation for 30 mins in complete darkness at room temperature. A UV visible

spectrophotometer set at 518 nm was employed in order to measure the absorbance of solution. Every test sample was made in a methanol-containing blank solution. In this assay, 0.3mM DPPH served as the negative control and L-ascorbic acid as the positive control.

Morin's scavenging ability was calculated by the equation given below.

Scavenging ability of Morin (%) = [(Ablank - Asample) / Ablank] × 100

A sample indicates Morin or control absorbance, while a blank indicates control absorbance.

A graph of inhibition against concentration (IC_{50}) was used to determine an amount of drug required to control approximately 50% of free radicals.

Lipid peroxidation assay (LPO)

Following (Awah et al., 2010), an assay was conducted to test lipid peroxidation. The white part or yolk of an egg is comprised of lipids. 500 µl of egg yolk (10% v/v in PBS) was mixed with 100 µl of various sample concentrations, and volume got subsequently increased to 1ml with the use of MilliQ water. Following that, 50 ml of FeSO4 (75mM) and 20 ml of ascorbic acid (100mM) were combined with the mixture. Later, treat the mixture for an hour at 37°C for producing lipid peroxidation. Each sample was then heated for 30 minutes at 95 degrees Celsius with 800 milliliters of distilled water, 200 milliliters of EDTA (100mM), and 1500 milliliters of TBA reagent. Later, mixture was taken for centrifugation at 3000 rpm after chilling for ten minutes, and the absorbance at 532 nm was determined. Lipid peroxidation's inhibition was determined by using an equation below. The TBA reagent was made by mixing 3.0 grams of TBA, 120 grams of TCA, and 10.4 milliliters of 70% HClO4.

Morin's capacity for scavenging (%) = [(Ablank-Asample)/Ablank] × 100

A sample indicates Morin or control absorbance, while A blank indicates control absorbance.

A graph of inhibition against concentration was plotted to determine IC_{50}, which is the amount of medicine needed for scavenging free radicals by 50%.

Experimental animals

Mice weighing 25-30 g were purchased. Every animal was kept in the predefined, standard laboratory conditions, fed a normal diet of pellet chow, and given water *ad libitum*. When handling and caring for animals, everything was processed in compliance with the National Institutes of Health's (NIH) Guide for use as well as care of the animals in laboratory. Ethical approval for animal was taken from ORIC University of Sindh, Jamshoro. The committee of ethics from the University of Sindh, Jamshoro gave its clearance to the experimental procedures.

TPA Induced Acute Inflammation of Ear

Morin's anti-inflammatory efficacy was evaluated using a previously developed acute model of TPA (Akram et al., 2015). 30 minutes before receiving 2 µg/ear of TPA treatment, t the right ear's internal and external regions received either vehicle (20 µL of acetone) or indomethacin (0.2 mg/ear) topically by spraying. Left ear was given a control. At 0, 1, 2, 3, and 4 hours after treating with TPA, digital calliper was used to calculate each ear's thickness. Mice were taken to be sacrificed after receiving TPA for four hours, and biopsy punch was used to take 6mm plugs out of the center of both ears. The disparities of weight or volume between the left and right ears were evaluated in order to calculate the degree of edema.

Oxazolone Induced Chronic Inflammation of Skin

Oxazolone-induced chronic atopic dermatitis model was develop (Shin YongWook et al., 2005). After shaving the mice's dorsal skin, 1.5% of oxazolone from 100 L in ethanol was administered firstly to make them more sensitive. On day seven, the right ear of an animal was massaged on right and left sides with 1% oxazolone taken from 20µL in a 4:1 mixture of acetone and olive oil. This task was repeatedly performed all three days (days 10, 13, and 16) consecutively. The right ear was given either 0.01 or 0.05 mg/ear of Morin, a control, or 0.05 mg/ear of indomethacin 30 minutes prior to and 3 hours after each oxazolone test. Digital callipers were used to measure the thickness of the right ear on each oxazolone challenge day. Animals were sacrificed following a final 24-hour oxazolone challenge, and the utilization of biopsy punch was done to extract the right ear discs (6mm) so that, weight of edema can be determined.

RESULTS AND DISCUSSION

Radical scavenging activity in ABTS

The ABTS assay was used to examine four distinct concentrations of Morin, ranging from 0 to 100 µM. The data suggests that, the Morin compound effectively inhibited ABTS+ free radicals depending on dose manner. Figure 1 depicts IC_{50} 13.86 (µM), demonstrating that even at low dosages, it effectively and strongly suppresses free radicals.

Scavenging activity of radical in DPPH

Radical test of DPPH was performed for calculating capacity of Morin to squench free radicals. The antioxidant properties of a drug are frequently assessed using this technique (Huang et al., 2005). The results of Morin's DPPH

radical scavenging abilities are shown in figure 2. Morin in particular showed considerable and dose-dependent free radical scavenging ability of DPPH. The predicted IC_{50} was calculated to be 23.6 (µM).

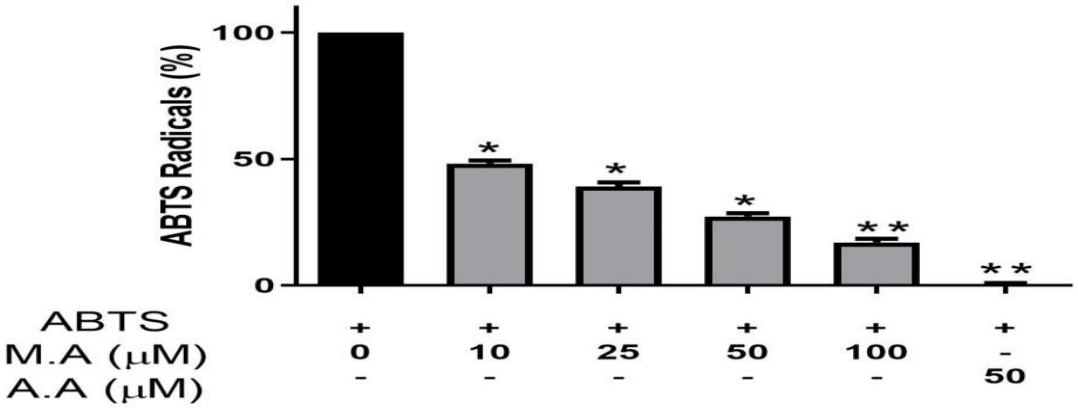

Figure 1: Scavenging of free radicals by Morin. Data demonstrates Morin's dose-dependent inhibition at different concentrations, ranging from 0 µM to 100 µM. The standard deviation and mean are shown by error bars. Graph pad prism was used to conduct the pair t-test for comparing the mean with the control (ascorbic acid). * $p < 0.05$ and ** $p < 0.01$ were deemed significant in statistics while comparing with control group.

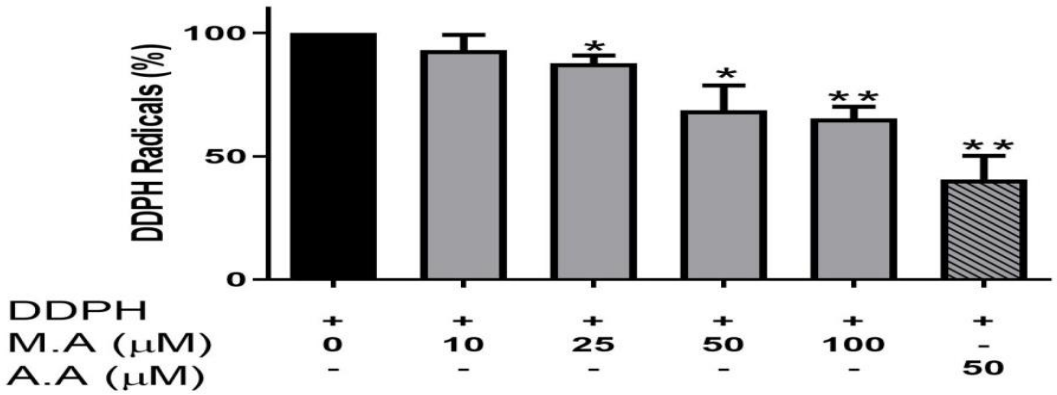

Figure 2: Concentrations of DPPH free radicals are scavenged by Morin compounds. The data demonstrates Morin's inhibition depending on dose of variable concentrations, from 0 µM to 100 µM. Standard deviation is shown by the error bars. Graph pad prism was used to do the pair t-test for mean comparison with the control. * $p < 0.05$, ** $p < 0.01$ while comparing with DPPH-treated group; # $p < 0.05$, ## $p < 0.01$ after it is compared to control group.

Malondialdehyde concentration in the lipid oxidation assay is inhibited by Morin

Lipid peroxidation, It is a popular technique for evaluating antioxidant activity which is brought on by the oxidative breakdown of unsaturated fatty acids. A marker for measuring lipid peroxidation is malondialdehyde. The amount of oxidative stress is measured using the aldehyde product. It creates the chromogen TBAMDA complex,When there is interaction between two thiobarbituric acid molecules and malondialdehyde in an acidic solution. The chromogen can be identified using a spectrophotometer (Rai and Phadke, 2006). Here, the results showed that Morin significantly reduced the concentration of malondialdehyde in a dose-dependent manner and scavenged free radicals. It was also determined that the data was significant. Morin's capacity to lower malondialdehyde's percentage with an IC_{50} of 91.81 µM is shown in Figure 3.

Morin's protective activity in acute dermatitis model induced by TPA in mice

An acute model of skin inflammation was induced using TPA. Anti-inflammatory qualities of Morin were evaluated *in vivo* by generating edema in a mouse's ear by inducing inflammation. The right ear received ethanol treatment 30 minutes prior to TPA application, along with Morin (0.2 mg or 0.5 mg) and indomethacin (0.5 mg). The left ear served as the control. A biopsy punch was used to remove a disc, and a digital vernier calliper was used to assess the edema volume at the fourth hour. When only topical Morin (0.5 mg/ear) was topically applied, it significantly decreased elevated volume caused by edema, as seen in Figure 4(A). The weight of the ear disc decreased following four hours of TPA treatment, further demonstrating Morin's protective function as depicted in Figure 4 (B). This study illustrates Morin's anti-inflammatory qualities in the ear edema of mice model induced by TPA.

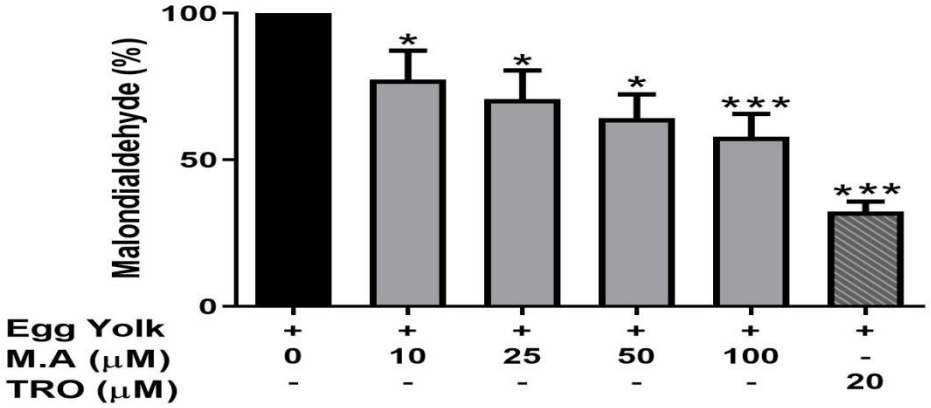

Figure 3: The levels of malondialdehyde are controlled by Morin. The data demonstrates how Morin inhibits malondialdehyde depending on dose manner at various dilutions, ranging from 0μM to 100μM. Standard deviation is represented by error bars. ** p < 0.01 vs. LPO-treated group; # p < 0.05, ## p < 0.01 vs. control group; at* p < 0.05, p < 0.01.

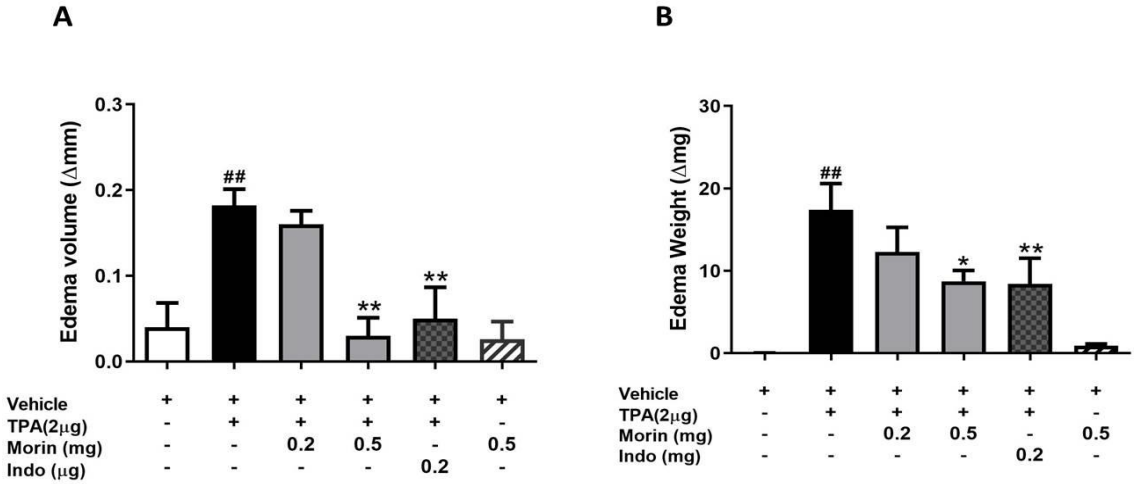

Figure 4: The TPA model demonstrates the topical Morin's anti-inflammatory activity. The figure illustrates the Morin's anti-inflammatory activity,applied topically to mice. Prior to 30 minutes, phorbol 12 myristate 13-acetate (TPA; 2 μg per ear) was administered to induce skin inflammation. The right ear was treated topically with either Morin or 0.2 mg of indomethacin (INDO). The quantity of ear edema was measured using the edema volume, as shown in (A), and edema weight after four hours of TPA application as shown in (B). The mean SD is used to display statistics. Tukey's test and ANOVA were employed to determine significant. Comparing * p 0.05, ** p 0.01, and # p 0.05, ## p 0.01. group treated with TPA versus the control group.

Protective effects of Morin in a oxazole-induced chronic dermatitis mice model

Further investigation of Morin was done in a chronic dermatitis model of mice, in which oxazolone caused inflammation. Oxazolone applied often to the skin increased the symptoms of dermatitis, including erythema, erosion, abrasion, dryness, and edema volume. When administered topically, Morin showed a significant reversal of inflammatory changes. Infiltration of inflammatory cells was shown to have decreased. As seen in figure 5(A-B), Morin likewise decreased the ear's weight and volume caused by oxazolone depending on dose manner. Additionally, data was determined to be substantial. Results support Morin's anti-inflammatory capability in lowering persistent skin irritation.

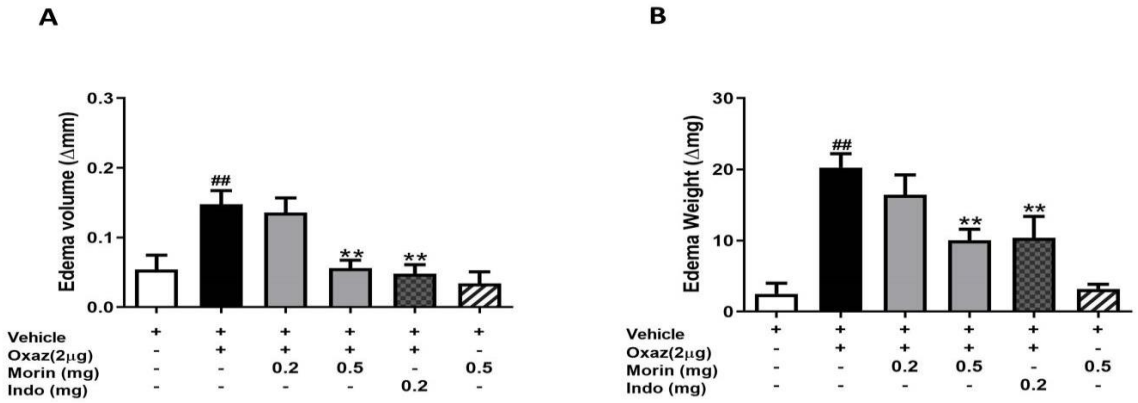

Figure 5: Topical Anti-inflammatory Activity Of Morin in Oxazolone model. The figure illustrates the anti-inflammatory activity of administered topical Morin in mice with oxazolone-induced chronic dermatitis. Thirty minutes before receiving oxazolone (2 μg/ear), Morin or indomethacin (INDO; 0.2 mg) was applied topically to the ear on the right side . Thickness of edema was used to determine the amount of ear edema, as shown in (A), and the edema's weight after four hours of oxazolone administration is shown in (B). The mean SD is used to illustrate the data. After determining significance using ANOVA, Tukey's test was applied. ## p 0.05, ## p 0.01 versus the control group; * p 0.05, ** p 0.01 versus the TPA-treated group.

DISCUSSION

Although concerns about the scarcity of studies on possible therapies for dermatitis in the fields of pharmacology as well as toxicology with reference to skin inflammation, triggered by chemical, are becoming more prevalent. Since natural flavonoids have anti-oxidant and anti-inflammatory qualities both *in vivo* and *in vitro*, they have drawn a lot of attention (Rai and Phadke, 2006, Domitrović et al., 2015, Hatnapure et al., 2012). Morin has also proved to be the potent anti-inflammatory agent, working on pulmonary inflammation, osteoarthritis, and mastitis in investigations by (Pinho-Ribeiro et al., 2015, Tianzhu et al., 2014).

Additionally, it is evident from current study that Morin has a part for treating inflammation. Prior studies have shown that COX-2 selective inhibitors can lower inflammation and stop cytokine-induced inflammation from degrading cartilage (Chen et al., 2012, Mastbergen et al., 2002). Our investigation showed that Morin is an excellent anti-inflammatory agent, and the results are consistent with the Karger study (De Boer et al., 2009). According to Karger's research, Morin suppresses IL-1-induced inflammation by blocking NF-B activation, which is useful in treating bone arthritis. The inhibition of inflammatory mediators is the cause of the anti-inflammatory action, even though the underlying mechanism is unclear. Being a naturally occurring bioflavonoid molecule, Morin could be useful in the development of new drugs. It is anticipated that Morin may also prevent inflammation in skin by inhibiting NF-B activation.

Instances of inflammatory cytokines that have been linked to the emergence of skin inflammation are TNF- and IL-1(Qu et al., 2018). An increase in the inflammatory response could result from these inflammatory cytokines causing the synthesis of more inflammatory mediators. Research carried out *in vivo* has shown that NF-B activation may occur when chondrocytes are stimulated by IL-1(Kagari and Shimozato, 2002). The transcription of NF-B activation may be the cause of the target genes, including NO, PGE2, and MMPs (Lianxu et al., 2006). The synovial fluid of dermatitis patients had higher concentrations of inflammatory

mediators (Tak and Firestein, 2001). It is also anticipated that Morin will considerably reduce the inflammatory mediators.

The Nrf2 transcription factor is crucial for regulating the body's reaction to stress due to oxidation (Kanyama et al., 2000). It is evident from the current research that Nrf2 regulates cartilage integrity and guards against osteoarthritis (Nguyen et al., 2009). The Nrf2/HO-1 Passage of signalling was found being essential for regulating response induced by inflammation in osteoarthritis brought on by type 2 diabetes in a previous research (Cai et al., 2015). Conversely, HO-1 overexpression might mitigate the severity of osteoarthritis (Vaamonde-Garcia et al., 2017). Moreover, It is evident from studies earlier, that Nrf2 triggering possibly reduce NF-B stimulation (Sebastián et al., 2018). However, most of the studies proved that several organic medicines such as herbs could lessen responses triggered by the inflammation linked to osteoarthritis by triggering Nrf2 signalling pathway (Buelna-Chontal and Zazueta, 2013, Kong et al., 2016). Additionally, Karger et al. demonstrated that when Nrf2 and HO-1 were produced, Morin's anti-inflammatory effects were inhibited, and that Nrf2 was removed. The studies showed that Morin's anti-inflammatory activity in chondrocytes was mediated by triggering Nrf2 signalling pathway. According to prior research, Morin inhibits NF B activation, which stops IL-1 from causing human chondrocytes to produce inflammatory mediators (Xue et al., 2017). Although the exact chemical process is still unknown, we expect that Morin also inhibits the release of NF-B activation, which in turn stops liberating inflammatory mediators, hence an anti-inflammatory response is produced. Furthermore, for understanding signalling mechanism that causes skin inflammation, Morin needs to be thoroughly investigated.

Extremely reactive chemicals known as free radicals, which have the potential to harm biological components in an attempt to stabilize themselves. Inflammatory diseases like rheumatoid arthritis, cancer, and autoimmune diseases can also be brought on by them. The free radical chain can be broken by antioxidants that are beneficial to cancer by giving free radicals electrons and changing them into stable molecules. Antioxidants are useful for restricting the spread of free radicals by transferring their electrons and forming stable compounds. Because of their ability to combat free radicals, natural plants are thought to be good for health. Flavonoids, tannins, and phenolic acids are some of their secondary metabolic products that are strong antioxidants and protective agents. Our research showed that the potent antioxidant Morin significantly reduces reactive oxygen species, which in turn lessens the precipitation of inflammation.

CONCLUSION

In conclusion, our study showed that a recently created flavonoid, Morin, has potent antioxidant and anti-inflammatory qualities. The research demonstrated efficacious anti-inflammatory and antioxidant properties in Morin. The qualities are to be used as a novel therapeutic agent with less adverse effects to treat inflammation induced by skin.

AUTHORSHIP CONTRIBUTIONS

Concept – S.K., G.K.; Design – GK., M.A., S.B.; Supervision –G.K, M.A.; Resources – S.K., S.B, J.A., S.A.S.. S.A, Y.Q.; Materials – S.K., S.B,J.A.; Data Collection and/or Processing – S.K., G.K., M.A, S.A.S, S.B.S.A, Y.Q,; Analysis and/or Interpretation – M.A.,G.K, S.K, S.A.; Literature Search – S.K., G.K, P.S. Y.Q; Writing – S.K, G.K, S.B, P.S ; Critical Reviews –G.K., M.K, P.S, S.B.

CONFLICT OF INTEREST STATEMENT

No conflict of interest has been declared by the authors.

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