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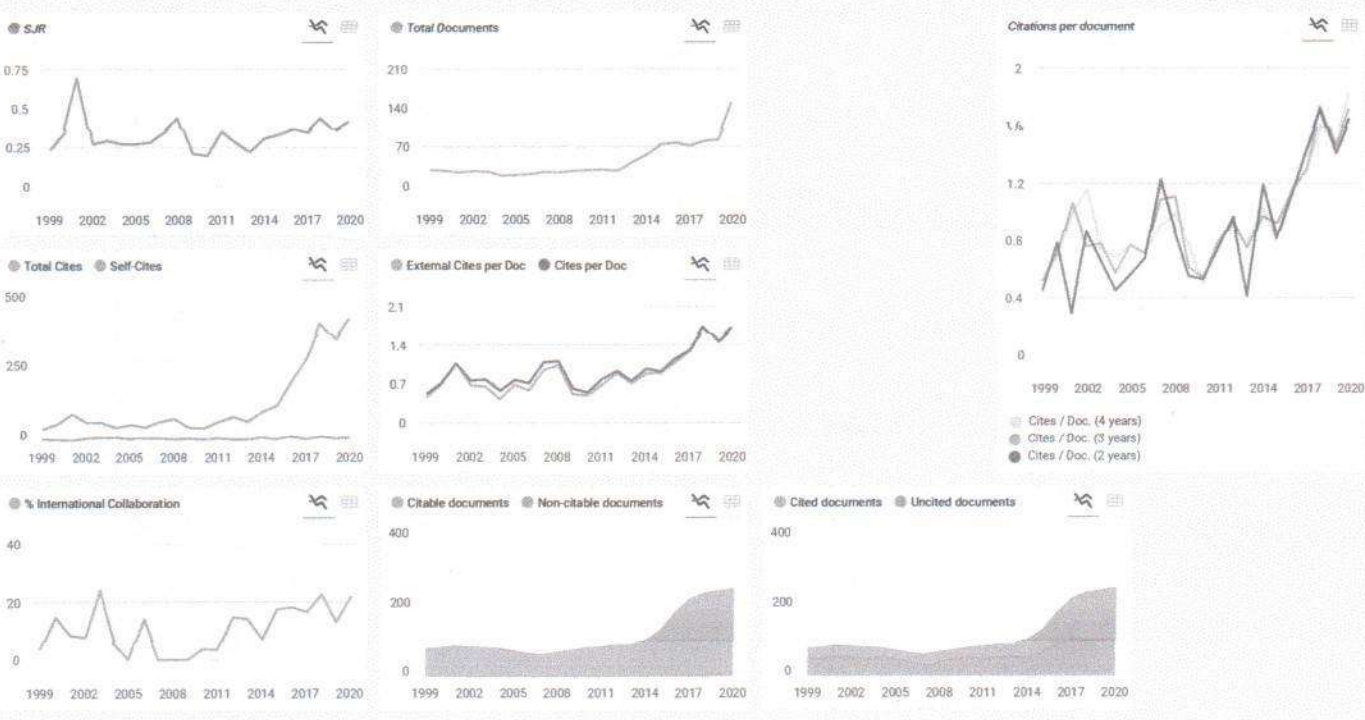
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Issue of [Journal of Basic and Clinical Physiology and Pharmacology](#)

**CONTENTS**

**JOURNAL OVERVIEW**

Accessible June 25, 2021

## Frontmatter

Page range: i-ii

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

## Original Articles

Requires Authentication June 25, 2021

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

*Yohana Febriani Putri Peu Patty, Mufarrihab, Yunita Nita*

Page range: 285-295

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

Requires Authentication 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](#)

Requires Authentication 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](#)

Requires Authentication 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, Kornikanok Ingkaninan*

Page range: 313-317

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

Requires Authentication 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](#)

Requires Authentication 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](#)

Requires Authentication June 25, 2021

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

*Chrismawan Ardianto, Aniek Setya Budiatin, I Nengah Budi Sumartha, Nurrahmi Nurrahmi, Mahardian Rahmadi, Junaidi Khotib*

Page range: 335-340

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

Requires Authentication June 25, 2021

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

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

Page range: 341-347

More ▾ Cite this

Requires Authentication 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 Budiati, Dwi Setyawan, Junaidi Khotib

Page range: 349-355

More ▾ Cite this

Requires Authentication June 25, 2021

### Knowledge and attitudes of healthcare professionals on prescribing errors

Desak Ketut Ermawati, Ida Ayu Alit Widhiartini, Endang Budiarti

Page range: 357-362

More ▾ Cite this

Requires Authentication 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

Requires Authentication 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 Budiati, Siswandono Siswodihardjo, Junaidi Khotib

Page range: 373-377

More ▾ Cite this

Requires Authentication 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

Requires Authentication 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 Widjowaty, Galih Satrio Putra, Tutuk Budiati, Katsuyoshi Matsunami

Page range: 385-392

More ▾ Cite this

Requires Authentication 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 Widiandani

Page range: 393-401

More ▾ Cite this

Requires Authentication 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

Requires Authentication 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, Erida Zairina

Page range: 415-419

More ▾ Cite this

Requires Authentication June 25, 2021

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

Denny Ardianto, Suharjono, Soedarsono, Umi Fatmawati

Page range: 421-427

More ▾ Cite this

Requires Authentication June 25, 2021

### Shallot skin profiling, computational evaluation of physicochemical properties, ADMET, and molecular docking of its components



**against P2Y<sub>12</sub> 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

Requires Authentication 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

Requires Authentication 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

Requires Authentication 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 Noorizka Veronika Achmad, Arie Sulistyarni, Yunita Nita, Arief Bakhtiar, Muhammad Amih

Page range: 453-458

More ▾

Cite this

Requires Authentication 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

Requires Authentication 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, Alian Nur Rosyid

Page range: 467-472

More ▾

Cite this

Requires Authentication 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

Requires Authentication 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

Requires Authentication 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

Requires Authentication June 25, 2021

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

Prihartini Widlyanti, Hartmut Kuehn, Soetjipto Soetjipto

Page range: 491-496

More ▾

Cite this

Requires Authentication 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 Setiyo Budiati, Ilham Bagus Sagitaras, Ika Putri Nuthayati, Nismatun Khairah, Khoirotin Nisak, Imam Susilo, Junaidi Khotib

Page range: 497-504

More ▾

Cite this

Requires Authentication June 25, 2021

**N-nitrosodiethylamine induces inflammation of liver in mice**

Devy Maqlidya Cahyani, Andang Miatmoko, Berlian Sarasitha Hariawan, Kusuma Eko Purwanti, Retno Sari

Page range: 505-510

More ▾ Cite this

Requires Authentication 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, Amitasari Damayanti, Septiyan Dwi Santoso, Enggar Restryarto, Wifqi Hadinata, Iwan Sahrial Hamid

Page range: 511-516

More ▾ Cite this

Requires Authentication 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 Dewi Aryani, Siswandono Siswodihardjo, Widji Soeratri, Nadia Fitria Indah Sari

Page range: 517-525

More ▾ Cite this

Requires Authentication 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

Requires Authentication June 25, 2021

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

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

Page range: 533-540

More ▾ Cite this

Requires Authentication 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 Zulkarnain, Nadhifa Zahra

Page range: 541-545

More ▾ Cite this

Requires Authentication 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

Requires Authentication June 25, 2021

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

Samirah, Aniek Setiya Budiati, Ferdiansyah Mahyudin, Junaidi Khotib

Page range: 555-560

More ▾ Cite this

Requires Authentication 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

Requires Authentication 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, Subarjono, Christoper P. Alderman

Page range: 567-570

More ▾ Cite this

Requires Authentication June 25, 2021

**Correlation of dietary iron intake and serum iron with thyroid stimulating hormone (TSH) and free thyroxine (FT<sub>4</sub>) levels in adult hyperthyroid patients**

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

Page range: 571-576

More ▾ Cite this

Requires Authentication 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 Atfiyah*

Page range: 577-582

[More](#) [Cite this](#)[Requires Authentication](#) 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, Siswandojo*

Page range: 583-587

[More](#) [Cite this](#)[Requires Authentication](#) 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 Unborowati, Damayanti Damayanti, Anang Endaryanto, Cita Rosita Sigit Prakoeswa*

Page range: 589-593

[More](#) [Cite this](#)[Requires Authentication](#) 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](#)[Requires Authentication](#) 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](#)[Requires Authentication](#) June 25, 2021**Drug utilization study and cost analysis of adult  $\beta$ -thalassemia major patient therapy at Dr. Soetomo General Hospital Surabaya***Hasna Qatrunnada, Suharjo, Siprianus Ugroseno Yudho Bintoro, Siti Wahyuni*

Page range: 611-616

[More](#) [Cite this](#)[Requires Authentication](#) June 25, 2021**The role of hyperbaric oxygen to platelet aggregation in noninsulin-dependent diabetes mellitus (NIDDM)***Prihartini Widiyanti, Purnomo Suryahudoyo*

Page range: 617-621

[More](#) [Cite this](#)[Requires Authentication](#) 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](#)[Requires Authentication](#) June 25, 2021**The role of chondroitin sulfate to bone healing indicators and compressive strength***Herry Wibowo, Prihartini Widiyanti, Syaifulah Asmiragani*

Page range: 631-635

[More](#) [Cite this](#)[Requires Authentication](#) 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 Suprapti*

Page range: 637-644

[More](#) [Cite this](#)[Requires Authentication](#) June 25, 2021**Analysis of stress ulcer prophylaxis drug regimentation in surgical patients***Dhani Wijaya, Suharjo, Fendy Matulatan, Elfri Padelo*

Page range: 645-649

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

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### 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

Requires Authentication June 25, 2021

### The thermodynamic study of *p*-methoxycinnamic acid inclusion complex formation, using $\beta$ -cyclodextrin and hydroxypropyl- $\beta$ -cyclodextrin

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

Page range: 663-667

More ▾ Cite this

Requires Authentication 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

Requires Authentication 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, Tjka Yasmin Rahmayanti, Bagus Putu Putra Suryana

Page range: 675-680

More ▾ Cite this

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

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Page range: 681-686

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

Page range: 687-691

More ▾ Cite this

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Lisa Narulita, Suharjono, Kuntaman, Mohammad Akram

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Nunuk Dyah Retno Lastuti, Nur Rusdiana, Poedji Hastutieik

Page range: 701-705

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

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Page range: 707-714

More ▾ Cite this

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### 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

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**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)**

Ilf Hanifa Nurrosyidah, Ni Made Mertaniasih, Isnaeni

Page range: 723-727

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Page range: 729-735

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Siti Mudaliana

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**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 Aprihiani Gani, Aniek Setiya Budiati, Siswandono Siswodihardjo, Junaidi Khotib

Page range: 795-803

More ▾ Cite this

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

Burhan Ma'arif, Hilwa Fitri, Nisfatul Lailatus Sa'idah, Luqman Alfani Najib, Achmad Hamdan Yuwafi, Ria Ramadhani Dwi Atmaja, Fidia Rizkiyah 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**

Honey Dzilri Marhaeny, Aty Widyawaruyanti, Tri Widiandani, Achmad Fuad Hafid, Tutik Sri Wahyuni

Page range: 809-815

More ▾ Cite this

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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

Page range: 817-822

More ▾ Cite this

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**Endophytic fungi inhabiting *Physalis angulata* L. plant: diversity, antioxidant, and antibacterial activities of their ethyl acetate extracts**

Kartika Dyah Pahupi, Muhammad Ilyas, Andria Agusta

Page range: 823-829

More ▾ Cite this

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**Exploration of several plants from Baung Forest on bone formation cell models**

Retno Widyowati, Neny Purwitasari, Rice Disi Oktarina, Wiwied Ekasari, Saarah Khairunnisa, Hsin-I. Chang

Page range: 831-837

More ▾ Cite this

Requires Authentication June 25, 2021

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

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

Page range: 839-844

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**Antioxidant and antiviral potency of *Begonia medicinalis* fractions**

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

Page range: 845-851

More ▾ Cite this

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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 Widyawaruyanti

Page range: 853-858

More ▾ Cite this

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

Rahmi Annisa, Mochammad Yuwono, Esti Hendradi

Page range: 859-865

More ▾ Cite this

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

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

Page range: 867-873

More ▾ Cite this

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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, Mufarrihah, Anila I. Sukorini, Neny Purwitasari

Page range: 875-880

More ▾ Cite this

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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

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

Page range: 881-887

More ▾ Cite this

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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

Page range: 889-894

More ▾ Cite this

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### Effect of hydrocortisone on hypocortisolism caused by pituitary adenoma

Niswah N. Qonita, Hanik B. Hidayati

Page range: 895-898

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[Linguistics and Semiotics](#)  
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# 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

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## Abstract

**Objectives:** To determine the inhibition effect of *epigallocatechin gallate* (EGCG) and green tea extract on neuronal necroptosis based on necroptosis morphology.

**Methods:** *In vivo* study was performed on male *Rattus norvegicus* middle cerebral artery occlusion (MCAO) model divided into five groups, MCAO-control groups, EGCG 10 mg/kg BW/day, EGCG 20 mg/kg BW/day, EGCG 30 mg/kg BW/day, and green tea extract 30 mg/kg BW/day for 7 days treatment. MCAO model was made by modification method using Bulldog clamp. After 7 days of treatment, all *R. norvegicus* were sacrificed. After that, examination using Hematoxylin–Eosin stain was conducted to look at necroptosis morphology in each group.

**Results:** We found that there are significant differences between control group and the other three groups (EGCG 20 mg/kg BW/day, EGCG 30 mg/kg BW/day, and green tea extract ( $p < 0.05$ )). There is a significant correlation between the number of neuron cell necroptosis and both EGCG and green tea extract ( $p < 0.05$ ). The correlation is negative, which means both EGCG and green tea extract will decrease the number of neuron cell necroptosis. EGCG will decrease neuron cell necroptosis starting from the dose of 20 mg/kg BW/day. EGCG 30 mg/kg BW/day produces the best result compared to other doses.

**Conclusions:** *Camellia sinensis* (green tea) with its active compound EGCG decreases neuronal necroptosis morphology in MCAO models.

**Keywords:** *Camellia sinensis*; EGCG; green tea; necroptosis; neuron.

## Introduction

Stroke is characterized by abrupt neurological deficit due to focal brain injury in the brain by vascular etiology [1]. Based on WHO Global Health Estimates 2016, stroke is on the second place in the list of noncommunicable diseases that cause death. The national prevalence of stroke in Indonesia in the population above 15 years old is 10.9 per mil. The highest prevalence is found in East Kalimantan with 14.7 per mil. On the other hand, the lowest prevalence is found in Papua with 4.1 per mil. The incidence of stroke increases with age. It mostly occurs in the population above 75, which is 50.2%, followed by 65–74 year old group with 45.3% [2].

Ischemic stroke is a specific type of stroke commonly found in patients rather than hemorrhagic stroke, by percentage of 85% for ischemic stroke and 15% for hemorrhagic stroke [3]. Ischemic stroke happens when there is occlusion in brain vasculature generating obstruction in the brain blood vessel which results in reduced blood flow in the brain [4]. Standardized therapy given to patients with stroke is thrombolysis therapy. The only drug approved by FDA (Food and Drug Administration) to be utilized 3 h after the onset of stroke is intravenous recombinant tissue plasminogen activator (rTPA) [5]. Prior research has showed that the first generation of thrombolytic drugs such as Streptokinase and Urokinase were not effective for treating patients with ischemic stroke [6].

Necroptosis is programmed necrosis and caspase-independent cell death. The main features of necroptosis are organelle swelling and rupture of cell membrane and wall mediated by the death signal pathway [7]. Based on

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previous research, necroptosis plays a role in middle cerebral artery occlusion (MCAO) rat *in vivo* process, and its mechanism can be distinguished with apoptosis [8].

Ischemic stroke process initiated by adenosine triphosphate (ATP) derivation in the brain leads to lactic acid accumulation and dysfunction of the intracellular pump [9, 10]. Interferon-gamma (INF- $\gamma$ ), interleukin 1 beta (IL-1 $\beta$ ), IL-6, and tumor necrosis factor (TNF- $\alpha$ ) activated by the death of astrocyte leads to the increasing number of lactic acid [10, 11]. TNF- $\alpha$  pathway will activate necroptosis process [12]. Dysfunction of intracellular pumps produces ROS (reactive oxygen species), which leads to escalating necroptosis process through some pathways such as autophosphorylation receptor-interacting protein 1 (RIP1) [13].

The second most consumed drinks in the world is green tea [14]. The catechin major component of green tea is epigallocatechin gallate (EGCG) [15]. EGCG can be used as an antioxidant, which reduces reactive oxygen species (ROS) and increases antioxidant enzyme. Based on ferric reducing antioxidant power (FRAP), positive correlation is shown by the antioxidant substance of green tea. Green tea has a better antioxidant activity than oolong and black tea [16]. Early therapy of 0.5% green tea extract in 3 weeks will produce inhibition effects towards brain ischemia processes such as peroxidation lipid, level of DNA oxidative damage, neuronal cell death, and infarct in the brain [17].

The information above shows the role of green tea with its active compound EGCG in inhibiting neuronal cell death through necroptosis pathway. Further research on *Camelia sinensis* (green tea) with its active compound EGCG in inhibiting neuronal cell death through necroptosis pathway needs to be done to identify the effect of green tea in decreasing neuronal cell necroptosis in ischemic stroke.

## Materials and methods

This study was designed as randomized posttest only MCAO-control group design true experimental. The study was done by using *Rattus norvegicus* middle cerebral artery occlusion (MCAO) model treated with green tea and its active compound EGCG with the approval of Research Ethics Committee of Health Faculty, Faculty of Medicine, Universitas Airlangga. This research was conducted in animal laboratories at the Faculty of Pharmacy, Airlangga University for animal treatment. The morphological examination of neuron cell necroptosis was carried out at the Pathological Anatomy Laboratory of FK UNAIR for 4 months.

The sample of this study included 55 healthy male *R. norvegicus* MCAO models with weight of 200–275 g that met the inclusion and exclusion criteria. The sample was divided into three groups: MCAO-control groups, EGCG 10 mg/kg BW/day, EGCG 20 mg/kg BW/day, EGCG 30 mg/kg BW/day, and green tea extract 30 mg/kg BW/day for 7 days. Treatment was done by simple random sampling with

the assumption that all the subjects were treated in a similar method, from taking research subjects to work and laboratory conditions. One group contained 11 rats with a total of 55 rats in all groups.

Before making the MCAO model, male *R. norvegicus* were adjusted to the new environment for 7 days. MCAO model was made by modification method using bulldog clamp to occlude cerebral media artery for 180 min. After the anesthesia stopped, we grabbed the rats by the tail 1 m above the floor and evaluated if there is flexion movement of two front leg toward contralateral of the hemisphere which indicated that the ischemia process was successful, that will cause necroptosis. Next, green tea treatment was done once a day for 7 days. We introduced the green tea treatment by dissolving green tea with aqua bidest with concentration of 1 mg/mL and giving it to the rats by gavage feeding needle. EGCG was obtained and analyzed by Xi'an rongsheng biotechnology and we used pure EGCG 98.7% (HPLC analysis document number 2019070630). Green tea extract used was labeled Meditea (IDM000580138), containing 2.5% of EGCG in 50 g sample analyzed by Angler BioChemlab on HPLC analysis, with certificate number 183689.

After that, all the rats were sacrificed using decapitation method to acquire the brain tissue. After being sacrificed, the brain tissue was taken from the hemisphere that had an infarction of 1.5 cm in front and behind the bregma and was used for histopathological examination. The brain tissue was stained by Hematoxylin eosin. The proportion of necroptosis morphology was examined and classified based on D.C Allred M.D guideline of scoring, proportion classified in score 0–5 [18]. All histopathological examination was carried out directly by pathologist Imam Susilo.

Descriptive analysis and normality test of Kolmogorov–Smirnov were conducted for each group data. Because data distribution was abnormal, Kruskal–Wallis test was performed, followed by Mann–Whitney test to distinguish EGCG and green tea extract effect toward neuronal cell necroptosis morphology. Kruskal–Wallis test was used to compare necroptosis differences of all group. The analysis was then followed by Mann–Whitney test to compare necroptosis differences of each two group after we were sure that there were differences between all groups in Kruskal–Wallis test. Lastly, we performed a Spearman correlation test to find out the correlation of EGCG and green tea extract toward necroptosis morphology in MCAO model.

## Results

First, we conducted a descriptive analysis (to evaluate minimum–maximum, mean and standard deviation of our data), followed by a normality test for each group. Our data distribution is abnormal. So, we performed the Kruskal–Wallis test, and the results showed that data of the five groups is significantly different ( $p < 0.05$ ). Further, we conducted Mann–Whitney test to differentiate necroptosis morphology between each two groups presented in Table 1. We found that there are significant differences between the normal-control group and MCAO-control group ( $p < 0.05$ ), which indicates that the MCAO process happened as shown by the differences of neuronal cell necroptosis.

**Table 1:** Comparison of EGCG and green tea extract effect on neuronal cell necroptosis in MCAO model.

Group	Mean ± SEM	n	p-Value
Normal control group	0.44 ± 0.527	11	
MCAO control group	1.80 ± 0.422	10	0.00 <sup>a</sup>
EGCG 10 mg/kg BW	1.5 ± 0.522	12	0.254 <sup>b</sup>
EGCG 20 mg/kg BW	1.31 ± 0.480	13	0.049 <sup>b</sup>
EGCG 30 mg/kg BW	1.08 ± 0.289	12	0.003 <sup>b</sup>
Green tea extract 30 mg/kg BW	1.27 ± 0.467	11	0.043 <sup>b</sup>

<sup>a</sup>Compared to normal control group, <sup>b</sup>Compared to MCAO-control group. If p-value < 0.05 considered statistically significant.

As Table 1 indicates, there are significant differences of neuronal cell necroptosis morphology between the MCAO-control group and the other three groups (EGCG 20 mg/kg BW, EGCG 30 mg/kg BW, and green tea extract) with  $p < 0.05$ . There is a significant correlation between neuron cell necroptosis morphology and both EGCG and green tea extract ( $p < 0.05$ ). EGCG 10 mg/kg BW did not decrease neuron cell necroptosis morphology. As found in EGCG 20 mg/kg BW and EGCG 30 mg/kg BW group, EGCG can decrease neuron cell necroptosis. However, based on the p-value, 30 mg/kg BW dose is more effective than 20 mg/kg BW dose.

If we compared EGCG 30 mg/kg BW and green tea extract group, both significantly decreased neuronal cell necroptosis. However, EGCG is more effective as there is an increasing mean value in green tea extract group as presented in Table 1. The correlation is negative, which means an EGCG/green tea extract will decrease neuron cell necroptosis morphology. All of our data indicate that EGCG and green tea extract play a role in decreasing neuronal cell necroptosis during ischemic process. EGCG effect is dose-dependent as increasing EGCG dose increases the decreasing process of neuron cell necroptosis. The differences of each group in histopathological examination can be seen and compared in Figure 1, the necroptotic cell marked as green arrow with pale, fade, nonprominent, pyknotic and karyorrhexis nucleus. EGCG 30 mg/kg BW produced the most significant effect compared to the other groups as can be seen in statistical analysis in Table 1 and Figure 1.

## Discussion

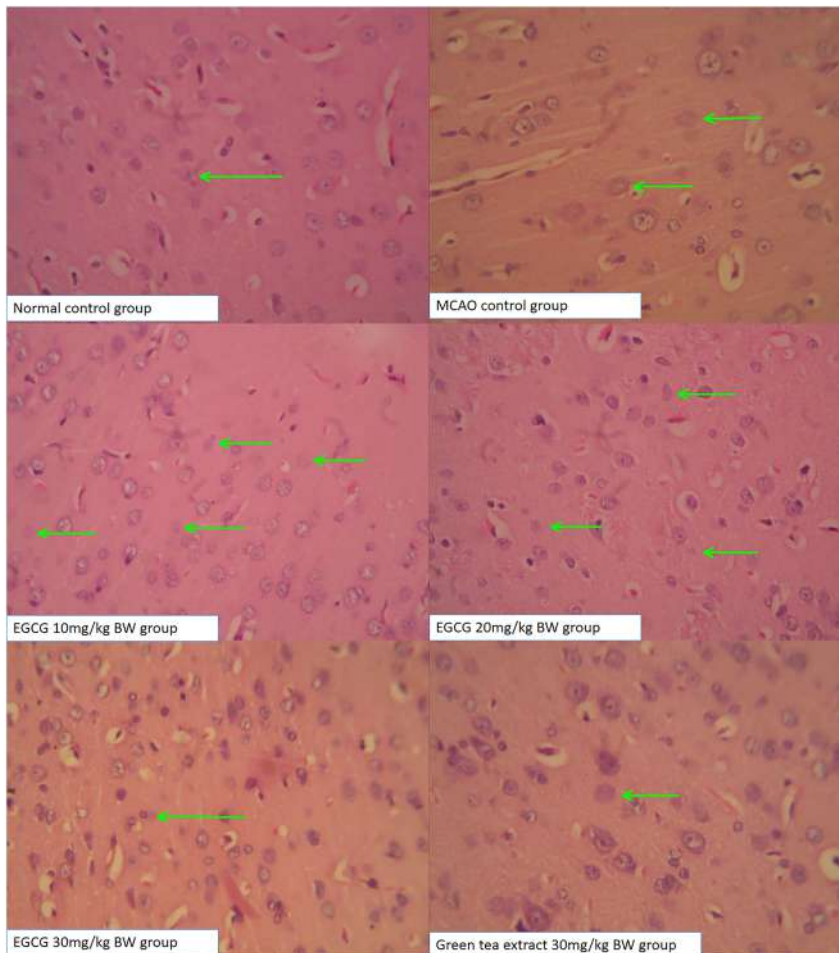
Thrombolysis therapy is the only available therapy for stroke currently and has 4–5 h to its therapy window. While it is too long from the onset, intracranial hemorrhage is commonly found as a major complication of

thrombolysis therapy [19]. Necroptosis described as programmed necrosis and apoptosis are regulated cell death mechanisms that happen during neurological damage process in stroke [20]. During its pathway, necroptosis will cause oxidative stress as result of an increasing number of reactive oxygen species. Mitochondrial respiratory chain primarily produces reactive oxygen species, xanthine oxidase and NADPH oxidases which leads to imbalance because of the spontaneous reperfusion or reperfusion caused by administration of pharmacological agents [21].

Green tea is commonly found in 30 countries and it is the most commonly consumed beverage worldwide [22]. Green tea is also used as a herbal plant in India and China [23]. The major catechin component of green tea is EGCG out of four catechin found in green tea [24]. Green tea antioxidant effect is already *in vivo* and *in vitro* approved. Its antioxidant effect shows similarity to antioxidant effect to  $\alpha$ -tocopherol. Green tea also contains five times antioxidants effect compared to black tea [22].

Inhibition process of necroptosis was done by decreasing ROS by antioxidant effect produced by EGCG. EGCG will inhibit ROS produced by inhibiting some mechanisms in the necroptosis pathway. First, damaged mitochondria produce ROS, which then stimulate RIP1 and receptor-interacting protein 3 (RIP3) oxidation in three sites of cysteine (c257, c268 and c586) which also promote autophosphorylation of RIP1 and RIP3 at Ser161 so that necroptosis pathway is activated [13]. The second is inhibition toward positive feedback of ROS to increase production of necrosome in necroptosis [25]. Third, EGCG is capable of activating caspase 3 and 8 after 8 h of green tea therapy [26, 27]. Activation of caspase 8 leads to the discontinuation of necroptosis pathway. EGCG also inhibits synthesis of some inflammatory mediators: TNF- $\alpha$ , IL-6 and IL-8 [28, 29]. Fourth, EGCG is able to decrease expression of tumor necrosis factor receptor 1 (TNFR1) and RIP3. TNFR1 and RIP3 start to decrease in administration of 20 mg/kg BW EGCG in rat with MCAO model [30].

Neuron cell undergoing necroptosis is shown as an arrow in Figure 1, neuron cell as pale, faded, nonprominent nucleus. By comparing the intensity of necroptosis cell, our study shows that there is reduction in neuronal cell death necroptosis morphology during histopathological examination. The administration of EGCG 20 mg/kg BW, EGCG 30 mg/kg BW, and green tea extract 30 mg/kg BW shows statistically significant reduction in neuronal cell necroptosis morphology. The most significant dose is EGCG 30 mg/kg BW. The EGCG effect is dose-dependent as there is an increase of EGCG effect as we elevated the dose.



**Figure 1:** Histopathological examination result of hemisphere area in three groups (left to right): MCAO-control group, EGCG group and green tea extract group. Necroptotic neuronal cell showed in green arrow by pale, fade, nonprominent, pyknotic karyorrhexis nucleus. Necroptotic cell count can be seen decreasing in green tea extract group and EGCG group compared to MCAO-control group.

Thirty milligram per kilogram body weight dose EGCG is more effective for decreasing neuronal cell necroptosis rather than green tea extract. This is because one sachet of green tea extract only consists of 2.5% EGCG. It can be concluded that 30 mg/kg BW dose of green extract contains 0.75 mg/kg BW EGCG. As shown by p-value and mean value of proportion score, green tea extract 30 mg/kg BW produces the same effect as EGCG 20 mg/kg BW. This is due to other catechin contents such as (ECG, EC, EGC) also protein, amino acid, fiber, fat, and pigment found in green tea extract. The other catechin contents of green tea mentioned before produce synergic effect that make same antioxidant effect as EGCG of green tea extract achieved in lower dose. So, to produce the same significant effect as EGCG 30 mg/kg BW, we need a dose of green tea extract of 45 mg/kg BW (Using the ratio of 30 mg/kg BW green tea extract (0.75 mg/kg BW EGCG) which produces the same effect as pure EGCG 20 mg/kg BW).

If we applied to humans, the dose of 30 mg/kg BW/day of EGCG in rats is equal to 4.8 mg/kg BW/day EGCG. If we

used a standard weight of 70 kg, we need 336 mg of EGCG each day to decrease neuronal cell necroptosis. Using the same method, we need 504 mg of green tea extract each day. Generally, people consume three cups of green tea a day; 240 ml in each cup of green tea contains 187 mg of EGCG. So, each day people consumed 560 mg of EGCG [31]. As mentioned before, we need 336 mg of EGCG or 504 mg of green tea extract each day, and the average daily consumption of three cups a day is enough to achieve the dose of EGCG/green tea extract.

## Conclusions

*Camellia sinensis* (green tea) with its active compound EGCG decreases neuronal cell necroptosis morphology in MCAO models. EGCG effect is dose-dependent starting from 20 mg/kg BW and significantly reduces neuronal cell necroptosis in 30 mg/kg BW dose and 45 mg/kg BW for green tea extract.

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**Ethical approval:** Ethical approval was obtained from The Health Research Ethics Committee, Faculty of Medicine, Universitas Airlangga. Standardized animal protocol applied for all experimental animal included in this study.

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