Magnolol may contribute to barrier function improvement on imiquimod-induced psoriasis-like dermatitis animal model via the downregulation of interleukin-23

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Abstract. Psoriasis is a chronic, recurrent, immune-mediated disease involving the skin and joints. Epidermal hyperproliferation, abnormal keratinocyte differentiation, angiogenesis with blood vessel dilatation, and excess T helper type-1 (Th-1) and Th-17 cell infiltration are the main histopathological features of psoriasis. Magnolol is a polyphenolic compound that exerts its biological properties through a variety of mechanisms such as the NF-κB/MAPK, Nrf2/HO-1 and PI3K/Akt pathways. Magnolol has been demonstrated to exert a number of therapeutic effects on dermatological processes, including acting as an anti-inflammation, antiproliferation and antioxidation agent. However, few studies have been published on the effect of magnolol on psoriasis. Therefore, the present study aimed to elucidate the mechanism of action of magnolol on psoriasis. BALB/c mice were treated topically with imiquimod (IMQ) to induce psoriasis-like dermatitis, and were randomly assigned to the control, vehicle control, low- and high-dose magnolol, and 0.25% desoximetasone ointment treatment groups in order to investigate skin barrier function, any changes in the levels of cytokines and for the histological assessment. High doses of magnolol were indicated to be able to improve the barrier function following IMQ-induced barrier disruption. Magnolol activated peroxisome proliferator-activated receptor-γ, and also significantly inhibited the protein expression of interleukin (IL)-23, IL-1β, IL-6, tumor necrosis factor-α and interferon-γ. However, administering a high dose of magnolol did not lead to any improvement in the clinical and pathological features of the psoriasis severity Taken together, these results demonstrated that downregulation of IL-23 may contribute to barrier function improvement in a psoriatic skin model.

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Abbreviations: PPAR-γ, peroxisome proliferator-activated receptor-γ; IMQ, imiquimod; DXM, 0.25% desoximetasone ointment; EtOH, ethanol; TEWL, transepidermal water loss; DAB, diaminobenzidine

Key words: interleukin-17, interleukin-23, psoriasis, magnolol, imiquimod, skin barrier

Introduction

A healthy skin barrier can be attributed to well-differentiated corneocytes, correctly arranged extracellular lipid bilayers, balanced activities of antimicrobial peptides and enzymes, and a physiologically weak acidic pH environment on the skin surface (1). Inflammatory skin conditions, such as psoriasis and atopic dermatitis, present with impaired skin barrier function (1). Psoriasis is a chronic, recurrent immune-mediated disease and affects people of all ages, most commonly in individuals aged between 15-30 years old (2-4). Epidermal hyperplasia, acanthosis, hyperparakeratosis, angiogenesis with blood vessel dilatation and excess T helper type-1 (Th-1) and Th-17 lymphocyte infiltration are the main histopathological features of psoriasis (2-5). Furthermore, the interleukin (IL)-23/IL-17 axis model for psoriasis proposes that IL-23 activates Th17 lymphocytes, resulting in the subsequent release of proinflammatory cytokines, including IL-17, leading to the psoriatic phenotype (5,6). Although genetic, immunological and environmental factors have been proposed as being the cause of this condition, the exact cause of psoriasis has yet to be elucidated, and the mechanisms underlying psoriasis continue to be poorly understood (3,4,7).

Magnolol (5,5'-diallyi-2,2'-dihydroxy biphenyl; $C_{18}H_{18}O_2$, MW=266.33 Da) is one of the major active polyphenolic ingredients isolated from *Magnolia officinalis* (known as houpu magnolia) (8,9). The considerable efficacy of magnolol has been confirmed through an assessment of its anti-inflammatory, antiproliferative, anti-photoaging and anti-free radical activity (8,10-14). Magnolol has also been

indicated to be an agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ) (15-17). The key functions of PPAR-γ in the epidermis include maintenance of skin barrier homeostasis, regulation of the stratum corneum surface pH and water-holding capacity, controlling cell differentiation and responding to inflammatory responses via PPAR-γ activation, thus resulting in increased cell survival and reduced apoptosis in UV-induced damage studies (18,19). However, the effect of magnolol on psoriasis has been less well reported, although it may be hypothesized that magnolol could contribute towards permeability barrier homeostasis via PPAR-γ in psoriatic skin. Therefore, the present study aimed to investigate the therapeutic effects, as well as the effect on the skin barrier, of magnolol on an imiquimod (IMQ)-induced psoriatic-like dermatitis model. The underlying mechanisms governing this interaction were also investigated.

Materials and methods

Materials. Magnolol was purchased from Merck KGaA. Esperson (0.25% Desoximetasone ointment) was purchased form Sanofi S.A. All other chemicals were of analytical grade.

Animals. A total of 15 male BALB/c mice (8-12 weeks old; purchased from National Laboratory Animal Center, Tainan, Taiwan), weighing 22±2 g, were housed under standard laboratory conditions with sufficient food and water that was accessible at all times, as well as with minimized handling, odors, noises and vibrations in the Laboratory Animal Center of the Cathay General Hospital (12 h light/dark cycles and 24±2˚C ambient temperature). A total of three mice were placed in each group. The duration of the experiment was 11 days. The animal health and behavior were monitored every day via body weight and food intake measurement. All animal experiments were performed and approved by the Institutional Animal Care and Use Committee (IACUC) of Cathay General Hospital (IACUC registration no. 107-028). During the experimental period, each animal was housed in a separate cage with wooden bar toys, complying with the IACUC regulations. To minimize distress during hair shaving, mice were placed in the induction anesthesia chamber (10x10x20 cm) with 4% isoflurane in oxygen (flow rate=0.5 l/min), followed by 2% isoflurane in oxygen (flow rate=0.2 l/min) for maintenance of anesthesia via a facemask. During the experimental period, the mice were euthanized via excessive isoflurane exposure followed by cervical dislocation to confirm successful euthanasia as a humane endpoint for this study, when cachexia led to a body-weight loss of 10% or more. No mice suffered spontaneous mortality or were euthanized because of a body-weight loss of 10% or more during the experiment. For euthanasia, mice were placed in the induction anesthesia chamber with 5% isoflurane in oxygen (flow rate=0.5 l/min) exposure continued for at least 1 min after respiratory arrest, followed by cervical dislocation to confirm successful euthanasia. All animals were sacrificed on day 11 at the end of the experiment to obtain the skin samples for further investigation.

Establishment of the IMQ-induced psoriasis-like skin animal model. Psoriasiform dermatitis was induced in mice following a widely used protocol (20-23) through the topical application of a dose of 62.5 mg 5% Aldara IMQ cream (3M Pharmaceuticals) on the shaved dorsal skin for six consecutive days, once daily, prior to the experimental period (days 0-6) (20-23).

Experimental protocols. A total of 18 mice were used in the present study. Three untreated (normal) mice were used as negative control specimens for morphology, PPAR-γ and cytokine array studies. For the barrier function study, 15 mice were randomly assigned to the following groups: i) The control group (only induced by IMQ); ii) vehicle group, treated with ethanol (EtOH; IMQ-induced plus EtOH treatment); iii) low-dose magnolol group (IMQ-induced, 100 μg/ml magnolol dissolved in EtOH treatment); iv) high-dose magnolol group (IMQ-induced, 300 μg/ml magnolol dissolved in EtOH treatment) and v) 0.25% desoximetasone ointment (DXM) group [IMQ-induced plus Esperson (0.25% Desoximetasone ointment; Sanofi S.A.) treatment as a positive control]. Following the successful induction of the psoriasiform skin, the mice continued to receive IMQ application, followed by their respective treatments until day 11. In the treatment phase (days 6-11), 3-4 h post-IMQ application, mice were treated once daily with 100 μl magnolol, EtOH solution or 60 mg DXM on the dorsal skin.

Assessment of barrier functions. Barrier function parameters, including transepidermal water loss (TEWL), skin hydration and erythema values, were measured on the dorsal surface of mice prior to the application of drugs on day 0 (used as normal barrier functions value baseline), and subsequently on days 6 and 11 using an MPA-II system equipped with Tewameter TM300, Corneometer CM825 and Mexmeter MX18 probes (Courage and Khazaka Electronic GmbH).

Collection of skin specimens. Three untreated mice were sacrificed 48 h after hair shaving, and the specimens served as negative controls for inflammatory cytokine analysis. Treated (barrier function study) mice were sacrificed on day 11 after the final barrier function assessment. Full-thickness mouse skin was separated into two samples for histological staining.

Immunohistochemical staining for PPAR-γ. Skin specimens were fixed in 10% formalin solution and embedded in paraffin at 4˚C overnight. Sections of 5 μm thickness were cut and stained with primary antibodies against PPAR-γ (1:25; cat. no. GTX19481; Rabbit origin; GeneTex, Inc.) using a Ventana BenchMark XT automated stainer (Ventana Medical Systems, Inc.). Samples were incubated with the PPAR-γ primary antibody (1:25; cat. no. GTX19481; Rabbit origin; GeneTex, Inc.) in universal ready to use blocking reagent (cat. no. 760-050; Ventana Medical Systems Inc.) for 60 min at 37˚C, and then the incubation was continued overnight at 4˚C. Subsequently, the samples were incubated with the universal mouse and rabbit ready to use secondary biotinylated antibody using an ultraView Universal DAB ready to use Detection kit (cat. no. 760-500; Ventana Medical Systems Inc.) for 1 h at room temperature. The levels of diaminobenzidine (DAB) were subsequently visualized. Samples were then counterstained with hematoxylin for 4 min at 37˚C, and examined under a light microscope at a magnification of x200 (BX41; Olympus Corporation).

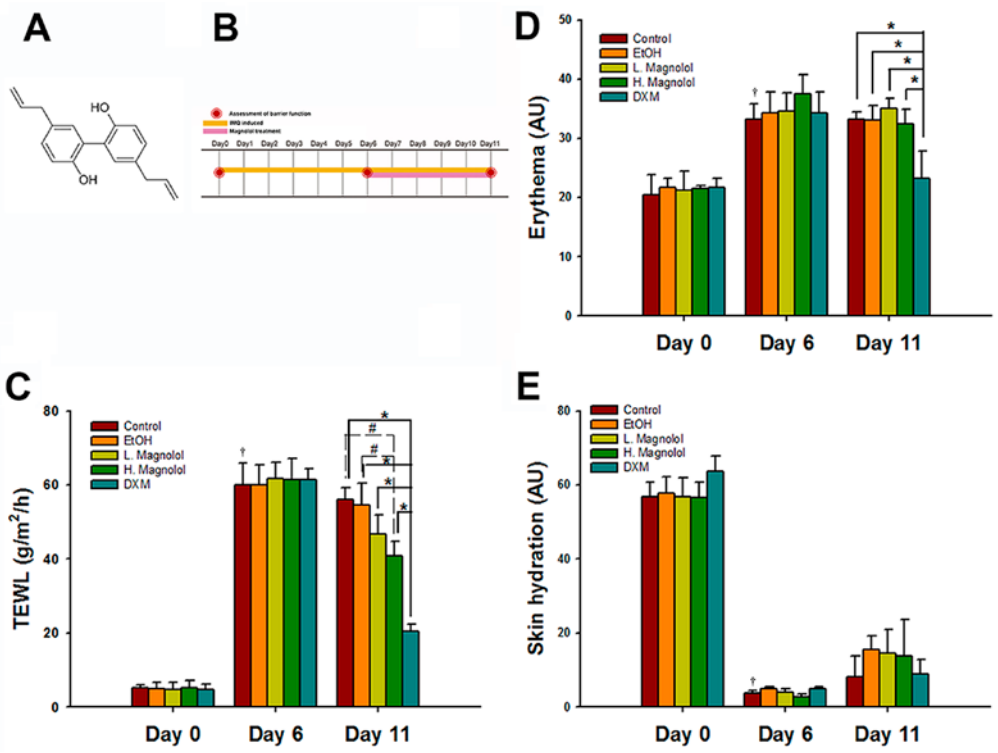

Figure 1. Magnolol improves the barrier function in IMQ-induced psoriasis-like dermatitis. (A) Chemical structure of magnolol. (B) Study design. Mice were administered a daily topical application of a dose of 62.5 mg Aldara IMQ cream (5%) on the shaved dorsal skin for 6 consecutive days (days 0-6). After the successful induction of psoriasiform skin, the mice continued to receive IMQ until day 11. After 3-4 h IMQ application, the mice subsequently received 100 μl either magnolol, EtOH solution or 60 mg DXM on the dorsal skin once daily (days 6-11). (C) TEWL, (D) skin hydration and (E) erythema values were measured on the dorsal surface of mice before the applications of drugs on day 0, and then monitored on days 6 and 11. (mean ± SD; n=3). †P<0.05, compared with Day 0 and Day 6 in control group; $^{\#}$P<0.05 and *P<0.05 (using two way mixed ANOVA, post hoc Bonferroni's test). IMQ, imiquimod; TEWL, transepidermal water loss; EtOH, ethanol, DMX, 0.25% desoximetasone ointment.

Immuno-intensity counting. To objectively evaluate the immunostaining results, the slides were scanned using a slide scanner (Pannoramic DESK II DW; 3DHISTECH Ltd.) at a magnification of x200. CellQuant and PatternQuant computer counting software (version 2.4.0) were used (all, 3DHISTECH Kft.). PatternQuant was programmed to recognize the regions of interest, and CellQuant was used to evaluate the H-Score. Each skin tissue was assigned an annotation, which was 1 mm wide and covered the whole thickness of the skin to the muscle layer. The H-score was defined in terms of its immune-intensity, and this was then multiplied by the staining percentage, providing a range of values from 0-300. The immuno-intensity was recorded as being 0 for no staining, 1 for faint staining, 2 for moderate staining, and 3 for intense staining, whereas the staining percentage was recorded from 0-100%. The immune-intensity and staining percentages were both determined using computer counting, as calculated by CellQuant, and counting was only permitted within the regions of interest recognized by PatternQuant.

Determination of the inflammatory cytokine protein levels via multiplex cytokines bead array. Studies have reported that IMQ-induced psoriasis-like skin elicits either the protein or mRNA expression of IL-17, IL-23, IL-1β, IL-6, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) in mice, and successful anti-psoriatic interventions should therefore inhibit the aforementioned cytokine expression (5,24-26). Therefore, in the current study, proteins were extracted from whole skin of 6 groups in order to determine the levels of IL-17A, IL-23, IL-1β, IL-6, TNF-α and IFN-γ using the LEGENDplex™ multiplex cytokines bead array kit (mouse inflammation panel; BioLegend, Inc.). Aliquots (50 μl) of protein samples were incubated with labeled microbeads for 2 h at room temperature, and subsequently, the concentration of each cytokine was determined using flow cytometry (using an Accuri C6 flow cytometer; BD Biosciences) according to the manufacturer's instructions. The concentration of each cytokine was then determined based on a known standard curve using LEGENDplex™ data analysis software version 8.0 (VigeneTech Inc.) (23).

Light microscopy. Skin samples were fixed in 10% formalin at 4˚C overnight. Sample sections (5 μm-thick) were cut, stained with hematoxylin for 8 min and then eosin for 30 sec both at room temperature (H&E), and examined under a light microscope at a magnification of x200 (BX41; Olympus Corporation).

Statistical analysis. Two-way mixed ANOVA followed by Bonferroni's post hoc test was performed using SPSS 20 software (IBM Corp.). All bar charts are presented as the mean ± standard deviation using Sigmaplot 10.0 software (Systat Software, Inc.). P<0.05 was considered to indicate a statistically significant difference.

Results

Magnolol improves the barrier function of IMQ-induced psoriasis-like dermatitis. The chemical structure of magnolol

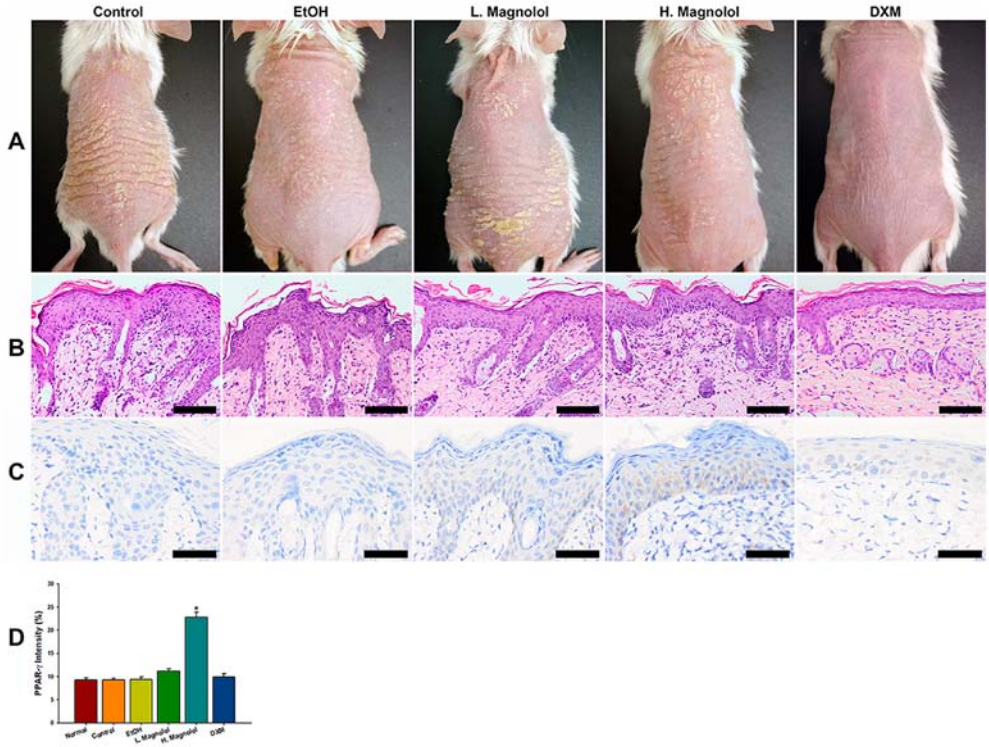

Figure 2. DXM inhibits hyperproliferation of keratinocytes. (A) Morphology of all the groups, revealing the presence of scales, erythema and dry skin. (B) Histopathological staining using H&E revealed epidermal acathotic hyperplasia, abnormal keratinocyte differentiation, superficial dermal capillary dilatation and infiltration of various inflammatory cell types in all groups. However, the Esperson (DMX) treatment group showed much better gross and pathological features of severity index compared with all the other groups. (C) Magnolol activates PPAR-γ protein expression. The high-dose magnolol group showed positive staining of PPAR-γ. (D) The immuno-intensity of PPAR-γ. The high-dose magnolol treatment group revealed a higher intensity of PPAR-γ compared with all the other groups. Scale bar, 50 μm. Yellow arrow head indicated neutrophil cell. (mean ± standard deviation, n=3); *P<0.05 (using two-way mixed ANOVA, post hoc Bonferroni's test). H&E, hematoxylin and eosin; PPAR-γ, peroxisome proliferator-activated receptor-γ; DMX, 0.25% desoximetasone ointment.

and the study design are presented in Fig. 1A and B, respectively. The barrier function measurement values of the control group on day 0 represented the normal baseline values (TEWL, 7.39±1.20 g/m^2/h; skin hydration, 58.25±5.84 arbitrary units (AU); and erythema, 16.80±1.74 AU). Compared with the values on day 0 (as normal baseline), the TEWL (40.79±8.05 g/m^2/h) and erythema (31.23±4.17 AU) values in the control group increased significantly following the establishment of IMQ-induced psoriasis-like dermatitis over a period of 6 consecutive days (both P<0.05). By contrast, the skin hydration value (3.69±1.55 AU) of the control group decreased significantly on day 6 compared with that of day 0 (P<0.05; Fig. 1C-E).

High-dose magnolol (300 μg/ml) treatment led to a restoration of >30% of the TEWL value compared with the control and vehicle control groups on day 11 (both P<0.05). The topical application of DXM markedly reduced the TEWL and erythema values compared with all the other groups on day 11 (all P<0.05; Fig. 1C and D). However, magnolol treatment did not significantly affect erythema or skin hydration on psoriasis-like skin mice compared with the control and vehicle group on day 11 (all P>0.05; Fig. 1D and E).

DXM inhibits hyperproliferation of keratinocytes. The morphology of all 5 groups revealed the presence of scales, erythema and dry skin (Fig. 2A). The results of histopathology using H&E staining revealed epidermal acanthosis, parakeratosis, tortuous capillary dilatation in the papillary dermis, and the infiltration of various types of inflammatory cell in all groups (Fig. 2B). However, the DXM treatment group exhibited improved clinical and pathological features of the psoriasis severity compared with all other groups (Fig. 2A and B).

Magnolol activates the protein expression of PPAR-γ. To investigate whether magnolol acts as a PPAR-γ agonist on the epidermis, PPAR-γ protein expression levels were evaluated via immunohistochemical staining. The results demonstrated that magnolol activated PPAR-γ protein expression on the epidermis, which was more clearly observed in the cytoplasm (Fig. 2C). Fig. 2D demonstrated the results of the immune-intensity analysis of PPAR-γ via automatic computer counting. The high-dose magnolol treatment group exhibited higher immune-intensities of PPAR-γ compared with all the other groups (P<0.05).

Magnolol inhibits the protein expression levels of IL-23, IL-1β, IL-6, TNF-α and INF-γ in psoriasis-like skin. The potential underlying mechanisms of magnolol treatment in psoriasis-like skin were examined using the inflammatory cytokine panel. The cytokine array results revealed that the expression of all the cytokines were significantly increased in the control group (IMQ-induced only) compared with the normalgroup (untreated skin specimens, P<0.05). High-dose administration of magnolol led to the inhibition of IL-23, IL-1β, IL-6, TNF-α and INF-γ protein expression (all P<0.05), although not of IL-17A (P>0.05), compared with the control

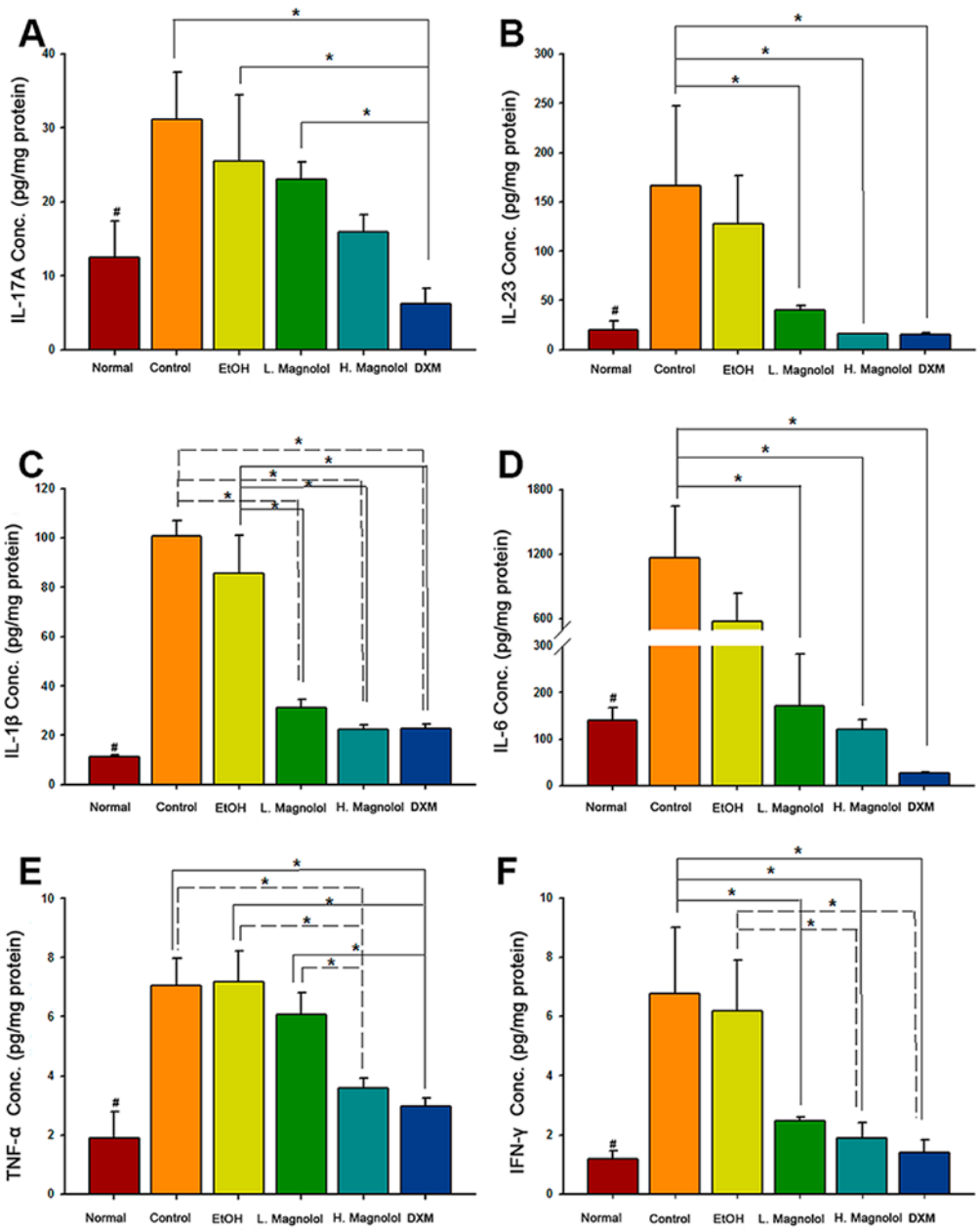

Figure 3. Magnolol inhibits the protein expression levels of IL-23, IL-1β, IL-6, TNF-α and INF-γ in psoriasis-like skin. (A) IL-17A, (B) IL-23, (C) IL-1β, (D) IL-6, (E) TNF-α and (F) IFN-γ protein expression levels were analyzed using a LEGENDplex™ kit (mean ± standard deviation, n=3); #P<0.05, compared with control group; *P<0.05 (using two-way mixed ANOVA, post hoc Bonferroni's test). IL, interleukin; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ.

group. Low-dose administration of magnolol led to the inhibition of IL-23, IL-1β, IL-6 and INF-γ protein expression (all P<0.05) although not of IL-17A and TNF-α (both P>0.05), compared with the control group. Both high and low administration of magnolol led to the inhibition of IL-1β compared with the EtOH group (both P<0.05). Additionally, DXM inhibited the expression of all inflammatory cytokines, compared with the normal group (P<0.05; Fig. 3).

Discussion

The effect of magnolol on psoriasis has been rarely reported. The present study has demonstrated that magnolol activates PPAR-γ, and also significantly inhibits the protein expression of IL-23, IL-1β, IL-6, TNF-α and INF-γ, which may contribute to skin barrier function. The IL-23/IL-17 axis has been reported to be a critical regulator for psoriasis and psoriatic arthritis (5). Previous studies have reported that IMQ-induced psoriasis-like skin elicits either protein or mRNA expression of IL-17, IL-23, IL-1β, IL-6, TNF-α and INF-γ in mice skin (5,24-26), and successful anti-psoriatic interventions should therefore inhibit the aforementioned cytokine expression (24-26), especially with respect to the downregulation of IL-17 and IL-23 expression (23). However, in the present study, administration of high and low-dose magnolol treatment did not effectively inhibit IL-17 or lead to any improvement in the clinical and pathological features of the psoriasis severity index.

PPARs have been indicated to perform essential roles in cutaneous homeostasis (18). PPAR-γ, as one of three PPARs

isoforms, has been indicated to exert anti-inflammatory effects on a variety of cell types, including macrophages, lymphocytes and connective tissue cells (27). PPAR-γ has been reported to be localized mainly in the nucleus during a number of cellular processes (28). It was recently demonstrated that the downregulation of PPAR-γ by its mitogen-activated protein kinase-dependent is redistributed from the nucleus to the cytosol for non-genomic activity (28,29). A previous study demonstrated that PPAR-γ mainly appears to localize in the cytoplasm in human keratinocytes, whereas it exhibits an exclusively nuclear localization in the suprabasal layer (30). The immunohistochemistry staining results presented in the current study exhibited a similar pattern. Therefore, PPAR-γ may control the cytoplasmatic activity through the same mechanism in keratinocytes. An *in vitro* study revealed that PPAR-γ regulated inflammatory signals by first inhibiting NF-κB nuclear translocation, and then downregulating the cytokine protein expression of IL-6, IL-8, IL-12, IL-21, IL-23, TNF-α and cyclooxygenase-2 (31). PPAR-γ is expressed in keratinocytes, and is also involved in the regulation of keratinocyte differentiation (18). Thiazolidinediones, a family of PPAR-γ ligands, have been indicated to reduce epidermal keratinocyte proliferation and promote epidermal keratinocyte differentiation in a repeated tape stripping-induced hyperproliferative animal model (18). These results may suggest that topical PPAR-γ agonists could be considered as a potential adjunctive therapeutic agent in hyperproliferative skin diseases, such as psoriasis (32).

The bark of *Magnolia officinalis* has been traditionally used in Asia for the treatment of a number of diseases, including anxiety, asthma and depression (33). Honokiol is another primary active compound that is isolated from *Magnolia officinalis*, and is also a PPAR-γ agonist (15-17). A previous study revealed that honokiol could effectively improve psoriasis treatment by inhibiting the NF-κB pathway in a transgenic mouse model (34). A previous study also indicated the effect and mechanism of magnolol on psoriasis mice induced by imiquimod via oral administration (35). To the best of our knowledge, the present study has been the first to demonstrate the topical anti-psoriatic effects as well as skin barrier function improvement of magnolol on IMQ-induced psoriasis-like dermatitis in mice.

The number of animals used in the current study was small (n=3). In future studies, the number of animals used should be increased. Further research is also required to enhance the topical distribution of magnolol to the skin and to investigate the therapeutic outcome of this treatment, as well as to clarify the pharmacological effects of magnolol on psoriasis.

The IL-23/IL-17 axis has been reported to be the critical regulator for psoriasis and psoriatic arthritis (5,6). In the present study, it has been demonstrated that magnolol activates PPAR-γ, and is able to improve barrier function via downregulation of the IL-23 signaling pathway in an IMQ-induced psoriasis-like dermatitis mouse model. The results revealed that the downregulation of IL-23 may contribute to barrier function improvement, and could possibly serve a role in alleviating psoriasis-like dermatitis in animals. However, the application of magnolol alone, when applied topically to inhibit IL-23, may not be an effective method for psoriasis treatment. The potential of using systemic magnolol or topical magnolol treatment combined with topical glucocorticosteroid to treat psoriasis, however, is worth of further investigation.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

The study was conceptualized and designed by JWG, YPC, and SHJ. JWG wrote the initial version of the manuscript. JWG, YO, and CYW performed the animal studies and barrier function study. YPC and SHJ interpreted the animal image data regarding the severity of psoriasis. JWG and CYL performed the immunostaining and CYL performed the pathologic diagnosis. JWG performed the cytokines array and statistical analyses. HYT was responsible for reviewing and editing the paper. JWG, YPC, and SHJ provided supervision throughout the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All animal experiments were performed and approved by the Institutional Animal Care and Use Committee (IACUC) of Cathay General Hospital (IACUC registration no. 107-028).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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2022 Journal Performance Data for: Experimental and Therapeutic Medicine

ISSN
1792-0981

EISSN
1792-1015

JCR ABBREVIATION
EXP THER MED

ISO ABBREVIATION
Exp. Ther. Med.

Journal Information

EDITION
Science Citation Index Expanded (SCIE)

CATEGORY
MEDICINE, RESEARCH & EXPERIMENTAL - SCIE

LANGUAGES
English

REGION
GREECE

1ST ELECTRONIC JCR YEAR
2010

Publisher Information

PUBLISHER
SPANDIDOS PUBL LTD

ADDRESS
POB 18179, ATHENS 116 10, GREECE

PUBLICATION FREQUENCY
12 issues/year

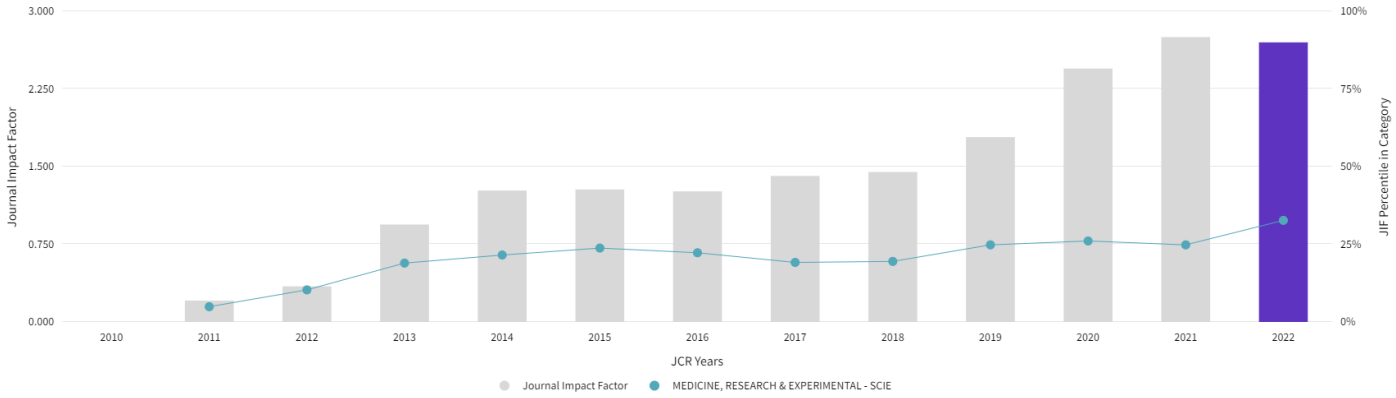
Journal's Performance

Journal Impact Factor

The Journal Impact Factor (JIF) is a journal-level metric calculated from data indexed in the Web of Science Core Collection. It should be used with careful attention to the many factors that influence citation rates, such as the volume of publication and citations characteristics of the subject area and type of journal. The Journal Impact Factor can complement expert opinion and informed peer review. In the case of academic evaluation for tenure, it is inappropriate to use a journal-level metric as a proxy measure for individual researchers, institutions, or articles. Learn more

2022 JOURNAL IMPACT FACTOR	2022 JOURNAL IMPACT FACTOR WITHOUT SELF CITATIONS
2.7	2.7

Journal Impact Factor Trend 2022



Journal Impact Factor is calculated using the following metrics

Citations in 2022 to items published in 2020 (**3,827**) - 2021 (**3,468**)	=	**7,295**	=	**2.7**
Number of citable items in 2020 (**1,227**) + 2021 (**1,453**)		**2,680**		

Journal Impact Factor without self cites is calculated using the following metrics

Citations in 2022 to items published in 2020 (**3,827**) + 2021 (**3,468**) - Self Citations in 2022 to items published in 2020 (**64**) + 2021 (**67**)	=	**7,295 - 131**	=	**2.7**
Number of citable items in 2020 (**1,227**) + 2021 (**1,453**)		**2,680**		

Journal Impact Factor Contributing Items

Citable Items (2,680)

TITLE	CITATION COUNT
ERK/MAPK signalling pathway and tumorigenesis Authors: Guo, Yan-Jun;Pan, Wei-Wei;Liu, Sheng-Bing;Shen, Zhong-Fei;Xu, Ying;Hu, Ling-ling Volume: 19 Accession number: WOS:000519726400049 Document Type: Review	310
COVID-19 and its consequences on mental health (Review) Authors: Tsamakis, Konstantinos;Lazaris, Andreas;Spandidos, Demetrios A.;Smyrnis, Nikolaos;Rizos, Emmanouil;Tsiptsios, Dimitrios;Ouranidis, Andreas;Mueller, Christoph;Schizas, Dimitrios;Terniotis, Christos; et al. Volume: 21 Accession number: WOS:000614845500001 Document Type: Review	33
Pulmonary fibrosis in the aftermath of the COVID-19 era (Review) Authors: Vasarmidi, Eirini;Tsitoura, Eliza;Spandidos, Demetrios A.;Tzanakis, Nikolaos;Antoniou, Katerina M. Volume: 20 Accession number: WOS:000563844300097 Document Type: Review	30
Anorexia nervosa: COVID-19 pandemic period (Review) Authors: Dumitrascu, Mihai Cristian;Sandru, Florica;Carsote, Mara;Petca, Razvan Cosmin;Gheorghisan-Galateanu, Ancuta Augustina;Petca, Aida;Valea, Ana Volume: 22 Accession number: WOS:000657346000001 Document Type: Review	29
Natural skin-whitening compounds for the treatment of melanogenesis (Review) Authors: Qian, Wenhui;Liu, Wenya;Zhu, Dong;Cao, Yanli;Tang, Anfu;Gong, Guangming;Su, Hua Volume: 20 Accession number: WOS:000549886400027 Document Type: Review	27

Showing 1-5 rows of 2,680 total (use export in the relevant section to download the full table)

Journal Impact Factor Contributing Items

Citing Sources (1,940)

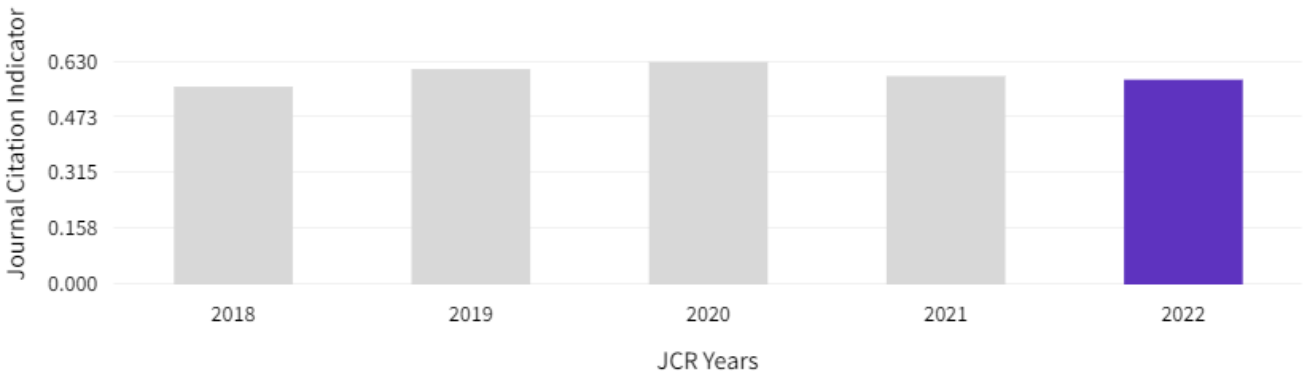
SOURCE NAME	COUNT
INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	298
FRONTIERS IN PHARMACOLOGY	171
FRONTIERS IN IMMUNOLOGY	139
EXPERIMENTAL AND THERAPEUTIC MEDICINE	131
BIOENGINEERED	96
AGING CLINICAL AND EXPERIMENTAL RESEARCH	95
FRONTIERS IN ONCOLOGY	82
FRONTIERS IN GENETICS	76
CELLS	75
MOLECULES	73
EVIDENCE-BASED COMPLEMENTARY AND ALTERNATIVE MEDICINE	71
BIOMEDICINE & PHARMACOTHERAPY	70
CANCERS	65
BIOMEDICINES	62
ANTIOXIDANTS	58
SCIENTIFIC REPORTS	57
OXIDATIVE MEDICINE AND CELLULAR LONGEVITY	55
DIAGNOSTICS	52
JOURNAL OF CLINICAL MEDICINE	52
NUTRIENTS	52

Showing 1-20 rows of 1,940 total (use export in the relevant section to download the full table)

Journal Citation Indicator (JCI)

0.58

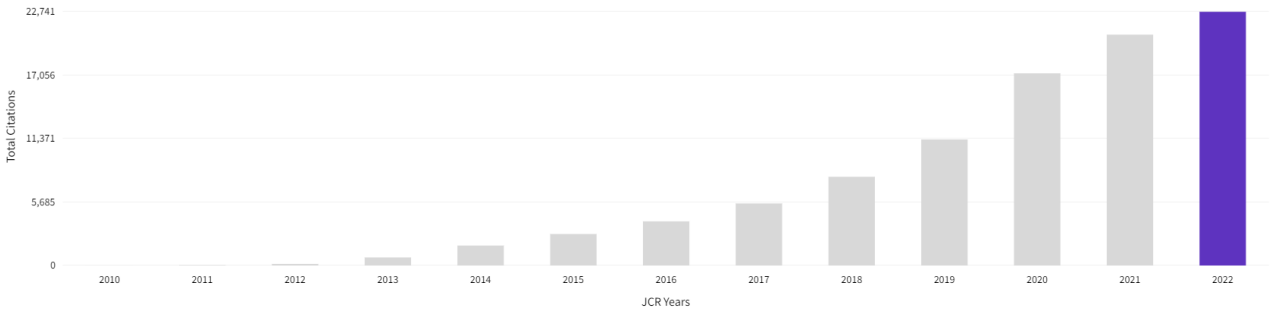
The Journal Citation Indicator (JCI) is the average Category Normalized Citation Impact (CNCI) of citable items (articles & reviews) published by a journal over a recent three year period. The average JCI in a category is 1. Journals with a JCI of 1.5 have 50% more citation impact than the average in that category. It may be used alongside other metrics to help you evaluate journals. Learn more



Total Citations

22,741

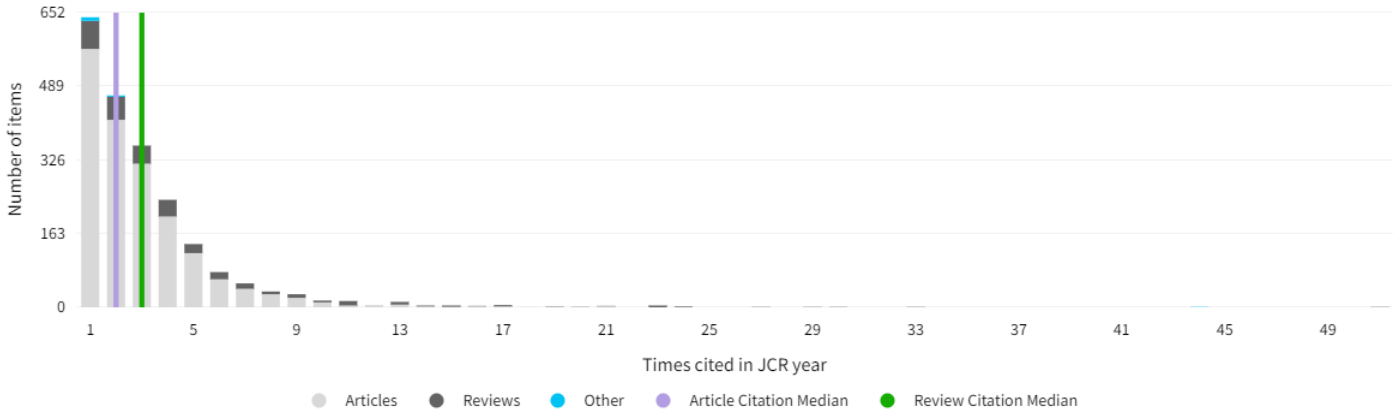
The total number of times that a journal has been cited by all journals included in the database in the JCR year. Citations to journals listed in JCR are compiled annually from the JCR years combined database, regardless of which JCR edition lists the journal.



Citation Distribution

The Citation Distribution shows the frequency with which items published in the year or two years prior were cited in the JCR data year (i.e., the component of the calculation of the JIF). The graph has similar functionality as the JIF Trend graph, including hover-over data descriptions for each data point, and an interactive legend where each data element's legend can be used as a toggle. You can view Articles, Reviews, or Non-Citable (other) items to the JIF numerator. Learn more

ARTICLE CITATION MEDIAN	REVIEW CITATION MEDIAN	UNLINKED CITATIONS
2	3	88



0 times cited

ARTICLES	REVIEWS	OTHER
501	68	54

Open Access (OA)

The data included in this tile summarizes the items published in the journal in the JCR data year and in the previous two years. This three-year set of published items is used to provide descriptive analysis of the content and community of the journal.Learn more

Items

TOTAL CITABLE
3,402

% OF CITABLE OA
98.94%

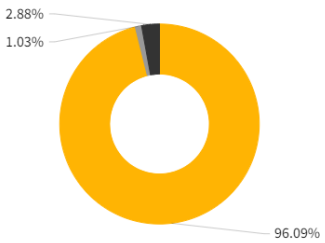
CITABLE

GOLD OPEN ACCESS
3,366 / 96.09%

SUBSCRIPTION OR BRONZE
36 / 1.03%

NON-CITABLE

OTHER (NON-CITABLE ITEMS)
101 / 2.88%



Citations*

TOTAL CITABLE
7,721

% OF CITABLE OA
99.26%

CITABLE

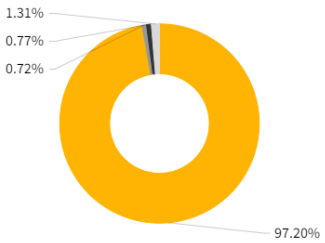
GOLD OPEN ACCESS
7,664 / 97.20%

SUBSCRIPTION OR BRONZE
57 / 0.72%

NON-CITABLE

OTHER (NON-CITABLE ITEMS)
61 / 0.77%

UNLINKED CITATIONS
103 / 1.31%



* Citations in 2022 to items published in (2020-2022)

Rank by Journal Impact factor

Journals within a category are sorted in descending order by Journal Impact Factor (JIF) resulting in the Category Ranking below. A separate rank is shown for each category in which the journal is listed in JCR. Data for the most recent year is presented at the top of the list, with other years shown in reverse chronological order. Learn more

EDITION

Science Citation Index Expanded (SCIE)

CATEGORY

MEDICINE, RESEARCH & EXPERIMENTAL

92/136

JCR YEAR	JIF RANK	QUARTILE	JIF PERCENTILE
2022	92/136	Q3	32.7
2021	105/139	Q4	24.82
2020	104/140	Q3	26.07
2019	105/139	Q4	24.82
2018	110/136	Q4	19.49
2017	108/133	Q4	19.17
2016	100/128	Q4	22.27
2015	95/124	Q4	23.79
2014	97/123	Q4	21.54
2013	101/124	Q4	18.95
2012	109/121	Q4	10.33
2011	107/112	Q4	4.91
2010	106/106	Q4	N/A

Rank by Journal Citation Indicator (JCI)

Journals within a category are sorted in descending order by Journal Citation Indicator (JCI) resulting in the Category Ranking below. A separate rank is shown for each category in which the journal is listed in JCR. Data for the most recent year is presented at the top of the list, with other years shown in reverse chronological order.Learn more

CATEGORY

MEDICINE, RESEARCH & EXPERIMENTAL

105/189

JCR YEAR	JCI RANK	QUARTILE	JCI PERCENTILE
2022	105/189	Q3	44.71
2021	113/195	Q3	42.31
2020	106/188	Q3	43.88
2019	112/187	Q3	40.37
2018	118/185	Q3	36.49
2017	117/185	Q3	37.03

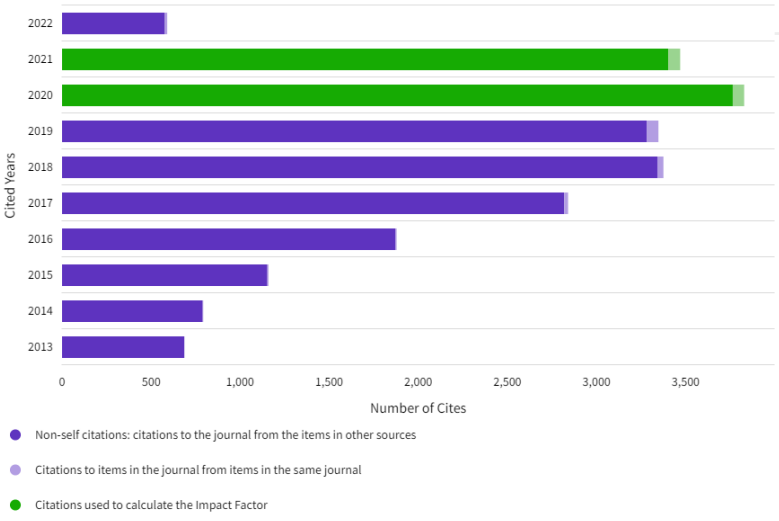
Citation network

Cited Half-life

4.0 years

The Cited Half-Life is the median age of the items in this journal that were cited in the JCR year. Half of a journal's cited items were published more recently than the cited half-life.

TOTAL NUMBER OF CITES	NON-SELF CITATIONS	SELF CITATIONS
22,741	22,456	285



# OF CITES FROM 2022	CUMULATIVE %	# OF CITING SOURCES
22,741 citations	**100.00%**	**3,695 sources**
590 citations	2.59%	317 sources
3,468 citations	17.84%	1,160 sources
3,827 citations	34.67%	1,384 sources
3,346 citations	49.39%	1,284 sources
3,374 citations	64.22%	1,276 sources
2,839 citations	76.71%	1,174 sources
1,877 citations	84.96%	957 sources
1,158 citations	90.05%	656 sources
792 citations	93.54%	484 sources
686 citations	96.55%	470 sources
Previous years: 784 citations		

