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CONTENTS LISTENING

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This issue All issues

[CONTENTS](#) [JOURNAL OVERVIEW](#)

[Publicly Available](#) June 25, 2021

Frontmatter

Page range: *i-ii*

[Cite this](#)

[Download PDF](#)

Original Articles

Unlicensed June 25, 2021

Cost of illness of diabetes mellitus in Indonesia: a systematic review

Yohana Febriani Putri Peu Patty, Mufarrihah, Yunita Nita

Page range: *285-295*

[More ▾](#)

[Cite this](#)

Unlicensed June 25, 2021

Social media health interventions to improve diabetes mellitus patient outcome: a systematic review

Riza Alfian, Umi Athiyah, Yunita Nita

Page range: *297-304*

[More ▾](#)

[Cite this](#)

Unlicensed June 25, 2021

Developing pharmacokinetics-pharmacodynamics model of valproic acid syrup based on prediction of population pharmacokinetics parameter and seizure frequency in Indonesian pediatric epilepsy outpatients

I Komang Prawira Nata Nugraha, Anita Purnamayanti, I Gusti Ngurah Made Suwarba, Nani Parfati

Page range: *305-311*

[More ▾](#)

[Cite this](#)

Unlicensed June 25, 2021

Acetylcholinesterase inhibitory activity of extract and fractions from the root of *Rauvolfia serpentina*(L.) Bth.ex Kurz

Suciati, Debora Poerwantoro, Aty Widyawaruyanti, Kornkanok Ingkaninan

Page range: *313-317*

[More ▾](#)

[Cite this](#)

Unlicensed June 25, 2021

Green tea and its active compound epigallocatechin-3-gallate (EGCG) inhibit neuronal apoptosis in a middle cerebral artery occlusion (MCAO) model

Abdulloh Machin, Imam Susilo, Djoko A. Purwanto

Page range: *319-325*

[More ▾](#)

[Cite this](#)

Unlicensed June 25, 2021

The effects of quercetin on nicotine-induced reward effects in mice

Mahardian Rahmadi, Dian Suasana, Silvy Restuning Lailis, Dinda Monika Nusantara Ratri, Chrismawan Ardianto

Page range: *327-333*

[More ▾](#)

[Cite this](#)

Unlicensed June 25, 2021

Resveratrol ameliorates physical and psychological stress-induced depressive-like behavior

Chrismawan Ardianto, Aniek Setiya Budiati, I Nengah Budi Sumartha, Nurrahmi Nurrahmi, Mahardian Rahmadi, Junaidi Khotib

Page range: *335-340*

[More ▾](#)

[Cite this](#)

Unlicensed June 25, 2021

Translation and cross-cultural adaption of an instrument measuring patient's well-being under treatment for schizophrenia

Julaeha Julaeha, Umi Athiyah, Margarita Maria Maramis, Agus Sugianto, Andi Hermansyah

Page range: 341-347

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Quercetin promotes behavioral recovery and biomolecular changes of melanocortin-4 receptor in mice with ischemic stroke

Tuhfatul Ulya, *Chrismawan Ardianto*, Putri Anggreini, Aniek Setiya Budiadin, Dwi Setyawan, Junaidi Khotib

Page range: 349-355

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Knowledge and attitudes of healthcare professionals on prescribing errors

Desak Ketut Ernawati, Ida Ayu Alit Widhiartini, Endang Budiarti

Page range: 357-362

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Inhibition of Ras and STAT3 activity of 4-(tert-butyl)-N-carbamoylbenzamide as antiproliferative agent in HER2-expressing breast cancer cells

Aguslina Kirtishanti, Siswandono Siswodihardjo, I Ketut Sudiana, Desak G. A. Suprabawati, Aristika Dinaryanti

Page range: 363-371

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Predicting the molecular mechanism of glucosamine in accelerating bone defect repair by stimulating osteogenic proteins

Maria Apriliani Gani, Ahmad Dzulfikri Nurhan, Aniek Setiya Budiadin, Siswandono Siswodihardjo, Junaidi Khotib

Page range: 373-377

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Larvicidal toxicity and parasporal inclusion of native *Bacillus thuringiensis* BK5.2 against *Aedes aegypti*

Salamun, Fatimah, Ahmad Fauzi, Seling N. Praduwana, Ni'matuzahroh

Page range: 379-384

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Synthesis, ADMET predictions, molecular docking studies, and *in-vitro* anticancer activity of some benzoxazines against A549 human lung cancer cells

Melanny Ika Sulistyowaty, Retno Widayati, Galih Satrio Putra, Tutuk Budiati, Katsuyoshi Matsunami

Page range: 385-392

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Thymoquinone and its derivatives against breast cancer with HER2 positive: *in silico* studies of ADMET, docking and QSPR

Adinda Adelia Wulandari, Achmad Aziz Choiri, Fitria, Tri Widandani

Page range: 393-401

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Assessment of patient understanding of their conventional cardiac medicines and herbal prepared/derived products: preliminary survey and interviews with selected community-dwelling elderly patients in the Philippines

Jay P. Jazul, Trisha Michaela G. Arciga, Mary Angelie C. Ante, Danavin Gwyneth B. Berlin, Loise Francoise L. Ravana, Samantha A. Reyes, Jashanjit Singh

Page range: 403-413

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The development and validation of the health belief model questionnaire for measuring factors affecting adherence in the elderly with hypertension

Rodhiyatul Fithri, Umi Athiyah, Elida Zairina

Page range: 415-419

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Analysis of the side effect of QTc interval prolongation in the bedaquiline regimen in drug resistant tuberculosis patients

Denny Ardianto, Suharjo, Soedarsono, Umi Fatmawati

Page range: 421-427

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Shallot skin profiling, computational evaluation of physicochemical properties, ADMET, and molecular docking of its components against P2Y12 receptor

Juni Ekowati, Kholidah Febriani, Itsna N. A. Yaqin, Adinda A. Wulandari, Indra H. Mulya, Kholis A. Nofianti, Achmad Syahrani

Page range: 429-437

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Analysis of HMGB-1 level before and after providing atorvastatin standard therapy in coronary artery disease patients with type-2 diabetes mellitus compared to without type-2 diabetes mellitus

Widya Handayani, Suharjono, Mohammad Yogiarto

Page range: 439-446

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Analysis of matrix metalloproteinase-9 levels among acute heart failure patients with ACE inhibitor therapy (Dr. Soetomo Regional General Hospital, Surabaya)

Ira Purbosari, Bambang Zubakti Zulkarnain, Muh Aminuddin, Umi Fatmawati

Page range: 447-451

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The correlation between self-related adherence, asthma-related quality of life and control of asthma in adult patients

Elida Zairina, Gesnita Nugraheni, Gusti Noorrizka Veronika Achmad, Arie Sulistyarini, Yunita Nita, Arief Bakhtiar, Muhammad Amin

Page range: 453-458

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Providing counseling through home pharmacy care (HPC) for hemodialysis patients with hypertension in lowering blood pressure

Rahmiyati Daud, Bambang Subakti Zulkarnain, Ivan Virnanda Amu

Page range: 459-465

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Community knowledge and attitude in recognizing asthma symptoms and using medication for asthma attacks: a cross-sectional study

Arina Dery Puspitasari, Bindaria Mutmaina Prabawati, Alfian Nur Rosyid

Page range: 467-472

[More](#) [Cite this](#)

Unlicensed June 25, 2021

A study of anticoagulant therapy in patients with coronary artery disease

Arina D. Puspitasari, Daniel Dwi Christiananta Salean, Didik Hasmono, Rudy Hartono, Meity Ardiana

Page range: 473-478

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The association of FKBP5 polymorphism with asthma susceptibility in asthmatic patients

Sura F. Alsaffar, Haider Abdulhameed Alqaraghuli, Jabbar H. Yenzeel, Haider F. Ghazi

Page range: 479-484

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Gastroprotective effect of fluvoxamine and ondansetron on stress-induced gastric ulcers in mice

Mahardian Rahmadi, Nily Su'aida, Pratiwi Yustisari, Wahyu Agung Dewaandika, Elma Oktavia Hanaratri, Mareta Rindang Andarsari, Sumarno, Toetik Aryani

Page range: 485-490

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Osteoblast iron genes: real time PCR and microarray hybridization approach under hyperoxia

Prihartini Widiyanti, Hartmut Kuehn, Soetjipto Soetjipto

Page range: 491-496

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Attenuation of hyperplasia in lung parenchymal and colonic epithelial cells in DMBA-induced cancer by administering *Andrographis paniculata* Nees extract using animal model

Aniek Setiya Budiati, Iham Bagus Sagitaras, Ika Putri Nurhayati, Nismatun Khairah, Khoirotin Nisak, Imam Susilo, Junaidi Khotib

Page range: 497-504

[More](#) [Cite this](#)

Unlicensed June 25, 2021

N-nitrosodiethylamine induces inflammation of liver in mice

Devy Maulidya Cahyani, Andang Miatmoko, Berlian Sarasitha Hariawan, Kusuma Eko Purwantari, Retno Sari

Page range: 505-510

[More](#) [Cite this](#)

Unlicensed June 25, 2021

AST/ALT levels, MDA, and liver histopathology of *Echinometra mathaei* ethanol extract on paracetamol-induced hepatotoxicity in rats

Angelica Kresnamurti, Dita Nurlita Rakhma, Amatasari Damayanti, Septiyan Dwi Santoso, Enggar Restryarto, Wifqi Hadinata, Iwan Sahrial Hamid
Page range: 511–516

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Development, characterization, molecular docking, and *in vivo* skin penetration of coenzyme Q10 nanostructured lipid carriers using tristearin and stearyl alcohol for dermal delivery

Ni Luh Devi Aryani, Siswandono Siswodihardjo, Widji Soeratri, Nadia Fitria Indah Sari

Page range: 517–525

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The effect of *Camellia sinensis* (green tea) with its active compound EGCG on neuronal cell necroptosis in *Rattus norvegicus* middle cerebral artery occlusion (MCAO) model

Abdulloh Machin, Ramidha Syaharani, Imam Susilo, Muhammad Hamdan, Dyah Fauziah, Djoko Agus Purwanto

Page range: 527–531

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Hepatoprotective effect of ethanolic extract of sugarcane (*Saccharum officinarum* Linn.) leaves

Ika P. Dewi, Rifdah B. Kwintana, Jihan U. Ulinnuha, Fadhillah Rachman, Fransiska M. Christianty, Diana Holidah

Page range: 533–540

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Correlation between the exposure time to mobile devices and the prevalence of evaporative dry eyes as one of the symptoms of computer vision syndrome among Senior High School students in East Java, Indonesia

Rozalina Loebis, Bambang Subakti Zulkarmain, Nadhifa Zahra

Page range: 541–545

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The effect of various high-fat diet on liver histology in the development of NAFLD models in mice

Mahardian Rahmadi, Ahmad Dzulfikri Nurhan, Eka Dewi Pratiwi, Devita Ardina Prameswari, Sisca Melani Panggono,

Khoirotin Nisak, Junaidi Khotib

Page range: 547–553

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Fabrication and characterization of bovine hydroxyapatite-gelatin-alendronate scaffold cross-linked by glutaraldehyde for bone regeneration

Samirah, Aniek Setiya Budiadin, Ferdiansyah Mahyudin, Junaidi Khotib

Page range: 555–560

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Health related quality of life among postmenopausal woman with hormone responsive HER2–breast cancer in Indonesia

Ria Etikasari, Tri Murti Andayani, Dwi Endarti, Kartika Widayati Taroeno–Hariadi

Page range: 561–565

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Gender differences in the blood glucose type 2 diabetes patients with combination rapid and long acting insulin therapy

Dinda M. N. Ratri, Arina D. Puspitasari, Cahyo W. Nugroho, Budi Suprapti, Suharjo, Christopher P. Alderman

Page range: 567–570

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Correlation of dietary iron intake and serum iron with thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels in adult hyperthyroid patients

Utami Harjantini, Yulia Lanti Retno Dewi, Diffah Hanim, Ida Nurwati

Page range: 571–576

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The effect of pillbox use and education by pharmacist toward medication adherence in diabetes mellitus patients in a Primary Health Care Center in Mataram

Mahacita Andanalusia, Yunita Nita, Umi Athiyah

Page range: 577–582

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Variation concentration effect of propyleneglycol, glycerin, and polyethyleneglycol 400 to physical properties and dissolution rate of loratadine liquisolid tablet

Mikhania Christiningtyas Eryani, Esti Hendradi, Siswandono

Page range: 583–587

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Role of *Centella asiatica* and ceramide in skin barrier improvement: a double blind clinical trial of Indonesian batik workers

Sylvia Anggraeni, Menul Ayu Umborowati, Damayanti Damayanti, Anang Endaryanto, Cita Rosita Sigit Prakoeswa

Page range: 589-593

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Secondary metabolite and antipyretic effects of *Maja (Crescentia cujete L.)* in fever-induced mice

Teodhora, Munawarohthus Sholikha, Asniatul Ania, Ika Maruya Kusuma

Page range: 595-601

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Hydration effect on kidney function and serum electrolyte in children with tumor lysis syndrome (TLS) and risk of TLS

Yulistiani, Claudia Tiffany, I. Dewa Gede Ugrasena, Mariyatul Qibtiyah

Page range: 603-609

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Drug utilization study and cost analysis of adult β -thalassemia major patient therapy at Dr. Soetomo General Hospital Surabaya

Hasna Qatrunnada, Suharjono, Siprianus Ugroseno Yudho Bintoro, Siti Wahyuni

Page range: 611-616

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The role of hyperbaric oxygen to platelet aggregation in noninsulin-dependent diabetes mellitus (NIDDM)

Prihartini Widiyanti, Purnomo Suryohudoyo

Page range: 617-621

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Cocrystal formation of loratadine-succinic acid and its improved solubility

Dwi Setyawan, Firdaus Rendra Adyaksa, Hanny Lystia Sari, Diajeng Putri Paramita, Retno Sari

Page range: 623-630

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The role of chondroitin sulfate to bone healing indicators and compressive strength

Herry Wibowo, Prihartini Widiyanti, Syaifullah Asmiragani

Page range: 631-635

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The effects of quercetin on the expression of SREBP-1c mRNA in high-fat diet-induced NAFLD in mice

Jamal Nasser Saleh Al-maamari, Mahardian Rahmadi, Sisca Melani Panggono, Devita Ardina Prameswari, Eka Dewi Pratiwi, Chrismawan Ardianto, Santhra Segaran Balan, Budi Suprpti

Page range: 637-644

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Analysis of stress ulcer prophylaxis drug regimentation in surgical patients

Dhani Wijaya, Suharjono, Fendy Matulatan, Elfri Padolo

Page range: 645-649

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The stability and irritability study of the chitosan-*Aloe vera* spray gel as wound healing

Dini Retnowati, Retno Sari, Esti Hendradi, Septiani Septiani

Page range: 651-656

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Effectiveness of citicoline in pediatric patients with refractive amblyopia in Surabaya, East Java, Indonesia

Rozalina Loebis, Bambang Subakti Zulkarnain, Fitri Amalia Siswanto

Page range: 657-661

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The thermodynamic study of *p*-methoxycinnamic acid inclusion complex formation, using β -cyclodextrin and hydroxypropyl- β -cyclodextrin

Dewi Isadiartuti, Noorma Rosita, Juni Ekowati, Achmad Syahrani, Toetik Ariyani, M. Ainur Rifqi

Page range: 663-667

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The effect of chitosan type and drug-chitosan ratio on physical characteristics and release profile of ketoprofen microparticles prepared by spray drying

Muhammad A. S. Rijal, Hanah Masitah, Fanny Purvitasari, Retno Sari

Page range: 669-673

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The maximum dose and duration in the therapy single use methotrexate to achieve remission by rheumatoid arthritis patients through disease activity score 28 (DAS28)

Anisyah Achmad, Tika Yasmin Rahmayanti, Bagus Putu Putra Suryana

Page range: 675-680

[More](#) [Cite this](#)

Publicly Available June 25, 2021

Knowledge, attitudes, and practices (KAP) towards COVID-19 among university students in Pakistan: a cross-sectional study

Shah Faisal, Junaidi Khotib, Eliida Zairina

Page range: 681-686

[More](#) [Cite this](#) [Download PDF](#)

Unlicensed June 25, 2021

The impact of glutaraldehyde on the characteristics of bovine hydroxyapatite-gelatin based bone scaffold as gentamicin delivery system

Aniek Setiya Budiati, Maria Apriliani Gani, Chrismawan Ardianto, Samirah, Sahrti Yudiaprijah Daeng Pattah, Fitroh Mubarakah, Junaidi Khotib

Page range: 687-691

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Analysis of the use of antibiotics profile and factors of surgical site infections study on digestive and oncology surgeries

Lisa Narulita, Suharjono, Kuntaman, Mohammad Akram

Page range: 693-700

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Second internal transcribed spacer (ITS-2) as genetic marker for molecular characterization of *Sarcoptes scabiei* in rabbits from several areas of East Java, Indonesia

Nunuk Dyah Retno Lastuti, Nur Rusdiana, Poedji Hastutie

Page range: 701-705

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Design of gossypetin derivatives based on naturally occurring flavonoid in *Hibiscus sabdariffa* and the molecular docking as antibacterial agents

Nuzul W. Diyah, Isnaeni, Shabrina W. Hidayati, Bambang T. Purwanto, Siswandono

Page range: 707-714

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Discovery of new targeting agents against GAPDH receptor for antituberculosis drug delivery

Muhammad Amirul Asyraf Noh, Siti Sarah Fazalul Rahiman, Habibah A Wahab, Amirah Mohd Gazzali

Page range: 715-722

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The effect of red passion fruit (*Passiflora edulis* Sims.) fermentation time on its activity against Extended Strain Methicillin-Resistant (ESBL) *Escherichia coli* and Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Iif Hanifa Nurrosyidah, Ni Made Mertaniasih, Isnaeni

Page range: 723-727

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Antibiotic use on acute respiratory tract infection nonpneumonia and nonspecific diarrhea in Primary Health Care Centre in Banjarbaru City, South Kalimantan, Indonesia

Rizky Liesty Wardani, Suharjono, Kuntaman, Agus Widjaja

Page range: 729-735

[More](#) [Cite this](#)

Unlicensed June 25, 2021

Screening of anti-HIV activities in ethanol extract and fractions from *Ficus fistulosa* leaves

Siti Qamariyah Khairunisa, Dwi Wahyu Indriati, Lidya Tumewu, Aty Widyaruyanti, Nasronudin Nasronudin

Page range: 737-742

[More](#) [Cite this](#)

Unlicensed June 25, 2021

The characteristics of lactic acid bacteria isolated from fermented food as potential probiotics

Victoria Yulita Fitriani, Budi Suprapti, Muhammad Amin

Page range: 743-749

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

Profile of *gyrA* gene mutation in clinical isolate of levofloxacin resistant *Escherichia coli*

Alifia Risma Fahmi, Suharjono, Kuntaman

Page range: 751-754

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

Antimicrobial activity of *Centella asiatica* and *Gigantochloa apus*

Siti Mudaliana

Page range: 755-759

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

Drug-related problems of antibiotic use in gastroenteritis related to patient therapy outcomes at Universitas Gadjah Mada Hospital

Fivy Kurniawati, Nanang Munif Yasin, Farida Aulia, Gidfrie Vinanda Krisha

Page range: 761-766

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

The impact of suitability of empirical antibiotics use on therapeutic outcome of respiratory tract infection patients at inpatient wards of Universitas Gadjah Mada Academic Hospital

Fivy Kurniawati, Nanang Munif Yasin, Safina Nur Azizah, Silvia Ayu Purbaningtyas

Page range: 767-771

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

Genetic profile mutation *rpoB* in clinical isolate of rifampicin-resistant *Staphylococcus aureus*

Risa Zulfiana, Suharjono, Kuntaman

Page range: 773-776

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

Hematological side effect analysis of linezolid in MDR-TB patients with individual therapy

Novan Yusuf Indra Pratama, Bambang Subakti Zulkarnain, Soedarsono, Umi Fatmawati

Page range: 777-781

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

Adverse drug reaction and its management in tuberculosis patients with multidrug resistance: a retrospective study

Wenny Putri Nilamsari, Muhammad Fajar Rizqi, Natasya Olga Regina, Prastuti Asta Wulaningrum, Umi Fatmawati

Page range: 783-787

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

Analysis of prophylactic antibiotic use and risk factor of postoperative infection in urological surgery patients

Ratri Rokhani, Suharjono, Kuntaman, Mohammad Akram

Page range: 789-794

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

Molecular docking studies of *Nigella sativa* L and *Curcuma xanthorrhiza* Roxb secondary metabolites against histamine N-methyltransferase with their ADMET prediction

Ahmad Dzulfikri Nurhan, Maria Apriliani Gani, Aniek Setiya Budiadin, Siswandono Siswodihardjo, Junaidi Khotib

Page range: 795-802

[More ▾](#) [Cite this](#)

Unlicensed June 25, 2021

Prediction of compounds with antiosteoporosis activity in *Chrysophyllum cainito* L. leaves through *in silico* approach

Burhan Ma'arif, Hilwa Fitri, Nisfatul Lailatus Saidah, Luqman Alfani Najib, Achmad Hamdan Yuwafi, Ria Ramadhani

Dwi Atmaja, Fidia Rizkiah Inayatillah, Meilina Ratna Dianti, Hening Laswati, Mangestuti Agil

Page range: 803-808

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Phyllanthin and hypophyllanthin, the isolated compounds of *Phyllanthus niruri* inhibit protein receptor of corona virus (COVID-19) through *in silico* approach

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***Cratoxylum sumatranum* stem bark exhibited antimalarial activity by Lactate Dehydrogenase (LDH) assay**

Lidya Tumewu, Fendi Yoga Wardana, Hilkatul Ilmi, Adita Ayu Permanasari, Achmad Fuad Hafid, Aty Widyawaruyanti

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In vitro antimalarial activity of *Garcinia parvifolia* Miq. Stem extracts and fractions on *Plasmodium falciparum* lactate dehydrogenase (LDH) assay

Marsih Wijayanti, Hilkatul Ilmi, Einstenia Kemalahayati, Lidya Tumewu, Fendi Yoga Wardana, Suciati, Achmad Fuad Hafid, Aty Widayawaryanti

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Antioxidant and antiviral potency of *Begonia medicinalis* fractions

Muhammad Sulaiman Zubair, Siti Qamariyah Khairunisa, Evi Sulastrri, Ihwan, Agustinus Widodo, Nasronudin, Ramadanil Pitopang

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Artocarpus sericarpus* stem bark contains antimalarial substances against *Plasmodium falciparum

Lidya Tumewu, Lutfah Qurrota A'yun, Hilkatul Ilmi, Achmad Fuad Hafid, Aty Widayawaryanti

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Formulation and characterization of *Eleutherine palmifolia* extract-loaded self-nanoemulsifying drug delivery system (SNEDDS)

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Analytical method for the determination of curcumin entrapped in polymeric micellar powder using HPLC

Helmy Yusuf, Nina Wijjani, Rizka Arifa Rahmawati, Riesta Primaharinastiti, M. Agus Syamsur Rijal, Dewi Isadiartuti

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Challenges in the provision of natural medicines by community pharmacists in East Java Province, Indonesia

Hanni P. Puspitasari, Dhita Fatmaningrum, Sa'adatus Zahro, Shofi Salsabila, Zulfia A. Rizqulloh, Ana Yuda, Mufarrifah, Anila I. Sukorini, Neny Purwitasari

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In vitro and in silico analysis of phytochemical compounds of 96% ethanol extract of semanggi (*Marsilea crenata* Presl.) leaves as a bone formation agent

Agnis P.R. Aditama, Burhan Ma'arif, Hening Laswati, Mangestuti Agil

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Inhibitory activity of *Urena lobata* leaf extract on alpha-amylase and alpha-glucosidase: in vitro and in silico approach

Yudi Purnomo, Juliah Makdasari, Faiqoh Inayah Fatahillah

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Case Report

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Effect of hydrocortisone on hypocortisolism caused by pituitary adenoma

Niswah N. Qonita, Hanik B. Hidayati

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Tuhfatul Ulya, Chrismawan Ardianto*, Putri Anggreini, Aniek Setiya Budiadin, Dwi Setyawan and Junaidi Khotib

Quercetin promotes behavioral recovery and biomolecular changes of melanocortin-4 receptor in mice with ischemic stroke

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Keywords: dorsal striatum; ischemic stroke; melanocortin-4 receptor; motor; preventable death; quercetin.

Abstract

Objectives: Ischemic stroke is known as a common causes of disability, lower psychological well-being as well as preventable death. The pathogenesis of ischemic stroke process becomes worse immediately after oxidative stress occurs. One of the flavonoids with antioxidant abilities is quercetin. This study was aimed to investigate quercetin administration on the behavioral functions (motor and sensory) and expression of melanocortin-4 receptor (MC4R) in mice with ischemic stroke.

Methods: Male ICR mice were divided into sham, stroke, stroke with quercetin 100, 150, and 200 mg/kg. The stroke model was performed by blocking the left common carotid artery for 2 h. Quercetin was intraperitoneally administered daily for seven days. Evaluation was conducted during two weeks after induction using ladder rung walking test and narrow beam test for motoric function and adhesive removal tape test for sensory function. On day-14 mice were sacrificed, MC4R expression in the dorsal striatum was determined using RT-PCR.

Results: Stroke decreased the motor, sensory function and MC4R mRNA expression in dorsal striatum. Quercetin improved motor and sensory function, and upregulated expression of MC4R.

Conclusions: Quercetin administration after ischemic stroke improves behavioral function, possibly through the upregulation of MC4R in the brain.

Introduction

Ischemic stroke is a major risk factor for disability and the third leading cause of death all worldwide [1]. The rapid oxidation of protein, nucleic acid, and lipid is very worrying in the brain. The pathogenesis process triggers signals for interrelated metabolic processes, specifically decreased ATP production, increased intracellular calcium, and the formation of free radicals end up with neuronal cell death [2]. The condition becomes worse immediately after oxidative stress occurs, followed by the production of surplus reactive oxygen species (ROS) [3].

Oxidative stress is defined as an imbalance between ROS and their quenching by an antioxidant system, due to the overproduction of ROS and lack of antidotes [4]. Lots of evidence has shown that oxidative stress is one of the pathophysiology of early and primary cell death in the pathogenesis of ischemic stroke [2]. Several antioxidants were examined to enhance the defense system against nerve cell degeneration in order to prevent the progression of the harmful mechanisms involved in ischemia [5, 6].

Flavonoids are plant secondary metabolites that have been widely studied. The flavonoid group has a chemical structure that plays a role in its activity as antioxidants [7]. Quercetin is a flavonoid with antioxidant activity due to the presence of catechol groups and OH groups, the antioxidant pharmacophores [8–10]. In cerebral ischemia, the melanocortin system has neuroprotective effects likely mediated by the melanocortin-4 receptor (MC4R). Stimulation of MC4R affords neuroprotection by counteracting inflammation process and apoptosis [11]. However, there is no evidence showing the quercetin effect on the ischemic stroke-induced motor and sensory impairment from day to day, and its correlation with MC4R expression in the dorsal striatum.

The dorsal striatum is known as an important brain area in motor regulation. Previous study showed that injury to the striatum affects the recovery of gait in stroke

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patients [12, 13]. Therefore, this study aimed to investigate the effects of quercetin administration as an antioxidant and neuroprotective agent on improving motor and sensory function and biomolecular change (MC4R expression) in dorsal striatum mice with ischemic stroke. This study used a left unilateral common carotid artery occlusion model to induce stroke in mice resulting in hypoxia on the brain tissue [14].

Materials and methods

Animals

Male ICR mice, weighing between 25 and 30 g were used. All mice were treated at a temperature of $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ with a humidity of $60 \pm 10\%$, free access to food and water was also provided. All experiments were carried out at the Animal Research Laboratory of the Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia. The experimental protocol was approved by the Animal Care and Use Committee (ACUC), Faculty of Veterinary, Universitas Airlangga.

Drug and stroke surgery

Quercetin (Tokyo Chemical Industry, Tokyo, Japan) was dispersed into a mixture of carboxymethyl cellulose and tween 80 (1:1), with preparation less than 30 min before injection.

After acclimatization, the mice were randomly divided into five groups ($n=8$ in each group): (1) Sham group, (2) stroke group, (3) stroke with quercetin 100 mg/kg, (4) 150 mg/kg, (5) 200 mg/kg. Xylazine and ketamine were administered for anesthesia. The animals are positioned supine on the surgical table. Around 1 cm incision in the neck midline was made. The left common carotid artery was exposed and blocked by surgical silk for 2 h and then released for reperfusion. The Sham group was subjected to the same procedure without a carotid block. Quercetin-treated groups received an intraperitoneal injection of quercetin 30 min after stroke surgery, another group received an intraperitoneal injection of tween 0.5%. Quercetin was administered once a day for seven days intraperitoneally.

Ladder rung walking test

The protocol, shown in Figure 1, was performed in accordance to the previous study [15] by using the ladder rung walking test apparatus shown in Figure 1, on day 0 (before stroke surgery), 1, 4, 7, 10, 14 after stroke induction. All mice were allowed to walk through the cylindrical stairs arranged with varying distances in 1-m course. Movement of the right mice hind limb in each step was observed. The camera was used for record it. Mice that slip show a decrease or impaired motor function. A seven-category scale was assessed according to the position of the foot placement on the rungs and the shape of error [16]. All animals were trained and tested five times per-session. Then, the average error score was analyzed. Error score data was presented as a percent of 100%.

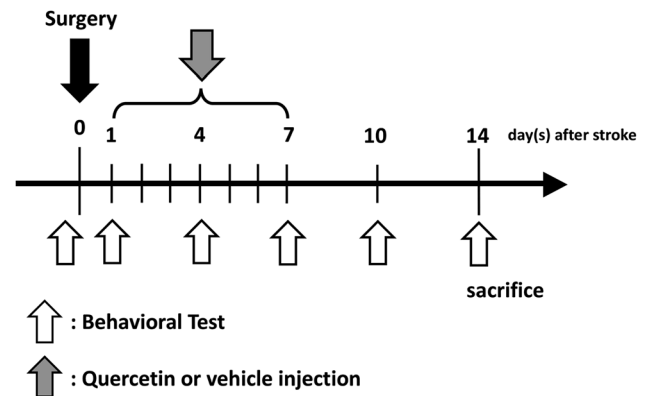


Figure 1: Schematic illustration of experimental design for examining the effect of quercetin on behavioral and biomolecular changes after ischemic stroke.

Narrow beam test

The protocol was performed following the previous study [16]. Mice were placed to cross the narrow beam apparatus. Mice were placed in the initial zone, and the stopwatch started immediately after the animal was released. The time was recorded when the animal starts walking past the start line and get a slip. The time taken by animals to reach the final platform at the end of the beam was also recorded, with a maximum time of 15 s. Both the time until mice are found to slip or fall, as well as the total time taken to cross the beam, were measured for five trials. The tests performed on day 0 (before stroke surgery), 1, 4, 7, 10, 14 (after stroke surgery).

Adhesive removal tape test

The protocol was performed following the previous study [17] with a few modifications. In this test, adhesive tapes of the same size (1×1 cm) is placed on the right forelimb of each animal with equal pressure. Each group was randomized to the order of adhesive placement (right or left). The initial contact time by left forelimb called time to touch, and the time required for the mice to remove the tape called time to remove in a maximum of 120 s was recorded. This test was performed regularly on day 0 (before stroke surgery) and days 1, 4, 7, 10, 14 (after stroke surgery).

Reverse Transcription - Polymerase Chain Reaction (RT-PCR) Analysis

On day 14, the brain was extracted, the dorsal striatum was dissected and liquid nitrogen was used to immediately freeze the sample. Storage was carried out at $-80\text{ }^{\circ}\text{C}$ until use. RT-PCR was performed according to Ardianto et al. [18]. The PureLink[®] RNA mini kit (Invitrogen, Cat No. 12183018A) was used to isolate the total RNA. GoScript[™] RT (Promega, Cat No. A5000) was used for reverse transcription. The following primers were used: MC4R (forward: 5'-TTA ATA CCT GCT AGA CAA CTC A-3', reverse: 5'-ATG TAT ACT TCC CTC CAC CTC TG-3'), and β -actin (forward: 5'-ACCCACACTGTGCCCATCTAA-3', reverse: 5'-GCCACAGGATTCCATTA CCCAA-3'). Amplification was conducted using thermal cycler (Applied

Biosystems, USA) for RT-PCR with total cycle of 33. The denaturation cycle was carried out at 94 °C for 30 s, followed by the annealing at 58 °C for 1 min, and the extension at 72 °C for 1 min. Electrophoresis (MSMIDI Duo, USA) was used to analyze PCR products. Ethidium bromide (Sigma-Aldrich) was used to dye 2% Agarose gel. The band was captured with the aid of UV transillumination. ImageJ software (NIH, MD, USA) was used for image analysis.

Statistical analysis

Data were presented as mean values \pm SEM. Behavioral test and body weight data were analyzed using a two-way ANOVA followed by the Bonferroni post-hoc test. Relative expression of MC4R was analyzed using a one-way ANOVA followed by the Bonferroni post-hoc test. The difference was considered significant if $p < 0.05$ (95%).

Results

The effect of quercetin on body weight

Animal body weight was measured to determine the effect of quercetin administration and stroke induction on nutritional deficits and metabolic disorders that might occur. The results of weight measurement showed that there were no significant differences between the study groups (Figure 2). In addition, there were no significant changes between giving quercetin at various doses to animal body weight.

The effect of quercetin on ladder rung walking test

Stroke group with vehicle administration showed a significant decrease in motor function compared to the Sham group (two way ANOVA, stroke, $F_{1,14}=38.59$, $p < 0.001$ vs. Sham) starting from day 1 through 14. In contrast, the stroke group treated with quercetin at doses of 100, 150, and 200 mg/kg showed a significant improvement in motor

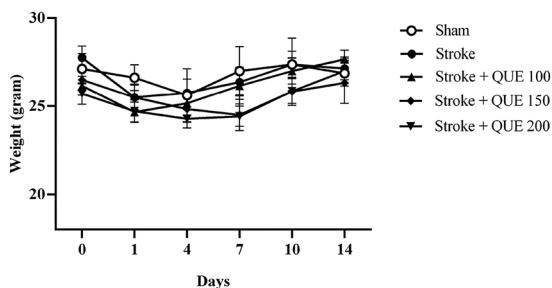


Figure 2: The effect of quercetin on body weight of mice induced ischemic stroke (mean \pm SEM) of 6–8 mice. Administration of quercetin were conducted repeatedly day 1–7. QUE, quercetin.

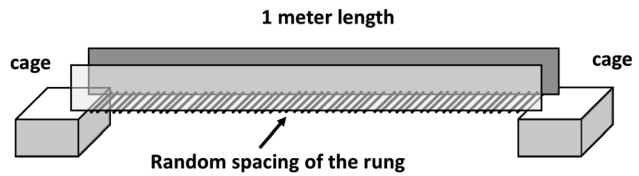


Figure 3: Ladder rung walking test apparatus for ladder rung walking test measurement.

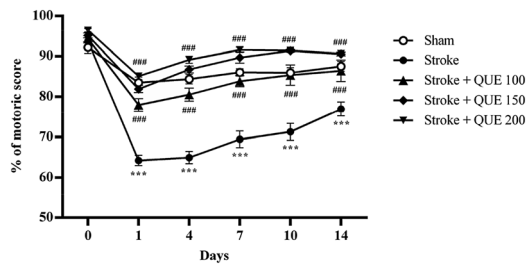


Figure 4: The motor function of ischemic stroke mice measured by ladder rung walking test (mean \pm SEM) of 6–8 mice. *** $p < 0.001$ vs. Sham group. ### $p < 0.001$ vs. stroke group. QUE, quercetin.

function when compared to the stroke group with vehicles, starting from day 1 and gradually increasing on days 4 through 14 (Figures 3 and 4).

The effect of quercetin on narrow beam test

In addition, we also examined the effect of quercetin on stroke induction on motor function improvement using the narrow beam test. The results of the latency to slip showed that the stroke group had a significantly lower motor function compared to the Sham group on day 4 (Figure 5A). This was evidenced by mice that slips faster than the Sham group. Furthermore, the stroke group showed a decrease in motor function by spent more time to reach the finish, the difference was significant compared to the Sham group on day 4 (Figure 5B).

In contrast, the stroke group with quercetin administration (200 mg/kg) showed significantly improved motor function by increased time latency to slip on day 4. Then, the stroke group with quercetin at a dose of 150 and 200 mg/kg significantly suppressed time to reach the finish compared with the stroke group starting on day 1 (Figure 5).

The effect of quercetin on adhesive removal tape test

The effects of stroke induction and quercetin administration on the sensory functions of mice showed the stroke

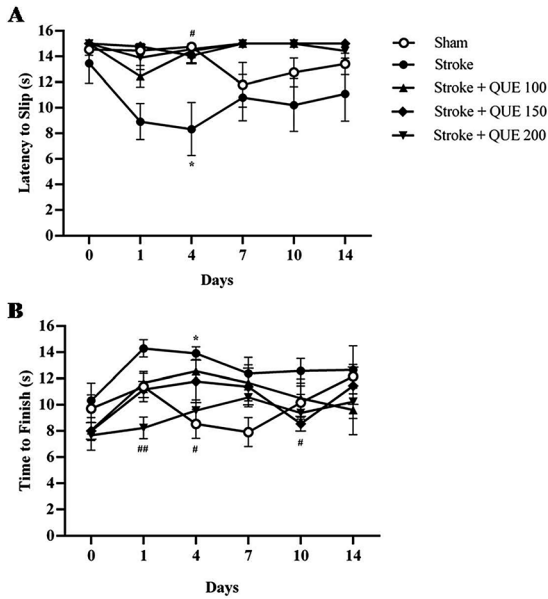


Figure 5: The effect of quercetin on motor function of ischemic stroke mice. (A) Latency to slip and (B) time to finish the beam were measured by narrow beam test (mean \pm SEM) of 6–8 mice. * $p < 0.05$ vs. Sham group. # $p < 0.05$, ## $p < 0.01$ vs. stroke group. QUE, quercetin.

group had a significantly lower function than the Sham group on the latency to touch (Figure 6A), and latency to remove (Figure 6B) values starting on day 1, followed by day 4 through 14.

Furthermore, administration of quercetin (150 and 200 mg/kg) was significantly improves sensory function compared to the stroke group in the latency to touch from day 1, whereas doses 100 mg/kg from day 4 through 14. Then, administration of quercetin doses of 150 and 200 mg/kg significantly suppressed the latency to remove time compared to the stroke group starting on day 1, whereas doses 100 mg/kg from day 7 (Figure 6).

The effect of quercetin on melanocortin-4 receptors

The results of examination MC4R expression in the dorsal striatum of the brain showed a significantly lower MC4R expression on stroke group compared to the Sham group (one way ANOVA, stroke, $F_{2,6}=357.6$, $p < 0.01$ vs. Sham). In contrast, the stroke group with 100 mg/kg quercetin administration significantly increased MC4R expression compared to the stroke group ($p < 0.001$ vs. stroke) on days 14 (Figure 7).

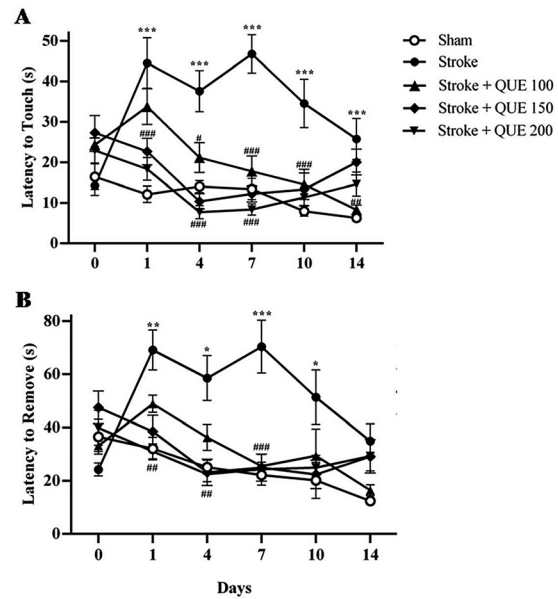


Figure 6: The effect of quercetin on sensory functions of mice induced by ischemic stroke. (A) Latency to touch the tape and (B) latency to remove the tape were measured by adhesive removal tape test (mean \pm SEM) of 6–8 mice. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. Sham group. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ vs. stroke group. QUE, quercetin.

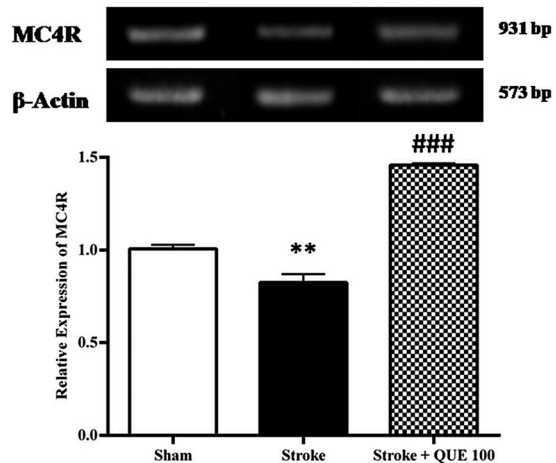


Figure 7: The effect of quercetin on relative expression of MC4R in dorsal striatum of mice induced by ischemic stroke (mean \pm SEM) of three mice. *** $p < 0.01$ vs. Sham group. ### $p < 0.001$ vs. stroke group. Bp, base pair; MC4R, melanocortin-4 receptor; QUE, quercetin.

Discussion

This study was designed to determine changes of behavioral function (motor and sensory) and biomolecular changes in MC4R expression in the brain of mice after

stroke induced by the left unilateral common carotid artery occlusion method, and the improvements due to quercetin treatment. This stroke induction method is known to cause impairment of motor and sensory function and lead to neuronal cell death in the brain [14].

Quercetin administration did not affect mice's body weight from day 1 to day 14. This result is in agreement with studies from Barrenex et al. [19] that dietary foods containing 0.5% quercetin for 28 days did not affect the body weight of mice compared to the control group. Similar results were shown by a high-sucrose diet containing 0.07, 0.2, and 0.02% quercetin for four weeks, which does not affect the body weight of rats [20].

The motor function examination results using the ladder rung walking test method showed a significant attenuation in motor function impairment after quercetin administration in days 1, 4, 7, 10, and 14 compared to the stroke group. Giving quercetin at a dose of 100, 150, and 200 mg/kg improves motor function in ischemic stroke conditions. Similarly, the results of the motor function test using the narrow beam test method also showed notable improvement with quercetin administration as compared to the stroke group. The result showed a dose-dependent trend of the effect of quercetin to improve motor function. A previous study reported that the post-injury administration of quercetin (50 mg/kg) improves the motor function between day 1 until 5 after trauma compared with the traumatic brain injury group [21]. Together, these results suggest that quercetin attenuates the stroke-induced motor function deficits.

Furthermore, our present data show stroke-induced sensory impairment that did not recover in a two-week examination period. Moreover, the present study revealed that quercetin (100, 150, and 200 mg/kg) decreased the time to touch and to remove the adhesive tape in ischemic stroke mice, starting from day 1 after stroke induction. A study from Chen et al. [22] showed that quercetin administration accelerates full sensory recovery in 18 days in mice with sciatic nerve-crush injury compared to the untreated mice. Together with our result, it is suggested that quercetin attenuates the sensory function impairment after an ischemic stroke attack. Furthermore, we found that all doses (100, 150, and 200 mg/kg) effectively improve stroke related-behaviors. Each dose has a certain level of speed in improving motor and sensory function. Although higher doses showed faster improvement, the three doses were not significantly different, meaning they were equally effective in improving motor and sensory function due to stroke in a relatively fast time.

It is well known that melanocortin system activity is involved in responding to the neuroinflammatory process

in the brain. The activation, as well as the upregulation of MC4R, has been the biomolecular marker representing the anti-inflammatory process [23]. MC4R is reported expressed in the dorsal striatum, one of the critical brain regions that regulate motor function [24]. Therefore, we investigate the expression of MC4R in the dorsal striatum and effect of quercetin. Since we already found that 100, 150 and 200 mg/kg dose of quercetin are effective in ameliorates the stroke related-behaviors, for MC4R expression analysis we used representative yet effective dose of quercetin which is 100 mg/kg. Our present study revealed that the MC4R mRNA level in the dorsal striatum decreased in stroke. Furthermore, we found that treatment with quercetin ameliorated the decrease MC4R mRNA level in the dorsal striatum. A previous study showing that MC4R mRNA was upregulated in the striatum after severe hypoxic-ischemic brain injury compared with control [25]. The present result suggests that the upregulated MC4R mRNA in the dorsal striatum may reflect the brain capability to reduce the inflammatory process and restore the deficit in brain function affected by an ischemic stroke.

Previous study showed that MC4R stimulation prevents mitochondrial stress and oxidative damage due to ethanol through the activation of the Nrf-2 pathway in neuron culture [26]. In addition, quercetin has been reported to modulate the activation of the Nrf-2-ARE pathway [27]. Nrf2-ARE pathway activation increases the expression of detoxification enzymes such as glutamate-cysteine ligase and synthesis of glutathione, an endogenous antioxidant [28]. In conclusion, our present results indicate that quercetin attenuates the motor and sensory deficits induced by an ischemic stroke in mice. Additionally, it is suggested that quercetin reverse the functional impairment through the upregulation of MC4R in the dorsal striatum. Further study is needed to clarify the direct evidence explaining how the quercetin affects the expression of MC4R.

Conclusions

This study shows that quercetin ameliorates motor and sensory impairment due to ischemic stroke conditions. Further, it is suggested that quercetin may promotes functional recovery from ischemic stroke condition by the MC4R upregulation.

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Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: All experiments were performed at the Animal Research Laboratory of the Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia in accordance with the Guide for care and use of laboratory animal issued by National Institution of Health revised in 1985. The experimental protocol was approved with letter No: 2.KE.111.07.2019 by the Animal Care and Use Committee (ACUC), Faculty of Veterinary, Universitas Airlangga.

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- UNIT/LEMBAGA/TEMPAT PENELITIAN** : Departemen Farmasi Klinik
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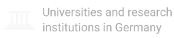
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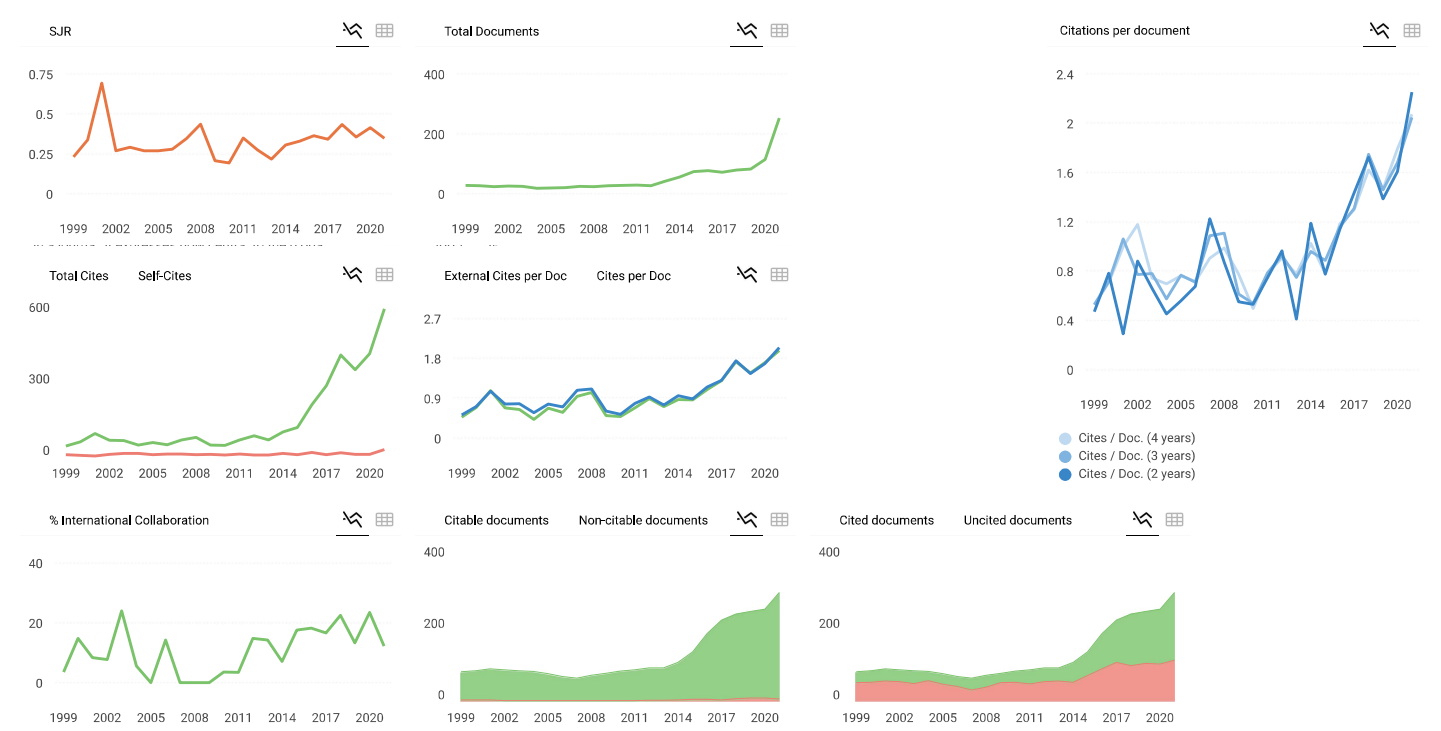
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