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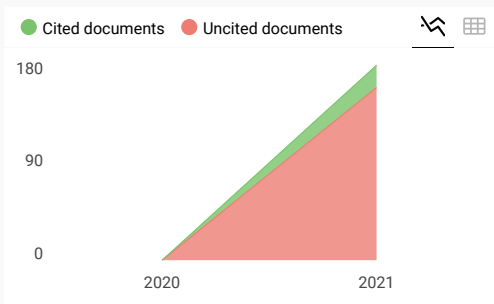
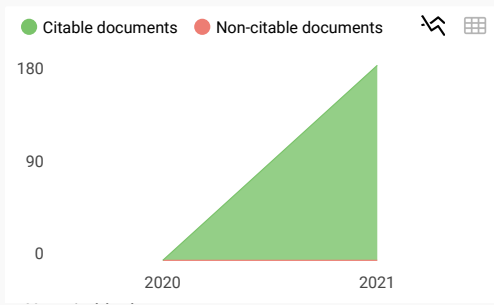
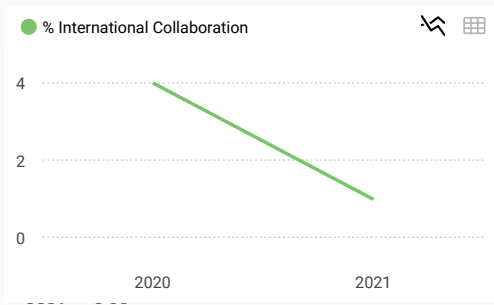
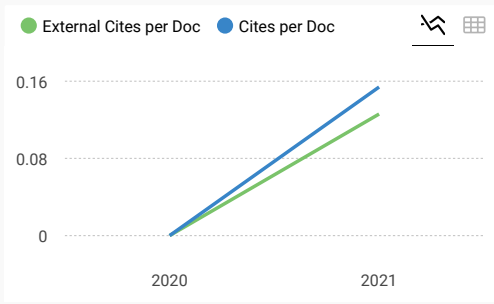
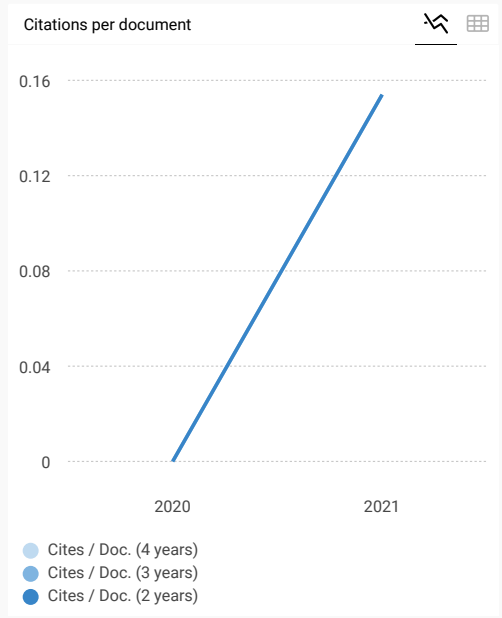
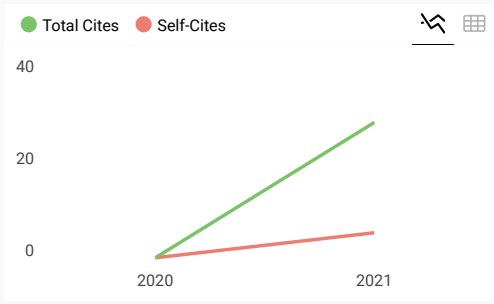
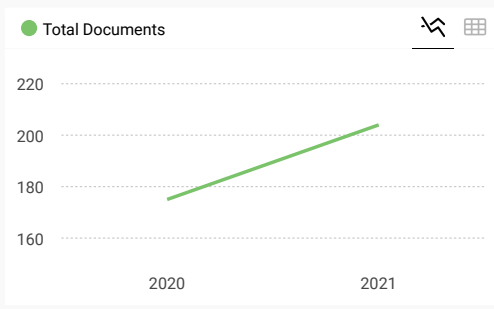
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ORIGINAL ARTICLE

Relationship between CD4 levels and mucocutaneous manifestations in HIV-AIDS patients at Dr. Soetomo General Academic Teaching Hospital, Surabaya, Indonesia (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3416>)

Citra Dwi Harningtyas, Damayanti, Maylita Sari, Muhammad Yulianto Listiawan, Diah Mira Indramaya, Linda Astari, Budi Utomo, Dwi Murtiastutik, Setyana Widyantari, Astindari, Afif Nurul Hidayati

Online First: Apr 13, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3416/2023>)

ORIGINAL ARTICLE




Correlation between sociodemographic and attitude of Malang citizens about self medication on urticaria
(<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3097>)

Erna Sulistyowatia, Dewi Martha Indria, Yohanita Nilam Sari

Online First: Apr 17, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3097/2029>)

ORIGINAL ARTICLE

The effect of metformin on autophagy by LC3 expression in Type 2 Diabetes Mellitus (T2DM) human skeletal muscle cell culture
(<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3203>)

Jongky Hendro Prajitno, Agung Pranoto, Robert Dwitama Adiwino, Soebagijo Adi Soelistijo

Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3203/2043>)

ORIGINAL ARTICLE

Factors that influence on Islamic caring behavior (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3107>)

Yanis Kartini, Nursalam Nursalam, Ahsan, Imamatul Faizah, Ratna Yunitasari

Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3107/2051>)

ORIGINAL ARTICLE

Comparison of serum and vitreous TGF- β 1 levels in proliferative diabetic retinopathy with and without panretinal photocoagulation laser therapy (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3225>)

Habibah Setyawati Muhiddin, Rosmiaty Zainal Abidin, Budu ., Junaedi Sirajuddin, Itzar Chaidir Islam, Andi Muhammad Ichsan

Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3225/2058>)

ORIGINAL ARTICLE


Antiproliferation and Apoptosis Effect of Cisplatin and Nanocurcumin on Ovarian Cancer SKOV3 Cell
(<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2937>)



Sigit Purbadi, Muhammad Yusuf, Wawaimuli Arozal, Aroem Naroeni, Hariyono Winarto, Andi Darma Putra, Gilbert Elia Sotarduga

Online First: Apr 30, 2022 |

 Abstract

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ORIGINAL ARTICLE

Effects of audio-visual affirmations on toddlers tantrum behavior (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3112>)

Nanik Handayani, Esty Puji Rahayu

Online First: Apr 19, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3112/2038>)

ORIGINAL ARTICLE

Change in ratio levels of KIM-1 / urine creatinine and increase serum creatinine levels in human immunodeficiency virus (HIV) patients receiving tenofovir-based antiretroviral (ARV) combination therapy (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3249>)

I Dewa Gede Teguh Krisna Murti, I Ketus Agus Somia, I Gde Raka Widiana

Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3249/2112>)

ORIGINAL ARTICLE

The outcome of hypospadias surgery and it's advanced treatment in Arifin Achmad General Hospital in January 2019 – December 2020 (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3287>)

Tu Bagus Odih Rhomdani Wahid, Tania Nugrah Utami, Rizka Annisa Harahap

Online First: Apr 26, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3287/2042>)

ORIGINAL ARTICLE


Evaluating Low Values of Early Diastolic Velocity (e') as a Predictor of Major Cardiovascular Events in Patients with Acute Myocardial Infarction (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3360>)

Vianney Tedjamulia, Ida Bagus Rangga Wibhuti, Ida Sri Iswari, Ketut Badjra Nadha



Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3360/2056>)


ORIGINAL ARTICLE

The prevalence and characteristics of perineal rupture during vaginal delivery at Sanglah General Hospital and Regional Hospitals in Bali from January 2018 until December 2019 period (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3067>)

I Wayan Megadhana, I Gede Suputra Indrawan, I Nyoman Hariyasa Sanjaya, Made Bagus Dwi Aryana

Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3067/2044>)

ORIGINAL ARTICLE

Diphtheria's Outbreak Control in Blitar District (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3093>)

Gamasiano Alfiansyah, Selvia Juwita Swari, Maya Weka Santi

Online First: Jun 16, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3093/2027>)


ORIGINAL ARTICLE

Exploring the role of the combination of propolis and vitamin D3 on VCAM-1 and Caspase-3 expression in preventing atherosclerosis in chronic kidney disease rats (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3194>)

Darmawan Ismail, Bambang Purwanto, Brian Wasita, Supomo, Ketut Putu Yasa, Soetrisno

Online First: Mar 29, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3194/2003>)

ORIGINAL ARTICLE


Relationship between plasma adiponectin levels and cellulite (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3634>)

Sari Indriyani, Imam Budi Putra, Nelva Karmila Jusuf

Online First: Apr 30, 2022 |



 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3634/2141>)


ORIGINAL ARTICLE

Combination of diabetic Foot Spa and Sauna Bathing Therapy Decreases the Level of Blood Glucose (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3105>)

Nur Ainiyah, Erika Martining Wardani, Difran Nobel Bistara, Yurike Septianingrum, Andikawati Fitriasaki, Firdaus

Online First: Apr 18, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3105/2030>)


ORIGINAL ARTICLE

Clinical and radiological profiles of metastatic brain tumor in Indonesia: A study at Dr. Soetomo Hospital, Surabaya (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3222>)

Nur Akbaryan Anandito, Djohan Ardiansyah

Online First: Apr 14, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3222/2014>)

ORIGINAL ARTICLE

The effect of workload and length of work on the occurrence of fatigue in workers in the informal industry (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3110>)

Merry Sunaryo, Ratna Ayu Ratriwardhani

Online First: Apr 19, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3110/2036>)

ORIGINAL ARTICLE

The difference of platelet-white blood cell ratio in severe preeclampsia and normotensive pregnancy (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3246>)

Nisrina Aisyah Nur Safirani, Faizah Fulyani, Putri Sekar Wiyati, Besari Adi Pramono

Online First: Apr 18, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3246/2055>)



ORIGINAL ARTICLE

The effect of Epigallocatechin-3-Gallate (EGCG) combined with low dose sorafenib in apoptosis and Platelet-Derived Growth Factor Receptor (PDGFR) expression in hepatocellular carcinoma rats (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2985>)

Emilia Rosita, Sigit Adi Prasetyo, Ignasius Riwanto, Wahyuni Lukita Atmodjo

Online First: Apr 13, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2985/2020>)

ORIGINAL ARTICLE

Relationship of age, body mass index (BMI), physical activity, salt intake, and stress with high blood pressure among rural dwellers in Kudat, Sabah (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3115>)

Khalid Mokti, Syed Sharizman Syed Abdul Rahime

Online First: Apr 30, 2022 |

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 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3115/2045>)


ORIGINAL ARTICLE

Mitomycin C, curcumin, and fibrin glue inhibit the cell proliferation and expression of TGF- β in human pterygium fibroblast (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3315>)

Muhammad Abdurrauf, Ferdian Ramadhan, Nurwasis, Ismi Zuhria, Betty Agustina Tambunan, Hari Basuki Notobroto, Budi Surahman, Evelyn Komaratih

Online First: Apr 14, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3315/2016>)


ORIGINAL ARTICLE

The clinical pictures of COVID-19 pediatric patients in dr. R. Soedarsono Regional General Hospital, Pasuruan, East Java, Indonesia (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3046>)

Peter Prayogo Hsieh, Hans Kristian, Allison Joseasta Marsya Permana, Monique Wongsodiharjo, Pramita Anindya Nugraheni, Pherenice Charisti, Wienta Diarsvitri

Online First: Apr 30, 2022 |

 Abstract

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ORIGINAL ARTICLE

The efficacy of probiotics supplementation on the lipid profiles of obese adolescents : a randomized trial (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3163>)

I Putu Gede Karyana, Ni Luh Sri Apsari, I Wayan Dharma Artana, I Ketut Suarta, Putu Veny Kartika Yantie, Ni Nyoman Metriani Nesa, I Gusti Ngurah Sanjaya Putra, Soetjiningsih

Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3163/2089>)

ORIGINAL ARTICLE

Role of malnutrition inflammation score and interleukin-6 on quality of life of regular hemodialysis patients (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3187>)

Ni Wayan Sri Wardani, I Gde Raka Widiana, Yenny Kandarini

Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3187/2115>)

ORIGINAL ARTICLE

Clinical improvement of patients with moderate-to-severe psoriasis treated with methotrexate at Dr. Soetomo General Hospital, Surabaya, Indonesia (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3417>)

Made Putri Hendaria, Afif Nurul Hidayati, Evy Ervianti, Muhammad Yulianto Listiawan, Damayanti, Irmadita Citrashanty, Sylvia Anggraeni, Menul Ayu Umborowati, Budi Utomo, Cita Rosita Sigit Prakoeswa

Online First: Apr 21, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3417/2024>)

ORIGINAL ARTICLE

Hematology profile of under five years old children suffered from acute diarrhea at Idaman Banjarbaru Hospital, Indonesia (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2668>)

Harapan Parlindungan Ringoringo, Jun Rahmawati Surya Mentari, Roselina Panghiyangani, Edi Hartoyo, Rahmiati Lao

Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2668/2185>)




ORIGINAL ARTICLE

Comparison of effects and differences in duration between exposure to conventional cigarette smoke and electronic cigarette vapors on changes in the number of hippocampal pyknotic pyramidal cell (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3098>)

Richard Wijaya, Poppy Kristina Sasmita, Iskandar Rahardjo Budiarto, Tena Djuartina

Online First: Apr 8, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3098/2007>)

ORIGINAL ARTICLE

Features of COVID-19 adult patients and the treatment in Indonesia: a retrospective cohort study (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2810>)

Dwi Aris Agung Nugrahaningsih, Eko Purnomo, Siswanto, Reviono, Alfi Yasmina, Muh Darwin Prenggono, Nanang Miftah Fajari, Mohammad Rudiansyah, Harsini, Rul Afiyah Syarif, Eti Nurwening Sholikhah

Online First: Apr 30, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2810/2083>)


ORIGINAL ARTICLE

The potential effect of intradermal Botulinum Toxin Type-A (BTA) injection to increase extended random skin flap survival (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3026>)

Caroline Fiona, Iswinarno Doso Saputro, Agus Santoso Budi

Online First: Jan 4, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3026/pdf>)


ORIGINAL ARTICLE

Persistence of anti-Salmonella O9 IgM as measured by Tubex® TF may contribute to the over-diagnosis of typhoid fever in endemic areas (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3035>)

I Wayan Adi Pranata, Aly Diana, Marco R Heryanto, Nurhayati Lukman, Herman Kosasih, Hofiya Djauhari, Deni PR Butarbutar, Susana Widjaja, Bacht Alisjahbana

Online First: Jan 30, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3035/pdf>)

ORIGINAL ARTICLE




The effect of ACTH4-10Pro8-Gly9-Pro10 on neurotrophin-3 expression in Sprague Dawley rat on acute spinal cord injury (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3143>)

Made Gemma Daniswara Maliawan, Eko Agus Subagio, Budi Utomo, Muhammad Arifin Parenrengi, Asra Al Fauzi, I Ketut Sudiana

Online First: Feb 4, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3143/pdf>)

ORIGINAL ARTICLE

High level of highly sensitivity c-reactive protein levels (hs-CRP) as a risk factor for preterm delivery (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2966>)

Marthin Kolelupun, I Gede Putu Surya, I Nyoman Hariyasa Sanjaya, Tjok Gde Agung Suwardewa, I Wayan Megadhana, I Gede Mega Putra, I Nyoman Gede Budiana, I Wayan Artana Putra

Online First: Feb 8, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2966/pdf>)


ORIGINAL ARTICLE

Retrospective Study on Very Early Relapse of Childhood Acute Lymphoblastic Leukemia at a Reference Centre in Indonesia (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2495>)

Nur Melani Sari, Namira Assyfa Nurazizah, Ronny Lesmana, Nur Suryawan, Susi Susanah

Online First: Feb 11, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2495/pdf>)

ORIGINAL ARTICLE

C-Reactive Protein (CRP)/Albumin Ratio (CAR) pre-treatment as a predictive factor of radiological response after neoadjuvant chemotherapy in Locally Advanced Rectal Cancer (LARC) patients at Dr. Soetomo General Hospital, Surabaya, Indonesia (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3004>)

Fariza Hakim Rio Branko, Tomy Lesmana

Online First: Feb 14, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3004/pdf>)

ORIGINAL ARTICLE

Identification of PST 10 bacterial isolate with α -hemolysis characteristic isolated from pig's tonsil (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3180>)



Hamong Suharsono, I Wayan Suardana, Rizki Kusuma Putri

Online First: Feb 18, 2022 |

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ORIGINAL ARTICLE

Correlation between Urea Creatinine Ratio (UCR) and lipid profile in COVID-19 patients
(<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2945>)

Indranila Kustarini Samsuria, Ariosta Ariosta, Untung Sujianto

Online First: Feb 21, 2022 |

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ORIGINAL ARTICLE

The variability of temperature, rainfall, humidity and prevalance of dengue fever in Manado City
(<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2722>)

Odi Roni Pinontoan, Oksfriani Jufri Sumampouw, Jansje Ticoalu, Jeini Ester Nelwan, Ester Cendrawati Musa, Joy Sekeeon

Online First: Feb 21, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2722/pdf>)


ORIGINAL ARTICLE

Clinical presentation of maternal death with COVID-19 in rural tertiary care center: A retrospective-descriptive Study
(<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3158>)

Devita Kurniawati, Budi Prasetyo, Hanindito Pandu, Arif Rahman Nurdianto

Online First: Feb 22, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3158/pdf>)

ORIGINAL ARTICLE

Characteristic of testicular torsion and predictors of testicular salvage: A retrospective study
(<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3157>)

Alfryan Janardhana, Besut Daryanto, Budi Suwarno, Arif Rahman Nurdianto



Online First: Feb 25, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3157/pdf>)

ORIGINAL ARTICLE

A novel scoring system to predict postoperative mortality after colorectal cancer surgery: a retrospective cohort study (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2988>)

Anita Hartono, Tomy Lesmana

Online First: Mar 9, 2022 |

 Abstract

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ORIGINAL ARTICLE

Aqueous Humour Malondialdehyde Level as Oxidative Stress Marker In Types Of Glaucoma (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2599>)

Maharani Maharani, Puspita Kusuma Dewi, Riski Prihatningtias, Arief Wildan, Trilaksana Nugroho, Edward Kurnia Setiawan Limijadi, Fifin L. Rahmi

Online First: Mar 14, 2022 |

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ORIGINAL ARTICLE

CD44 expression as a potential favorable marker for prognosis in mucoepidermoid carcinoma of salivary gland (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/2793>)

Stella Marleen, Lisnawati Rachmadi, Diah Rini Handjari, Kusmardi Kusmardi

Online First: Mar 22, 2022 |

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ORIGINAL ARTICLE


TNF-a serum Level between SARS-CoV-2 Infected Pregnant women with normal pregnant women in RSUD Dr. Soetomo Surabaya (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3377>)

Margaretha Claudhya Febryanna, Manggala Pasca Wardhana, Muhammad Ilham Aldika Akbar, Arif Rahman Nurdianto

Online First: Mar 23, 2022 |



 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3377/pdf>)


ORIGINAL ARTICLE

Combination effect of methotrexate with Narrowband Ultraviolet B (NB-UVB) phototherapy in psoriasis vulgaris patients in dermatology and venereology outpatient clinic Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3071>)

Emma Hidayati Sasmito, Iskandar Zulkarnain, Muhammad Yulianto Listiawan, Diah Mira Indramaya, Linda Astari, Budi Utomo, Afif Nurul Hidayati

Online First: Mar 24, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3071/pdf>)


ORIGINAL ARTICLE

Application of Moringa Oleifera leaves extract cream inhibits paw edema in white male Wistar rat (*Rattus norvegicus*) induced by carrageenan 1% (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3384>)

I Gusti Nyoman Darmaputra, I Gusti Ayu Sattwika Pramita, Ketut Kwartantaya Winaya

Online First: Mar 28, 2022 |

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 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3384/pdf>)


REVIEW

Medical Management of Kidney Stones: a review (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3343>)

Jody Felizio, Widi Atmoko

Online First: Mar 28, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3343/1998>)

REVIEW

Human umbilical cords mesenchymal stem cells for kidney diseases (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3085>)

Dianita Halimah Harahap, Gampo Alam Irdam

Online First: Mar 29, 2022 |

 Abstract

 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3085/2002>)




REVIEW

Medical education system in Coronavirus Disease 2019 (COVID-19) pandemic: what has been changed from the past era? (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3159>)

Ida Bagus Amertha Putra Manuaba, I Gede Putu Supadmanaba, I Gusti Ayu Sri Darmayani, Dwijo Anargha Sindhughosa, Made Violin Weda Yani

Online First: Jan 25, 2022 |

 Abstract

 PDF (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3159/pdf>)

CASE REPORT

Turner syndrome and tuberculosis in adolescent: a case report (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3243>)

Nyoman Titamarita Trisnawan, Florencia Christina Sindhu, Peter Prayogo Hsieh, Arya Putri Ratnasari, Alberto Afrian, Ancelia Limantara, Han's Christian, Made Ratna Dewi, I Wayan Bikin Suryawan

Online First: Apr 30, 2022 |

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 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3243/2062>)


CASE REPORT

Fatality in a pregnant woman with COVID-19 after a cesarean section: A case report (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3301>)

Edy Parwanto, Reza Aditya Digambiro, Erdiyan Astato, Assangga Guyansyah

Online First: Apr 30, 2022 |

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 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3301/2060>)


CASE REPORT

Diagnostic challenges in Waldenström macroglobulinemia: a case report (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3160>)

Stella Pravita, Ugroseno Yudho Bintoro, Putu Niken Ayu Amrita

Online First: Apr 8, 2022 |

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 pdf (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3160/2009>)




CASE REPORT

Diagnostic problem on patient with tuberculous colitis mimicking Crohn's disease (<https://www.balimedicaljournal.ejournals.ca/index.php/bmj/article/view/3370>)

Asep Harirohman, Herry Purbayu

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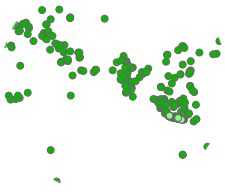
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RESEARCH ARTICLE

Matrix Metalloproteinase-3 Down Regulation and Cell Migration Inhibition in Human Pterygium Fibroblasts by Mitomycin-C, Curcumin and Fibrin Glue

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Abstract

BACKGROUND: Pterygium is an ocular surface disease that often occurs in tropical countries with a high recurrence rate. Matrix metalloproteinase-3 (MMP-3) play a key role in the inflammatory process of pterygium. This study aims to investigate the ability of curcumin and fibrin glue (FG) in suppressing the expression of MMP-3, and whether can be expected as adjuvant therapy to reduce pterygium recurrence.

METHODS: Human pterygium fibroblasts (HPF) obtained from primary cultured of pterygium were treated with no treatment, curcumin, mitomycin-C (MMC), and FG. MMP-3 expression was analyzed using immunocytochemistry and the intensity measurement was done using ImageJ software. Cell migration was measured by scratching and stratification of fibroblast culture after cell confluence, and assessed for 48 hours.

RESULTS: The expression of MMP-3 were lower in the HPF treated with 100 mol/mL curcumin, 200 mol/mL, and FG (2205.84±86.1 pg/mL, 1002.51±25.22 pg/mL, 1131.55±17.71 pg/mL, respectively) in comparison with untreated HPF (4703.49±108.9 pg/mL). The expression of MMP-3 were significantly different between groups ($p<0.001$). Cell migration of HPF after scratching with curcumin intervention at 200 mol/mL decrease from 178.67±2.85 (24 hours) to 88.83±1.48 (48 hours). Meanwhile the migration in FG group also decrease from 180.4±2.56 (24 hours) to 72.45±1.25 (48 hours).

CONCLUSION: Curcumin and FG able to reduce the expression of MMP-3 and inhibit the migration of HPF cells.

KEYWORDS: curcumin, mitomycin C, fibrin glue, human pterygium fibroblast, MMP-3

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Introduction

Pterygium is a degenerative and inflammatory disease of the conjunctiva with the clinical appearance of triangular fibrovascular tissue on the nasal side of the conjunctiva leading to the limbus. Risk factors associated with the development of pterygium include UV exposure, viral infections such as human papillomavirus, herpes simplex virus, and cytomegalovirus.(1-3)

The prevalence of pterygium around the world is quite alarming (ranging from 7% to 15%) and the term band pterygium is known for the region with the highest prevalence of pterygium across the equator. According to the 2010 Indonesian Basic Health Study, among the prevalence of pterygium among all detected eye disease cases in Indonesia reached 3.2% in both eyes and 1.9% in one eye.(1,3)

The relatively high recurrence rate after pterygium resection is another issue that clinicians must face. The

incidence of postoperative recurrence varied from 3.8% to 89%. The pathophysiology of recurrence is not fully understood, but the most likely causes are genetic factors, repeated exposure to risk factors, and surgical technique. Bare sclera technique was the first to be adopted and is still quite high in practice in Indonesia as a modality for the treatment of pterygium, but it is positively associated with a high recurrence rate (up to 24-89%). Treatment modification by using conjunctiva autografts or by adding adjuvant therapy, such as the antimetabolites 5-fluorouracil (5-FU) or mitomycin-C (MMC), as antimetabolic and antiapoptotic are often done by clinical practitioners. The use of antimetabolites was successful in reducing the recurrence rate of pterygium, but some serious complications including corneal edema, corneal perforation, or scleral calcification have become new obstacles.(1,3,4)

Recent studies have shown that herbs and spices have a significant attention as natural antioxidants. (5,6) Curcumin, which is a polyphenol derivative from turmeric, has pharmacological properties as antioxidants, antiapoptotic and antiproliferative properties. Curcumin has been found to have anti-inflammatory action through inhibition of nuclear factor kappa-B (NF- κ B), antioxidant action through inhibition of free radicals, suppression of lipid peroxidation, increase of antioxidant molecules in tissues and stimulation of the activity of antioxidant enzymes. Curcumin is able to inhibit the expression of matrix metalloproteinases (MMP), especially MMP-3, which is expressed by human pterygium fibroblasts (HPF), as well as the suppression effect of reactive oxidative species (ROS) of fibroblasts due to UV exposure, making curcumin a potential adjuvant therapy for the prevention of pterygium recurrence in the future.(7-9)

Fibrin glue (FG) is a blood-derived product that is used as a biological adhesive and was first introduced in 1909. FG acts by imitating the final step of the coagulation cascade when soluble fibrinogen is activated by thrombin. In the field of ophthalmology, it is an alternative therapy option that is often used in pterygium cases to prevent postoperative recurrence, accelerate wound healing by releasing anti-inflammatory cytokines. FG forms a seal on the wound after pterygium excision to accelerate the wound healing process, minimize recurrence, and prevent more postoperative complications.(10,11)

In this study, HPF cell cultures were treated with curcumin and FG *in vitro* to evaluate their ability in suppressing the expression of MMP-3 and fibroblast migration, and whether can be expected as adjuvant therapy to reduce pterygium recurrence.

Methods

Preparation of Curcumin and FG

Curcumin (Sigma-Aldrich, St. Louis, MO, USA) was dissolved with complete media Dulbecco's Modified Eagle's Medium (DMEM) then sonicated and filtered to create stock solutions at the concentrations of 100 and 200 mol/L.

FG was derived from graded centrifugation of peripheral blood with anticoagulants. A total of 40 mL of peripheral blood was taken from the cubital vein using a sterile syringe containing CPDA in a ratio of 9:1, aseptically. Blood was put into a sterile 10 mL centrifuge tube then centrifuged at 3000 rpm for 15 minutes. The plasma was stored in a sterile centrifuge tube and stored at -20°C for 24 hours, then centrifuged at 4°C, 3000 rpm for 15 minutes. Ten mL of the upper 2/3 of plasma was stored for the preparation of the fibrinogen component, and the platelet-rich plasma (PRP) was stored in sterile micro-tubes to be prepared as material for thrombin production. The plasma was then added with 1 mL ethanol, then incubated at 4°C for 30 minutes followed by centrifugation at 4°C at 3000 rpm for 15 minutes. The supernatant was discarded and the sediment was used as a component of fibrinogen. Thrombin was made by mixing the PRP component with 0.05 mL of 10% CaCl₂. FG was made by mixing the fibrinogen and thrombin in a ratio of 1:1.(12,13)

Sample Collection

Pterygium tissue was taken in the surgical installation of the Rumah Sakit Mata Masyarakat Jawa Timur. The tissue then transported directly to Biomedical Laboratory of Universitas Brawijaya for further *in vitro* evaluation and analysis. The protocol of this study was approved by Health Research Ethics Committee, Faculty of Medicine Universitas Airlangga (No: 131/EC/KEPK/FKUA/2021).

Culture and Passage of HPF

Local anesthesia with subconjunctival injection of 2% lidocaine was performed before removal of the pterygium tissue. A sterile cloth was placed on the operating area and the eyeball was disinfected using 5% povidone iodine and then rinsed with balance salt solution. Pterygium tissue retrieval was carried out with bare sclera technique according to the protocol developed by previous study (Figure 1).(7)

After the pterygium tissue was removed, the top of the specimen was taken about 2 mm from the edge and then cut into small pieces (<0.5 mm²). After being washed

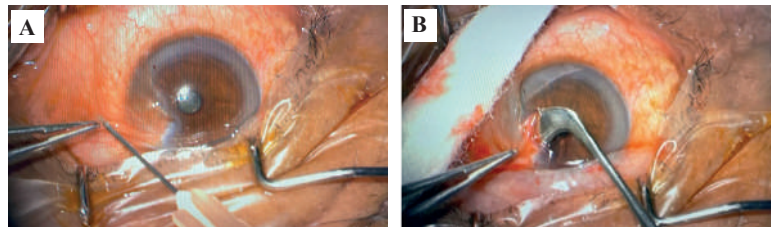


Figure 1. Pterygium excision technique with bare sclera. A: administration of lidocaine 2% before tissue excision; B: pterygium excision using a pterygium spoon.

using phosphate buffer saline (PBS), then the specimen was given red blood cell lysis buffer for 5 minutes and placed on a 100 mm culture dish. One mL of DMEM containing 15% fetal bovine serum (FBS), and penicillin-streptomycin were added to cover the tissue then placed overnight in an incubator at 37°C, and humidified. The medium was replaced daily with fresh culture medium + FBS. When the cells began to reach 80% confluency, FBS was reduced to 10% concentration and then sub-passed. P3-7 cultures were used in this study. Figure 2 showed the primary culture on pterygium tissue.

Cell's Characteristics and Vimentin Staining

The confluent cells were transferred to 24-well plate with a density of 2.5×10^4 cells/plate and then waited until the cells were adhered to the bottom of the plate, then washed 3 times with PBS for 5 minutes. Cells were washed 3 times with PBS for 5 minutes and with 0.1% PBS Triton-X 100 for 1 minute before incubated with 1% bovine serum albumin (BSA) for 30 minutes. The BSA solution was then discarded and incubated with primary antibody overnight. Cells were incubated with Goat Anti Rabbit IgG & LTIRTCVimentin (Cat No. ab6718, BD Biosciences, San Jose, CA, USA) and incubated with DAPI 1: 1000 for 5 minutes. Cells were then photographed with a fluorescence microscope at 40x magnification.

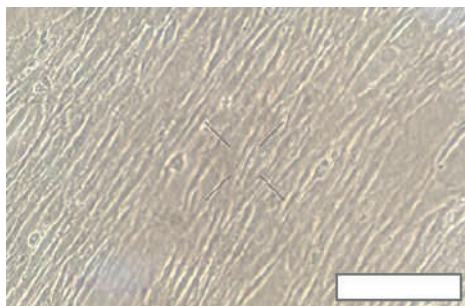


Figure 2. Primary culture on pterygium tissue. Fibroblast growth reached a confluence rate of 90-100% on day 14. White bar : 100 μ m.

Measurement of MMP-3 by Immunofluorescence Staining

Cells that were already confluent were harvested and planted on 24 well plate with a density of 2.5×10^4 for 24-48 hours. Then the wells were grouped into untreated, treated with MMC 0.2 and 0.4 mg/mL, treated with curcumin 100 and 200 mol/mL, and treated with FG. Untreated wells only contained cells and medium; MMC 0.2 and 0.4 mg/mL were given for 5 minutes to cells with medium, then washed once with PBS; curcumin was given at doses of 100 and 200 mol/mL to cells with medium; and FG was given until clots formed, then removed and washed once with PBS. Each well was then added 3-4% formaldehyde for 15 minutes and washed with PBS.

Every well were washed again with 0.1% of PBS Triton-X 100 (Cat No. T8787, Sigma Aldrich) for 5 minutes and incubated with 1% BSA for 30 minutes at room temperature. The fluid was discarded and then incubated with primary antibody MMP-3 Rabbit Polyclonal Antibody (Cat No. bs-0431R, Bioss Antibody, Woburn, MA, USA) overnight at 4°C. Antibody was washed with PBS, incubated with MMP-3 secondary antibody 1:1000 for 1 hour. Results were read using a fluorescence microscope, and the expression levels were analyzed using ImageJ software version 1.51 (National Institutes of Health, Bethesda, MA, USA). The MMP-3 expression level was counted as corrected total cell fluorescence (CTCF), determined using the formula: integrated density - (area of selected cells x mean fluorescence of background values).(2)

Cell Migration and *in vitro* Scratch Wound Assay

Confluent pterygium fibroblasts were implanted on 24-well plate with a density of 5×10^4 cells per well and incubated for 24-48 hours to achieve 70-80% confluence. The wells were grouped into untreated, treated with 0.4 mg/mL MMC, treated with 200 mol/mL curcumin, and treated with FG.

The cells that had been given the intervention were then scratched perpendicular to the plate using a 200 μ L micropipette and photographed using an Olympus

CKX53 microscope (Olympus Corporation, Tokyo, Japan). Migration distance was measured with imageJ software version 1.51 (National Institutes of Health).

Statistical Analysis

Comparative data between inhibition of fibroblast migration with the interventions and comparison of MMP-3 expression were tested using the one-way Anova test. Tukey Post-Hoc test was carried out to determine the significant difference between one group and another. The *p*-value is considered significant if *p*<0.05. All statistical data was processed using SPSS 26.0 software (IBM Corporation, Armonk, NY, USA).

Results

Expression of MMP-3 After the Intervention of MMC, Curcumin, and FG

The results of analysis showed that the highest expression of MMP-3 was found in the untreated group, and the lowest was in the 0.4 mg/mL MMC group. Groups treated with curcumin showed lower MMP-3 expression compare to the untreated group as the negative control, where 200 mol/mL curcumin group showed lower MMP-3 level than 100 mol/mL curcumin group (Table 1). This showed that 200 mol/mL curcumin had a stronger MMP-3 suppression effect that is quite comparable with FG (1002.51±25.22 vs. 1131.55±17.71).

One-Way Anova test followed by Post-Hoc Tukey analysis showed that the comparison of all treatment groups was *p*<0.001, which suggested that the comparison of MMP-3 expression in all groups was statistically significant. Figure 3 showed pterygium fibroblast cells were stained with MMP-3 antibody and DAPI to assess the comparasion of MMP-3 expression in all treatment groups. MMP-3 was obviously seen in untreated group, meanwhile was found less in 0.4 mg/mL MMC group.

Inhibition of Fibroblast After the Intervention of MMC, Curcumin, and FG

The migration distance showed that the fastest migration happened in the untreated group, while the slowest migration happened in the 0.4 mg/mL group after 48 hours of intervention (Table 2). The 200 mol/mL curcumin and FG groups had less significant differences after 24 hours of intervention. The group that was given 200 mol/mL curcumin had slower migration inhibition after 48 hours when compared to FG group (figure 4).

Statistical test using One-Way Anova followed by Post-Hoc Tukey showed a significant comparison (*p*<0.05) in all intervention groups. This suggested that the comparison of HPF migration rate after stretching with and without intervention were statistically significant.

Discussion

Pterygium additionally exhibits several tumor-like features including invasion, metaplasia of epithelial cells, presence of oncogenic viruses, inactivation of tumor suppressor genes, and absence of heterozygosity. The pathogenesis of pterygium and its recurrence after excision is still not completely understood, identification of effective drugs that able to suppress the proliferative system of pterygium is urgently required.(2,14)

MMPs have crucial function in pterygium formation because of the excessive fibroblast proliferation and invasion happens at the apex of the pterygium with destruction of the corneal stroma and basal lamina. Pterygium cells will produce MMP which dissolves the basal lamina and triggers the growth of stromal fibroblasts.(2,14) Overexpression of MMP on basal limbal epithelial cells is the primary reason of pterygium development. Extracellular matrix (ECM) modulation through MMP occurs in the early phase of pterygium invasion, numerous studies have proven a sturdy affiliation among MMP and tumor development/

Table 1. MMP-3 expression in human pterygium fibroblasts after intervention.

Group	Mean±SD	Minimum	Maximum	<i>p</i> -value
Untreated	4703.49±108.98	4532.22	4892.56	<0.001
0.2 mg/mL MMC	593.99±24.4	546.72	641.32	
0.4 mg/mL MMC	270.60±15.88	245.41	288.32	
100 mol/mL Curcumin	2205.84±86.1	2072.31	2303.21	
200 mol/mL Curcumin	1002.51±25.22	973.42	1034.45	
FG	1131.55±17.71	1113.56	1152.36	

p-value tested with One-Way Anova.

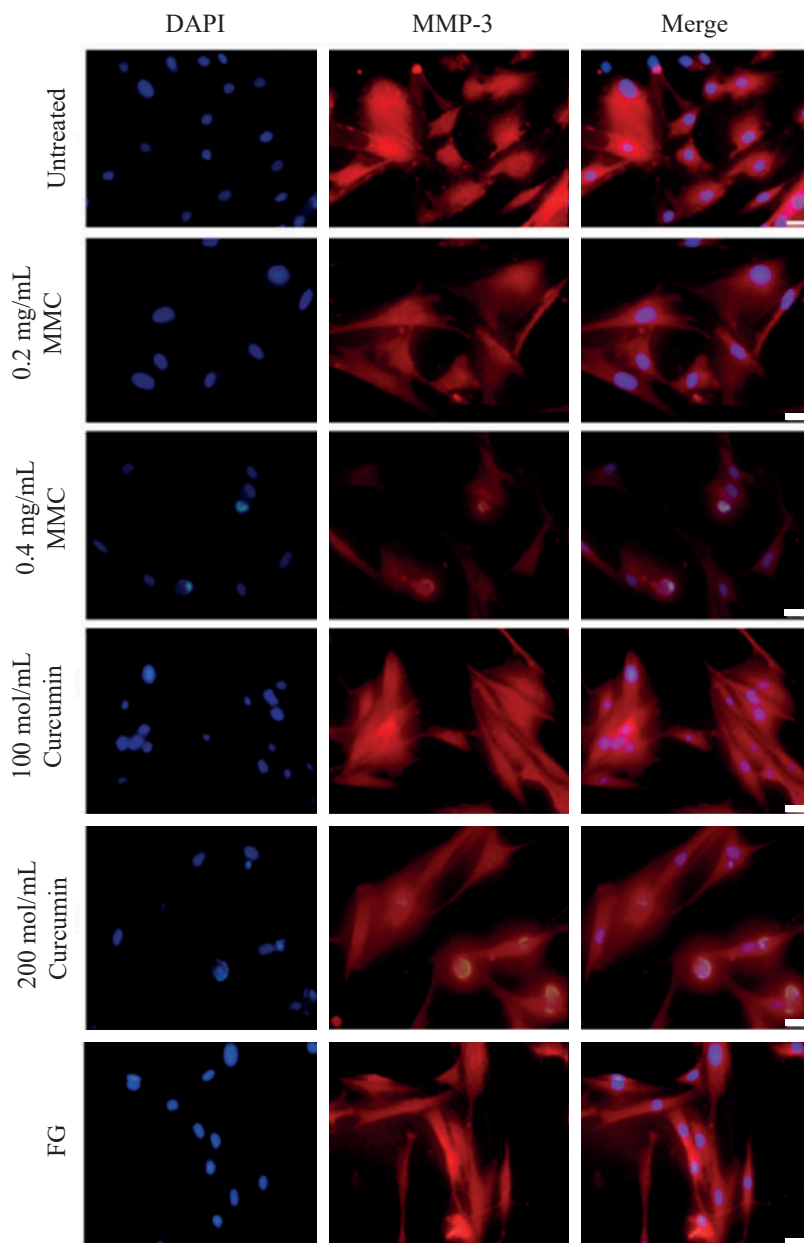


Figure 3. Pterygium fibroblast cells stained with MMP-3 antibody and DAPI. Observed with inverted fluorescence microscope; White bar: 30 μ m.

invasion. Invasion of pterygium lesions will growth MMP activity.(15-19).

Pterygium will result in activation of fibroblast tissue, specifically on the top of the pterygium, ensuing in cleavage of fibrillar collagen within the basal lamina, particularly because of MMP-1 and MMP-3. Degradation of the ECM results in the release of stimulating cytokines which includes vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) that cause angiogenesis and MMP-3 has a major effect on angiogenesis because it triggers angiostatin. MMP-3 additionally has large outcomes due to the fact it may activate pro-MMPs such as MMP-1, MMP-9 and MMP-13 so that they play a role in cell migration, proteolysis and angiogenesis.(2,14,19) In this

study, it was proven that the highest MMP-3 expression was found in the untreated group, while the lowest expression was found in the 0.4 mg/mL MMC group, followed by the 0.2 mg/mL MMC group. The curcumin intervention also had a suppressive effect on MMP-3 that was more than 50% while compared to the untreated group, especially higher in the 200 mol/mL curcumin group. The suppressive impact of FG was quite similar to of curcumin, so it may be suggested that in this study curcumin and FG have been able to exert a suppressive effect on the expression of MMP-3 in pterygium fibroblast tissue.

Curcumin has been extensively studied as an antifibrosis agent. Previous *in vitro* and *in vivo* study showed curcumin is able to inhibit liver fibrosis and prevent liver

Table 2. Migration distance of human pterygium fibroblast cells after scratching within 48 hours with intervention.

Group	Treatment Period	Mean±SD	Minimum	Maximum	p-value
Untreated	0H	221.33±3.57	216.23	225.34	0.000
	24H	141.59±3.12	137.32	147.22	0.003
	48H	32.46±1.25	30.28	34.35	0.001
0.4 mg/mL MMC	0H	233.60±2.87	230.38	237.32	0.000
	24H	210.34±2.57	206.52	215.08	0.000
	48H	132.05±1.65	129.88	135.06	0.002
200 mol/mL Curcumin	0H	228.89±3.75	222.99	233.87	0.000
	24H	178.67±2.85	174.34	183.21	0.001
	48H	88.83±1.48	85.28	91.21	0.001
FG	0H	231.62±3.17	227.16	235.88	0.000
	24H	180.40±2.56	175.32	183.52	0.001
	48H	72.45±1.25	70.77	74.67	0.002

p-value tested with One-Way Anova.

disease progression. Curcumin dampen the inflammation and reduce fibrosis through inhibition of the transforming growth factor (TGF)- β 1/Sma and drosophila MAD (Smad) signaling pathway.(19) Other studies reporting the use of curcumin on skin fibroblast cells to prevent photoaging showed that ROS are the basis for overexpression of UVB-modulated MMP-3. Curcumin has a robust antioxidant effect that may suppress ROS by means of suppressing the effects of NF- κ B and AP-1 DNA binding activity. UVB

induces phosphorylation of the janus kinase pathway and p38 and curcumin has been shown to regulate the activation of NF- κ B and AP-1 through the MAPK signaling pathway. (8,20)

The migration rate showed that the untreated group had the fastest migration, while the slowest migration rate was found in the of 0.4 mg/mL MMC group after 48 hours. The curcumin and FG groups had much less substantial differences at 24 hours and 200 mol/L curcumin

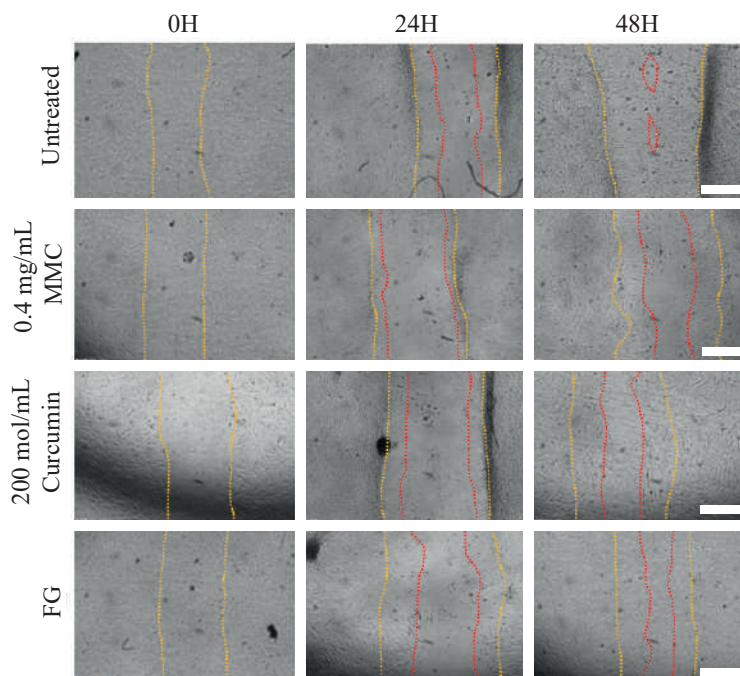


Figure 4. Fibroblast migration distance after scratching analysis. Comparison of pterygium fibroblast cells were scanned to assess cell migration at 0, 24 and 48 hours. Observed with inverted fluorescence microscope; Yellow line: the scratch border; Red line: as fibroblast migration; White bar: 100 μ m.

group had slower migration inhibition after 48 hours when compared to fibrin glue. This indicates that the comparison of the HPF migration rate with and without intervention is statistically significant. The scratching method performed in this study is an easy and effective step to trigger inflammation.(21) This is in accordance with the outcomes of previous study of fibroblast cells in the tenon conjunctival tissue model that was scratched with the conclusion the less the rate of migration of tenon's fibroblast cells to the wound place, the decrease the opportunity of extracellular matrix manufacturing resulting in fibrosis in that place.(12,22)

Another study confirmed the relationship among MMP expression and activity on pterygium fibroblast migration and its suppressive effect on Bevacizumab and cyclosporine A (CsA). The fibroblast migration ratio was assessed to investigate the recovery migration process which confirmed the migration speed suppression of MMP-3 and MMP-13 after bevacizumab and/or CsA intervention.(12)

An *in vitro* trial on cardiac fibroblasts and stated that curcumin had a higher inhibitory impact on fibroblast migration when compared to the control group and the MTT assay showed that the curcumin group also had a decrease proliferative effect than the control group, which is in line with the study.(23) This indicates that the rate of migration in the curcumin group might be slower when compared to the control group. This occurs most probably due to the suppressing effect of the mediators including TGF- β , MMP and other profibrotic mediators via the NF- κ B through tumor necrosis factor (TNF)- α dependent induction and mitogen-activated protein kinase (MAPK) signaling pathway.(20,23,24)

FG significantly inhibits collagen synthesis and induces collagen degradation in human tenons, in which the wound healing manner is regulated by inflammation. A decrease in the amount of collagen will eliminate the anti-inflammatory response and fibrin glue substantially inhibits collagen in the injured tenon model and is able to reduce wound formation and contractures.(24,25) In line with this study, which showed that in addition to reduce MMP-3 expression, FG was also able to reduce the speed of HPF migration although it was not as significant as the standard for adjuvant pterygium treatment, particularly MMC. Current study is the first study to analyze the inhibition of MMP-3 expression and HPF migration after the intervention of curcumin and FG. However, additional learning about other wound healing mechanisms is necessary to fully define and understand their effects.

Conclusion

Our findings suggest that curcumin and FG are able to suppress pterygium proliferation by inhibiting HPF migration and suppressing MMP-3 expression. Therefore, FG and curcumin have the potential to be an adjuvant therapy for MMC replacement in the management of pterygium.

Acknowledgments

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Authors Contribution

FR, LI and EK were involved in concepting and planning the research; FR and LI performed the data acquisition/ collection; JA interpreted the result of data and designed the figures and table; EF and IJ calculated the experimental data and performed the analysis; FR, IZ and EK drafted the manuscript and took parts in giving critical revision of the manuscript; FR and EK also collected the research funding.

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