DE GRUYTER

2018 · VOLUME 29 · ISSUE 6
ISSN 0792-6855 · e-ISSN 2191-0286

JOURNAL OF BASIC AND CLINICAL PHYSIOLOGY AND PHARMACOLOGY

DE G

www.degruyter.com/jbcpp

DE GRUYTER

JOURNAL OF BASIC AND CLINICAL PHYSIOLOGY AND PHARMACOLOGY

Ed. by Michal Horowitz

Objective

The Journal of Basic and Clinical Physiology and Pharmacology(*JBCPP*) is a peer-reviewed bi-monthly published journal in experimental medicine. JBCPP publishes novel research in the physiological and pharmacological sciences, including brain research; cardiovascular-pulmonary interactions; exercise; thermal control; haematology; immune response; inflammation; metabolism; oxidative stress; and phytotherapy. As the borders between physiology, pharmacology and biochemistry become increasingly blurred, we also welcome papers using cutting-edge techniques in cellular and/or molecular biology to link descriptive or behavioral studies with cellular and molecular mechanisms underlying the integrative processes.

Topics

- Behavior and Neuroprotection
- Reproduction
- Genotoxicity and Cytotoxicity
- Vascular Conditions
- Cardiovascular Function
- Cardiovascular-Pulmonary Interactions
- Oxidative Stress
- Metabolism
- Immune Response
- Hematological Profile
- Inflammation
- Infection
- Phytotherapy

Article formats

Research Articles, Reviews and Mini Reviews, Short Communications, Case Reports, Editorials and Letters to the Editor

SUBSCRIPTION RATES FOR 2019

Online:
Institutional
€ [D] 581.00 / US$ 872.00 / GBP 476.00*
Subscription
€ [D] 99.00 / US$ 149.00 / GBP 80.00*

Online ISSN: 2191-0286

Language of Publication: English

Subjects:
Clinical Medicine ▸ Clinical Medicine, other
Clinical Medicine ▸ Pharmacology, Toxicology

Of interest to: researchers and health professionals in the field of clinical physiology and pharmacology

CiteScore 2016: 1.01

SCImago Journal Rank (SJR) 2016: 0.349
Source Normalized Impact per Paper (SNIP) 2016: 0.495

Journal

*Prices in US$ apply to orders placed in the Americas only. Prices in GBP apply to orders placed in Great Britain only. Prices in € represent the retail prices valid in Germany (unless otherwise indicated). Prices are subject to change without notice. Prices do not include postage and handling if applicable. Free shipping for non-business customers when ordering books at De Gruyter Online. RRP: Recommended Retail Price.

Order now! orders@degruyter.com

to be 700 million people living with diabetes. The purpose of this systematic review was to provide an overview of the economic burden caused by Diabetes Mellitus for the government, health care providers, and for the community. Methods This systematic review was carried out by considering the related studies about the cost of illness, evaluation of disease costs, or therapeutic costs for various types of diabetes mellitus that were published in both English and Indonesian. The search engines PUBMED, DOAJ, SCOPUS, SCIENCE DIRECT, and GOOGLE SCHOLAR were used without date published restrictions. Results A systematic search identifies 18 eligible studies conducted in various regions in Indonesia. The study was retrospective with variation in their perspectives and methods to estimate the diabetes cost. Drug cost was the major contributor to direct medical cost followed by complications cost while other cost was affected by transportation cost, productivity losses, and time spent by family accompanying patients. Conclusions Diabetes mellitus creates a significant financial burden and affects the health care system as well as the individual and society as a whole. Research about the cost of diabetes in the future should be carried out on a large scale in order to get a more specific cost estimation.

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

Abstract

Objectives The use of modern technology and social media has revolutionized the way health information is distributed to diabetes mellitus patients. Social media can be used as a medium of providing health interventions to improve patient health outcomes. Social media is able to provide a more intensive communication facility between healthcare professionals and patients. We aim to systematically review and describe the effect of social media interventions on health outcomes of patients with diabetes mellitus. Methods A systematic review was carried out from three electronic databases (Pubmed, Scopus, and Medline). Eligible publications are studies that describe the application of social media interventions on the health outcomes of patients with diabetes mellitus. Results Fourteen studies were selected for this systematic review, 10 studies with a randomized controlled trial design, and 4 studies with a nonrandomized controlled trial design. Six studies only used interventions using social media, A blend of

face-to-face social media intervention was used in 6 studies, 2 studies used a combination of telephone and social media intervention. One study had treatment behavior outcomes with improvement in treatment behavior, 6 studies had clinical outcomes (an improvement in HbA1c values in the four studies), 6 studies had treatment behavior outcomes and clinical outcomes (1 study had improved treatment behavior and clinical outcomes, 3 studies had improved treatment behavior outcome only), and 1 study had medication adherence outcome (no improvement in medication adherence). Conclusions These findings indicate that the intervention using social media can improve the health outcomes of diabetes mellitus patients.

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

Abstract

Objectives Valproic acid (VPA) is a broad-spectrum antiepileptic drug with known efficacy profile in pediatric patients, despite of its narrow therapeutic index. There is lack of VPA's pharmacokinetics profile in Indonesian pediatric subjects, partly due to limited pediatric blood volume taken for conducting therapeutic drug monitoring. This study aimed to determine the correlation between VPA pharmacokinetics parameters based on population data and seizure frequency in pediatric epilepsy outpatients. Methods This observational study was conducted at Sanglah General Hospital during June–December 2019. The subjects of this research were 38 pediatric epilepsy patients who adhered to VPA syrup monotherapy for at least 3 weeks. Five subjects randomly selected for blood sample collection. Thus, VPA concentration level in the blood being analysed as a comparison to its concentration predicted from Yukawa's steady state equation. Monolix2019R2 ® software was used to identify VPA population pharmacokinetics–pharmacodynamics (PK–PD) parameters at steady state level. Results Population PK–PD of VPA syrup at steady state level were ka_pop = 6.25/h, Vd_pop = 3.36 L, Cl_pop = 3.17·e −11 mL/min, IC 50 _pop = 1.85·e −6 , correlation of Vd_pop and Cl_pop = 0.966. Kendall Tau Correlation of predicted VPA steady state concentration and frequency of seizure was −0.66. Mean prediction error between predicted steady state concentration of five subjects and their related blood levels was ≤25% and

considered as within clinically acceptable limit. Conclusions It needs further study to develop best matched PK–PD model of VPA syrup at steady state condition in pediatric epilepsy.

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

Abstract

Objectives Alzheimer's disease (AD) is a degenerative brain disease characterized by confusion, behavior changes, decline in memory and cognitive skills. One of the strategies in the treatment of AD is to use acetylcholinesterase (AChE) inhibitors. The current study aims to determine the AChE inhibitory activities of the extract and fractions of the root of Rauvolfia serpentina . Methods Extraction was carried out by maceration method using ethanol, followed by liquid–liquid partition using n -hexane, ethyl acetate and n -butanol. Further fractionation was conducted by using vacuum liquid chromatography (VLC). The AChE inhibitory assays were performed by using Ellmann's method. Phytochemical screening was carried out by TLC method. Results The ethanolic extract of R. serpentina showed inhibition against AChE enzyme with an IC 50 value of 7.46 µg/mL. The extract and fractions showed higher inhibition against butyrylcholinesterase (BChE) compared to AChE. Amongst three fractions obtained, the n -butanol fraction showed the strongest inhibition with an IC 50 value of 5.99 µg/mL against AChE. VLC fractionation of the n -butanol fraction yielded 13 subfractions (VLC 1–VLC 13). Four out of 13 subfractions gave more than 80% inhibition against AChE, namely subfractions 4–7, with IC 50 values ranging from 4.87 to 47.22 µg/mL. The phytochemical screening of these subfractions suggested the presence of alkaloids. Conclusions The ethanolic extract, as well as fractions of R. serpentina root, are potential for AChE inhibitor. The alkaloid compound may be responsible for this activity.

Unlicensed | June 25, 2021

Green tea and its active compound epigallocathechin-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

Abstract

Objectives To determine the effect of green tea with the active ingredient epigallocathechin-3-gallate (EGCG) on the inhibition of apoptosis in the middle cerebral artery occlusion (MCAO) model. Methods Four month old male Rattus norvegicus rats with a body weight of 200–275 g was used for the MCAO model and divided into five groups, and the treatment was carried out for 7 days. Before being sacrificed, the subject had 1 cc of blood drawn for high mobility group box 1 (HMGB-1) examination using enzyme-linked immunosorbent assay (ELISA), and after being sacrificed, the brain tissue specimen was taken to examine caspase-3 and B-cell lymphoma 3 (BCL-3) using immunohistochemistry methods. Results There was no significant difference in HMGB-1 results for the treatment group compared to the control group (P1: 384.20 ± 231.72 [p = 0.553]; P2: 379.11 ± 268.4 [p = 0.526]; P3: 284, 87 ± 276.19 [p = 0.140]; P4: 435.32 ± 279.95 [p = 0.912]). There is a significant increase in BCL-2 expression between the treatment group compared to the control group (P1: 2.58 ± 0.51 [p = 0.04]; P2: 3.36 ± 0.50 [p<0.001]; P3: 4.00 ± 0.42 [p<0.001]; P4: 3.60 ± 0.52 [p<0.001]). There was a significant difference in caspase-3 expression compared to the control group in the P3 group (P1: 4.33 ± 0.49 [p = 0.652]; P2: 4.09 ± 0.30 [p = 0.136]; P3: 3.58 ± 0.51 [p = 0.01]; P4: 3.89 ± 0.42 [p = 0.063]). There is no correlation between HMGB-1 and caspase-3 (r = −0.063; p = 0.613) or BCL-2 (r = −0.106; p = 0.396). There is significant negative correlation between caspase-3 and BCL-2 (r = −0.459; p = 0.000). Conclusions Green tea with the active ingredient EGCG can inhibit neuronal cell death through the apoptotic pathway and not through the activation of HMGB-1.

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

Abstract

Objectives Tobacco smoking remains the primary cause of preventable mortality and morbidity in the world. The complexity of the nicotine dependency process included the withdrawal effect that triggers recurrence being the main problem. Quercetin, known as an antioxidant, binds free radicals and modulates endogenous antioxidants through Nrf2 activations is expected as a potential agent to reduce the risk of nicotine dependence. This research aims to evaluate quercetin's effects on reducing the risk of nicotine

addiction. Methods Conditioned Place Preference (CPP) with a biased design was used to evaluate nicotine's reward effects in male Balb/C mice. Preconditioning test was performed on day 1; conditioning test was done twice daily on day 2–4 by administering quercetin (i.p.) 50 mg/kg along with nicotine (s.c.) 0.5 mg/kg or Cigarette Smoke Extract (CSE) (s.c.) contained nicotine 0.5 mg/kg; and postconditioning test was performed on day 5 continue with extinction test on day 6, 8, 10, 12, and reinstatement test on day 13. The duration spent in each compartment was recorded and analyzed. Results Nicotine 0.5 mg/kg and CSE 0.5 mg/kg significantly induced reward effects ($p<0.05$). There was no decrease of reward effect during the extinction-reinstatement stage of the postconditioning phase ($p>0.05$), while quercetin 50 mg/kg both induced along with nicotine or CSE was able to inhibit the reward effect of nicotine ($p>0.05$). Conclusions Quercetin reduced the risk of nicotine dependence and has a potential effect to use as a therapy for nicotine dependence, especially as a preventive agent.

Unlicensed | June 25, 2021

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

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

Page range: 335-340

Abstract

Objectives Depression is a mental disorder that profoundly affects all aspects of life, but currently, antidepressants have some problems with their effectiveness and side effects. Resveratrol is a compound that has the ability to regulate the hypothalamic-pituitary-adrenal axis. This study aimed to determine resveratrol's effect on physical and psychological stress-induced depressive-like behavior. Methods Mice were divided into control, physical stress, psychological stress groups. Treatment was conducted with fluvoxamine 20 mg/kg and resveratrol 20, 40, and 80 mg/kg for seven days. The depressive-like state was evaluated using a forced swim test (FST), tail suspension test (TST), and open field test (OFT). Results Physical stress and psychological stress induction increase the immobility time on FST and TST. Besides, there is an increase in time in central on OFT, which indicates an anxiety or mental illness-like behavior. However, the OFT examination on sniffing, rearing, grooming, and crossing behavior did not show a significant difference. Resveratrol 80 mg/kg and fluvoxamine 20 mg/kg were significantly reduced immobility time at TST compared to the physical stress group. While in psychological stress, resveratrol 80 mg/kg tended to decrease

immobility time but not significant. A significant increase in time in central duration was seen in the resveratrol 40 mg/kg compared to the psychological stress. Stress induction causes increased amygdala corticotrophin-releasing factor (CRF) mRNA expression. However, neither resveratrol nor fluvoxamine affected amygdala CRF mRNA expression. Conclusions Resveratrol ameliorates depressive-like behavior induced by physical and psychological stress.

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

Abstract

Objectives The Subjective Well-Being under Neuroleptic (SWN) Scale is a self-rating scale measuring the well-being of patients with schizophrenia under antipsychotic drug treatment. The instrument has been globally used, with issues regarding the well-being assessment scale across different cultures, patient characteristics, and country-setting remains a controversy. This study aimed to translate and culturally adapt the SWN scale into the Indonesian version (Indonesian Modified SWN or IM-SWN) and evaluate its validity and reliability. Methods The SWN instrument was translated and culturally adapted following internationally accepted procedures, including forward translation, expert panel review, backward-translation, pretesting and cognitive interviewing, and psychometric analysis for the final version of the scale. The translated instrument was tested on 108 schizophrenia patients. The instrument's validity and reliability were assessed using Pearson's correlation and Cronbach's Alpha coefficient. Additional analysis for the socio-demographic and psychometric properties of the patient was also conducted. Results The range of IM-SWN total score between 30 and 112. IM-SWN was found to have a high-reliability coefficient (0.897), and the internal consistency values of each question item ranged between 0.885 and 0.910. The results also showed a high correlation between five order factors (Physical functioning, mental functioning, self-control, emotional regulation, and social integration), with a total score of between 0.768 and 0.885. Conclusions This study highlighted that the IM-SWN is a valid and reliable instrument for measuring well-being among the Indonesian population with schizophrenia.

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 Budiatin, Dwi Setyawan, Junaidi Khotib

Page range: 349-355

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.

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

Abstract

Objectives This study aimed to evaluate the knowledge and attitudes of healthcare professionals on prescribing errors. Methods This was a cross-sectional study employing a questionnaire that consisted of 12 items on knowledge and 10 items on healthcare professionals' attitudes toward errors in prescribing process. The participants responded to the questionnaire with a 5-Likert scale of agreement. The domains assessed in the questionnaire

were respondents' knowledge and attitudes on prescribing errors, professionals responsible for the errors, and professionals' competence on drug dose adjustment. Additionally, the questionnaire had two case scenarios to further assess the healthcare professionals' knowledge of prescribing errors. There were 300 questionnaires administered to physicians, nurses, and pharmacists who attended conferences in Denpasar from July to October 2019. Results There were 30 physicians, 58 nurses, and 69 pharmacists who responded to the survey. A response rate of 52.3% (157/300) was obtained. All healthcare professionals agreed that errors may occur in prescribing, dispensing, and administration process. All healthcare professionals understood that physician is responsible for ensuring drug safety in prescribing process and also supported a standardized form on drugs which may need drug dose personalization. Concerning item on the importance of collaboration in drug dose adjustment, although the healthcare professionals agreed on the statement, they had significant differences on the level agreement on the statement ($p=0.029$). The healthcare professionals also supported having regular training on drug dose adjustment based on individual patients' regimentation. The healthcare professionals' responses showed that the significant differences found on the statement of healthcare professionals should have competency on personalized dose calculation ($p<0.001$). All healthcare professionals agreed that physicians should have competency on drug dose adjustment, yet physicians showed less agreement that other health professionals should have the competency. Conclusions All healthcare professionals understood that medication errors may occur during the prescribing process but showed different attitudes on professionals who had competence in drug dose calculation. They emphasize the need to have a standardized prescription format for medication with dose changes. The respondents also recommend having regular training on medication safety for healthcare professionals.

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

Abstract

Objectives Human epidermal growth factor receptor type 2 (HER2)-expressing breast cancer patients indicate poor prognosis in disease progression. HER2 overexpression can increase activities of Ras-mitogen

activated protein kinase (Ras-MAPK) pathway and Janus Kinase (JAK)-STAT3, increasing breast cancer cell proliferation as demonstrated by marker Ki67. Therapeutic options for HER2-expressing breast cancer are limited and have major side effects, so anticancer development as an antiproliferative is needed. From previous research, synthetic chemical 4-(tert -butyl)- N - carbamoylbenzamide (4TBCB) compound has cytotoxic activity in vitro on HER2-expressing breast cancer cells. This study wanted to determine the mechanism 4TBCB compound in inhibiting HER2 signaling through Rat Sarcoma (Ras) and signal transducer and activator of transcription 3 (STAT3) pathway in HER2-expressing breast cancer cells. Methods Breast cancer cells were isolated from the biopsy tissue of breast cancer patients. The isolated cells were cultured and given 4TBCB test compound with three concentrations (0.305, 0.61, and 1.22 mM) and lapatinib 0.05 mM as a comparison compound. Cancer cell cultures were stained with monoclonal antibodies phosphorylated HER2 (pHER2), phosphorylated Ras (pRas), phosphorylated STAT3 (pSTAT3), and Ki67. The expression of pHER2, pRas, pSTAT3, and Ki67 proteins was observed using the immunofluorescence method and the results were compared with control cells, namely cancer cells that were not given 4TBCB and lapatinib but stained with monoclonal antibodies. Results 4TBCB compounds (0.61 and 1.22 mM) and lapatinib can reduce pHER2, pRas, pSTAT3, and Ki67 expressions compared to control cells. Conclusions 4TBCB compounds (0.61 and 1.22 mM) can reduce pHER2, pRas, pSTAT3, Ki67 expressions and predicted to inhibit HER2 signaling through the Ras and STAT3 pathways in HER2-expressing breast cancer cells.

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 Budiatin, Siswandono Siswodihardjo, Junaidi Khotib

Page range: 373-377

Abstract

Objectives Bone defect is serious condition that is usually caused by traffic accident. Chitosan is a polymer developed as a scaffold to treat bone defect. However, the mechanism by which chitosan can accelerate bone growth in defect area is still unclear. This study aims to identify proteins which are crucial to the osteogenic properties of chitosan monomer using an in silico study. Methods Molecular docking was carried out on chitosan monomer, which are d -glucosamine and glucosamine 6-phosphate units against bone morphogenetic protein 2 (BMP-2), fibronectin, fibroblast growth factor (Fgf),

and phosphate transporter (PiT) using AutoDock Vina. Ligand preparation was carried out using Chem3D version 15.0.0.106, while protein preparation was performed using AutoDockTools version 1.5.6. Results The results showed that glucosamine 6-phosphate had the best binding affinity with fibronectin and PiT, which was −5.7 kcal mol −1 on both proteins, while d -glucosamine had the best binding affinity with PiT (−5.2 kcal mol −1). Conclusions This study suggests that the osteogenic properties of chitosan may be due to the presence of bonds between glucosamine units and fibronectin and/or PiT. However, in vitro studies need to be done to prove 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

Abstract

Objectives Native Bacillus thuringiensis BK5.2, isolated from soil of Baluran National Park, East Java, Indonesia, has been shown to be toxic against Aedes aegypti larvae. This study aims to determine the strength and the speed of the toxicity of B. thuringiensis BK5.2 against A. aegypti larvae in lethal concentration (LC) and lethal time (LT), as well as detection of toxin structure and parasporal inclusion. Methods LC values were determined by the mortality of A. aegypti third instar larvae after 24 and 48 h exposure to five various concentrations of B. thuringiensis BK5.2, while LT values were determined based on the mortality of A. aegypti third instar larvae due to exposure to LC 90 concentration at 0; 0.5; 1; 2; 4; 8; 10; 20; 24; and 48 h. Larvicidal toxicity was determined based on value of LC 50 and LC 90 (CFU/mL), as well as LT 50 and LT 90 (hours) analysed with Probit analysis. Parasporal inclusion was detected using transmission electron microscope (TEM) and scanning electron microscope (SEM). Results Based on bioassay, LC 50 and LC 90 values were 11.6 × 10 6 and 22.7 × 10 6 CFU/mL, respectively, at 24 h exposure, as well as 8.3 × 10 6 and 15.4 × 10 6 CFU/mL, respectively, at 48 h exposure, while the value of LT 50 and LT 90 were 19.0 and 26.6 h, respectively. Morphological observation of the dead larvae showed there was damage on abdomen and thorax region. Detection by TEM and SEM showed there was cuboidal parasporal inclusion. Conclusions Native B. thuringiensis BK5.2 has high toxicity against A. aegypti larvae and detected flatcuboidal toxin in parasporal inclusion.

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 Widyowati, Galih Satrio Putra, Tutuk Budiati, Katsuyoshi Matsunami

Page range: 385-392

Abstract

Objectives This study aims to synthesize a series of benzoxazines (1 – 5) to be examined as an epidermal growth factor receptor (EGFR) inhibitor by in-silico study. The overexpression of EGFR causes the growth of normal lung cells to become uncontrollable, which may lead to cancer formation. We also conducted the absorption, distribution, metabolism, excretions and toxicity (ADMET) properties evaluation and also examined in vitro anticancer assay on human lung cancer cells line, which is A549. Methods Benzoxazines (1 – 5) were synthesized by reacting anthranilic acid and benzoyl chlorides. The structures of the compounds were determined with 1 H, 13 C-NMR, HRMS, UV and FT-IR spectrometric methods. Prediction of ADMET was using online pkCSM, and the molecular docking studies were using MVD with EGFR-TKIs as the target (PDB ID: 1M17). In vitro assay of anticancer activity was performed by MTT assay. Results Compounds 1 – 5 were successfully synthesized in good yields (71–84%). The ADMET prediction showed that benzoxazines are able to be absorbed through GIT, metabolized by CYP 450, and not hepatotoxic. The title compounds have a greater Moldock Score than Erlotinib, and 3 has the highest activity against A549 compared with other benzoxazines, IC 50 =36.6 μg/mL. Conclusions Compound (3) more active as anticancer against Human cancer cells line compared with other benzoxazines.

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 Widiandani

Page range: 393-401

Abstract

Objectives The high prevalence of HER2-positive breast cancer has become a significant concern in the health sector. The problem is more complex with the side effects of breast cancer drugs currently used. Thymoquinone (TQ), the main bioactive compound in Nigella sativa , has been shown to have

anticancer activity. However, it is necessary to modify the structure of the thymoquinone derivatives to improve drug bioavailability. This study uses an in silico approach to predict pharmacokinetic profile, docking, quantitative structure–properties relationship (QSPR) of new thymoquinone-derived compounds as candidates cytotoxic agent for breast cancer with HER-2 positive. Methods The prediction of ADMET was using pkCSM online. Molecular docking was used to determine thymoquinone derivatives activity using Molegro Virtual Docker version 5.5 by docking the thymoquinone derivatives to the HER2 receptor targets, PDB ID 3PP0 and QSPR analysis using the IBM SPSS 21 version. Results The 35 thymoquinone derivatives showed good physicochemical and absorption properties and not hepatotoxic, so they are suitable for oral drugs. The molecular docking of 35 thymoquinone derivatives against 3PP0 proteins showed better activity than thymoquinone. One of the thymoquinone derivatives, TQ 15, showed the largest negative RS value, meaning that is predicted to have the highest anticancer activity. Based on the QSPR analysis, the essential parameter in determining 35 thymoquinone derivatives activity was the lipophilic and steric parameter. Conclusions Based on in silico test, thymoquinone derivative, TQ 15, had the potential to be further developed as a HER2-positive breast cancer drug.

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

Abstract

Objectives The aim of this study was to identify the patterns of medication load, its medication burden, coordination of healthcare and patient's understanding of their conventional cardiac medications and related herbal-derived preparations. Methods The study is a mixed-method both, quantitative and qualitative approach, which involved Filipino elderly patients (n=69) enrolled in the outpatient service of the National Center for Geriatric Health, Manila. Data were gathered through face-to-face surveys and interviews using a semi-structured questionnaire. Descriptive statistics were used during data analysis. Thematic analysis was also used to emphasize patterns in the responses of the participants. Results Respondents were knowledgeable on the name (86.9%), visual characteristics

(78.3%), and indication and administration of their medicine (88.4%). The frequency of their doctor's information on the possible side effects of the medicines was noted. The almost negligible difference in the proportions of those who asserted during the information dissemination on the medication side effect by their doctors was observed (<10.5%). Association on the age and awareness of any interaction on the drugs they are taking (p=0.032) and an association between the gender and awareness of the doctor/pharmacists about other drugs the patient is taking (p=0.033) were observed. During thematic analysis, elderly respondents were keen on the physician's advice than that of the pharmacist. This is due to the limited knowledge of elderly patients on the role of pharmacists to conduct medication counseling. Conclusions The majority of the elderly patients recognized the purpose and extent of medication. It was noted that pharmacists play a limited role in understanding selected Filipino elderly patients on their medication. Lack of communication between the patient and the pharmacist was noted as preliminary findings in the study. Respondents were not yet informed of the responsibility of the pharmacist to provide information regarding their medication. Integration of pharmacists' care for geriatric health must be strengthened and highly recommended. Supervision by the healthcare professionals, particularly by the pharmacists, must be fully established.

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

Abstract

Objectives This study aimed to validate the questionnaire on the health belief model questionnaire to assess health beliefs that could influence adherence to hypertension in the elderly. Methods The questionnaire was based on a study of the literature and discussion with experts. The questionnaire was then circulated via social media. Participants who met the following criteria were asked to participate in the study: (1) aged 60–79 years of age, (2) had antihypertensive medications in the last three months, and (3) had a mobile phone with an active number. The questionnaire consists of six domains: perceived susceptibility, perceived severity, perceived threat, perceived benefits, perceived barriers, and perceived self efficacy. The findings were grouped by domain and tested for reliability and validity using SPSS ver.24. Results Thirty participants completed the questionnaire. Each domain was tested for its reliability and validity at a value of 0.05. The result shows that

each domain had a Cronbach's alpha value greater than 0.7, with a total score of 0.89 indicating that all domains in the questionnaire were reliable. Furthermore, of the 49 items in the questionnaire, only two items were invalid while the rest of the items demonstrated their validity based on the Pearson Correlation (>r table 0.361; p<0.05). Conclusions This self administered health belief model questionnaire was a valid and reliable instrument to assess health beliefs in elderly with hypertension.

Unlicensed | June 25, 2021

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

Denny Ardhianto, Suharjono, Soedarsono, Umi Fatmawati

Page range: 421-427

Abstract

Objectives Indonesia is one of the top 20 countries with the highest prevalence of drug resistant tuberculosis (DR-TB) worldwide with a percentage of new cases of 2.4% and retreatment of 13%. Bedaquiline (BDQ) is one of the drugs that used in the individual long regimen treating DR-TB. BDQ is also combined with levofloxacin (LFX) and/or clofazimine (CFZ) that can cause QTc interval prolongation. The aim was to study the differences in the use of BDQ regimens to the lengthening of the QTc interval and to study risk factors (diabetes, hypokalemia, sex, BMI, and age) in BDQ regimen. Methods This study was an observational retrospective study with a total sampling method, which was conducted at Dr. Soetomo General Hospital Surabaya. Samples from this study were patients diagnosed with DR-TB at Dr. Soetomo General Hospital Surabaya in the period of January 2015–December 2019 who used BDQ regimen and met the inclusion criteria. The ECG data were analyzed from the mean of each group (BDQ regimen and risk factors), also analyzed using statistical analysis. Results Data obtained from total sample in this study were 73 patients. The most widely used different regimens in this study were the combination of BDQ + LFX by 36 patients (49.3%), BDQ + LFX + CFZ by 16 patients (21.9%), BDQ by 11 patients (15.1%) and BDQ + CFZ 10 patients (13.7%). Out of 73 patients, 52 patients (71.2%) experienced lengthening of the QT interval and grade 1 of QTc interval prolongation occurred in most patients and also the onset was mostly one month after using BDQ regimen. The side effects of QTc interval prolongation from groups of combination and risk factors were no difference in each month (p>0.05). Conclusions This study can be concluded that there were no differences in the QTc prolongation between the groups of BDQ regimen

(BDQ, BDQ + LFX, BDQ + CFZ and BDQ + LFX + CFZ) and the groups of risk factors.

Unlicensed | June 25, 2021

Shallot skin profilling, 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

Abstract

Objectives Medicinal plants are a source of many compounds that are useful in the pharmaceutical field for novel drug development. Polyphenols and the flavonoid group in plants are known to have several activities, such as relieving cardio vascular disease (CVD). The outer skin of the shallot which is disposed of as waste is known to have an antiplatelet activity which was tested in vitro assay. To date, there is no study reported on the ADMET profile and physicochemical properties of the active component of the shallot skins. Methods The extraction of shallot skins was conducted by ultrasonic irradiation using ethanol. The phytochemical screenings were carried out by TLC and color reaction. The profiling of its active ingredient was presented by GC-MS, HPLC and spectrophotometry UV–vis. Whereas their physicochemical properties were analyzed by ChemDraw 17.00 program and the ADMET predictions were studied using pkCSM online tool. The MVD program was operated in the docking study on protein P2Y12 (PDB ID 4PXZ). Results The extract showed the presence of polyphenol, flavonoids, quercetin, natalensine-3,5-dinitrobenzoate; bis[2-(2-fluorophenyl)-6-fluoroquinolin-4-yl]amine, benzo[a]heptalene, N -(trifluoroacetyl) methyl- N -deacethyl-colchicine. The ADMET prediction data displayed that the compounds in the extract have good absorption so that they can be used in the oral and transdermal routes. Some components in the extract have lower MDS than clopidogrel. Conclusions The ultrasonicated shallot skin extract can be used as additional resources of the active pharmaceutical ingredients and to have the potency to be developed as an oral or transdermal preparation.

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

Abstract

Objectives Coronary artery disease (CAD) is one of the main causes of death from cardiovascular disease, because heart attacks result in atherosclerosis which causes narrowing of the arteries. Atorvastatin has a pleiotropic effect as anti-inflammatory through one of the target levels of High Mobility Group Box-1 (HMGB-1). This prospective observational study aimed to analyze the effect of atorvastatin on serum HMGB-1 levels in CAD. Methods Samples were collected from prospective observation pre–post study in May–July 2018 with consecutive sampling method. Serum HMGB-1 levels were measured in patients with CAD who were given atorvastatin for CAD with type-2 diabetes mellitus compared without type-2 diabetes mellitus in a patient ward. Blood was collected on admission day and before the patient left the hospital. After centrifugation, serum samples were stored at −80 °C before measurement. We used an ELISA kit (IBL International) to determine HMGB-1 concentrations. This research protocol has been approved by the Ethical Committee of Dr. Soetomo General Hospital, Surabaya. Results We enrolled 38 patients and divided them into two groups which 19 patients on CAD with type-2 diabetes mellitus and 19 patients without diabetes mellitus. Serum HMGB-1 levels in CAD with type-2 diabetes mellitus were increased significantly (p = 0.049) and not significantly decreased in CAD without type-2 diabetes mellitus (p = 0.480). The HMGB-1 level was not significantly different between the two groups (p = 0.210). Conclusions HMGB-1 levels after providing atorvastatin in CAD with type-2 diabetes mellitus increased significantly, meanwhile, in CAD without type-2 diabetes mellitus did not decrease significantly. The HMGB-1 level was not significantly different between the two groups. Longer time and more point for the collected sample needed for further research.

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

Abstract

Objectives Heart disease is a clinical condition characterized by specific signs such as joint inflammation, weakness, and shortness of breath. Left ventricular remodeling can be experienced by patients with heart failure wherein a change in myocyte and nonmyocyte components occurs. One of the biomarkers in heart disease with myocardial fibrosis is matrix metalloproteinase-9 (MMP-9). Common therapy that is often given to patients with heart failure is ACE inhibitors. This main objective of this research is to investigate the effect of ACE inhibitor therapy on the degrees of MMP-9 as a biomarker among patients with heart disease. Methods This research applied one group pretest–posttest design to analyze the variation in the levels of MMP-9 as a biomarker for heart function. Twenty-three subjects with acute heart disease met that inclusion also exclusion criteria, who were selected using nonrandom sampling. Statistical analysis was conducted to specify the levels of MMP-9 before, after the administration of therapy. Results The most widely used ACE inhibitor drug was ramipril for 15 patients (65%), and the least used ACE Inhibitor drug was captopril for two patients (9%). Meanwhile, the mean MMP-9 levels before therapy was (1,915.26 pg/mL ± 260.84), and the mean MMP-9 levels after therapy was (1,916.93 pg/mL ± 383.12). The statistical analysis result revealed no significant difference in the degrees of Matrix Metalloproteinase-9 accumulation (p=0.378). Conclusions There was no significant reduction in the levels of Matrix Metalloproteinase-9 after pretest and posttest.

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

Abstract

Objectives Medication non-adherence mostly occurs in patients with a wide range of disease severity, including asthma. The aim of the study was to assess the self reported adherence to asthma therapy and investigate the relationship between adherence, asthma control and asthma-related quality of life. Methods The study was a cross-sectional study in which participants were recruited from an outpatient department, in one hospital in Surabaya. Patients (aged≥18 years) with asthma who had used any regular asthma medications were included. Standardised questionnaires, including Juniper's

Asthma Control Questionnaire (ACQ), Adherence to Refills and Medications Scales (ARMS) and Juniper's Asthma Quality of Life Questionnaire (AQLQ) were used. Results A total of 82 adults with asthma were recruited in the study. Male participants' mean age was 49.13 ± 14.10 years (n = 23). Approximately 59 participants (72.0%) were females, 30 participants (36.5%) were using Budesonide inhaler, and 73 participants (89.0%) never smoked. The mean of ACQ, AQLQ, and ARMS scores were 1.62 ± 1.19, 4.96 ± 1.24, and 16.98 ± 4.12, respectively. Of 82 patients studied 53 (64.6 %) had "uncontrolled asthma" and more than 85% participants both showed "non adherence" to asthma therapy and nearly 46% of them indicated that their quality of life was affected by asthma. There was a significant association between ACQ and AQLQ ($p<0.05$), whereas no statistically significant association was found between ACQ and ARMS. Conclusions The majority of patients reported non-adherence to asthma medications. Poor controlled asthma has been associated with lower asthma-related quality of life.

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

Abstract

Objectives Hypertension is one of the main factors in increasing the risk of cardiovascular disease with 51% reported cause of death in chronic kidney disease (CKD) patients with end-stage renal disease (ESRD). It is a comorbid that needs to be managed properly and gets special attention from various health disciplines including a pharmacist. Methods This was a quasi experimental study with pretest–posttest intervention using home pharmacy care (HPC) counseling both on the counseling and the noncounseling group. Initial data collection and informed consent was done at the Hemodialysis Unit Aloei Saboe and Toto Kabila Hospital, Gorontalo. The parameters in the study were patients' compliance to their medication using the Medication Adherence Questionnaire (MAQ) and Pill Count Adherence (PCA) questionnaires and the patient's blood pressure. Results Fifty-eight patients met the inclusion criteria and were divided into two groups (the counseling group and the noncounseling group). Based on MAQ and PCA, the level of patient medication adherence increased significantly in the counseling group compared to the noncounseling group with a significance value of $p<0.05$. Increasing adherence was correlated with patients' outcome of lowering blood pressure. More patients in the counseling group showed

decrease in systolic and diastolic blood pressure compared to the noncounseling group (86.2 vs. 17.2% for systolic BP and 69 vs. 10.3% for diastolic blood pressure (BP). Following adjusted confounding variables, counseling through HPC provided a chance of decreasing systolic blood pressure 32 times (95% CI: 7.198–144.550) and diastolic blood pressure 42 times (95% CI: 6.204–286.677). Conclusions HPC affects the improvement of patient medication adherence and reduction of blood pressure in hemodialysis patients with hypertension.

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

Abstract

Objectives Uncontrolled asthma may be life-threatening. Poor understanding of disease process and appropriate medication use appears to influence community attitude in facing asthmatic patients in an emergency, thereby contributing to increasing the risk of mortality. This study aimed to analyze community-level knowledge about asthma and attitude towards asthma management. Methods This observational, cross-sectional study was conducted among the community in Gresik, Indonesia, from March to July 2019. Participants included in this study were adults, who could read, write, and communicate well. Data were collected through questionnaires to evaluate the level of knowledge and attitude towards asthma. Results In total, 100 respondents were selected with 91% of women, with a mean age of 49.11 ± 14.42 years and with various levels of education. The respondents had good knowledge by getting a score of 76%. Knowledge regarding recognition of asthma symptoms was scored the highest (83%). However, knowledge about medication use for asthma was lacking, especially in identifying the medicine choice (21%) and inhaler use (48%). The respondents also showed a ‘positive’ attitude with a score of 89%. Most respondents (72%) agreed that when inhaled drugs were unable to relieve the asthma attack, they need to bring the patient to a hospital. Conclusions The level of respondent’s knowledge in recognizing asthma symptoms was good, but there were misconceptions about asthma medication, especially in inhaler use. Overall, the respondents had a positive attitude towards asthma perception and management.

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

Abstract

Objectives One of the methods used to treat coronary artery disease (CAD) is anticoagulant therapy, which involves administering anticoagulants to patients that inhibit the arrangement and actuation of clotting factors. Anticoagulant therapy in patients with CAD must be monitored and evaluated because its greatest side effect is the risk of bleeding. The research aimed to analyze anticoagulants used in therapy for CAD patients and identify potential adverse drug reactions and adverse drug interactions. Methods This was an observational study which collected data retrospectively at Bhayangkara Hospital Surabaya. Patient data had to meet the requirements for inclusion, which were patients treated for a diagnosis of CAD with anticoagulant therapy and were in conditions with or without complications and comorbid diseases. Data were obtained from 40 patient medical records. The data were then processed descriptively. Results Most patients were male (80%) and aged 61–70 years old (37.5%). Fondaparinux was administered to 18 patients at a dose of 1 × 2.5 mg SC. Furthermore, enoxaparin was administered to 15 patients at a dose of 2 × 60 mg SC, and seven patients received warfarin at a dose of 1 × 2–4 mg per oral. Conclusions The anticoagulants used in this study were fondaparinux 1 × 2.5 mg SC (45%), enoxaparin 2 × 60 mg SC (37.5%), and warfarin 1 × 2–4 mg PO (17.5%). Side effects of the anticoagulants were absent. However, drug interactions with aspirin, clopidogrel, and allopurinol increased the risk of bleeding.

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

Abstract

Objectives Inhaled corticosteroids are the most effective controllers of asthma, although asthmatics vary in their response. FKBP51 is a major component of the glucocorticoid receptor which regulates its responses to corticosteroids. Therefore, the present study aims to identify the role of

FKBP5 gene polymorphism in asthma susceptibility and corticosteroid resistance. Methods DNA was extracted from the blood of 68 asthmatic and 40 control subjects. FKBP5 gene fragments were amplified by PCR and sequenced by the Sanger method. The sequencing results were aligned by mapping on the reference sequences of National center of Biotechnology Information (NCBI) and single nucleotide polymorphisms (SNPs) which were checked. Finally, the genotype, allele frequency and odds ratio (OR) were calculated. Results The FKBP5 fragment sequencing revealed the presence of rs1360780 and one novel SNP found in 17 samples taken from asthmatic patients as compared to db SNP data in the NCBI database. The FKBP5 variant (rs1360780) indicated that the allele frequency of risk allele T was 41.18% in patients and 20% in control group members $p<0.001$ and OR=2.8 when compared to a wild C allele frequency of 58.82% in patients and 64% in the control group members. The novel SNP FKBP5 was compared to the SNP database in the NCBI database in which wild T allele was substituted with G. The novel SNP was submitted to the ClinVar Submission Portal at NCBI with accession number: rs1581842283 and confirmed an asthma susceptibility risk factor with allele G frequency of 11.76% in asthmatics and 2.5% in the control group members (OR=5.2, $p<0.05$), as compared to a wild T allele frequency of 88.24% in asthmatics and 97.5% in the control group members. Conclusions The risk allele T of rs1360780 and the novel SNP rs1581842283 risk allele G predict asthma susceptibility but show no association with corticosteroid resistant.

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

Abstract

Objectives The association between stress and gastric ulcers has been well reported. This study is divided into two parts: the first part of this study is consisted of analyzing the effect of fluvoxamine administration by intracerebroventricular (ICV) and intraperitoneal (IP) injections on stress-induced gastric ulcers. The second part investigates the effect of ondansetron in influencing the protection of the gastric mucous by giving fluvoxamine to the mice before being induced with stress. Methods Water immersion restraint stress (WIRS) was used to induce stress. Fluvoxamine 50 and 100 mg/kg by IP injection, fluvoxamine 9.3 µg, and 18.6 µg by ICV

injection 30 min before the induction of stress. Meanwhile, single drug and in combination administered to the mice, ondansetron 3 mg/kg was given by IP at 60 min, and fluvoxamine 50, 100 mg/kg orally at 30 min before stress induction. Results The obtained results show fluvoxamine 50 and 100 mg/kg by IP, and fluvoxamine 18.6 µg by ICV had significantly reduced ulcer index with $p<0.005$, $p<0.001$, and $p<0.005$ while fluvoxamine 9.3 µg showed the insignificant result. Fluvoxamine 50 mg/kg, fluvoxamine 100 mg/kg, and ondansetron 3 mg/kg monotherapy have a significant reduction in ulcers with $p<0.005$, $p<0.001$, and $p<0.05$, while the combination drugs showed an insignificant reduction in ulcers. Conclusions Fluvoxamine with different administration routes and ondansetron monotherapy before stress reduce the occurrence of gastric ulcers, while the combination drugs did not increase the protective effect of the gastric mucosa.

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

Abstract

Objectives Iron is essential for cell growth, differentiation, electron transfer, and oxygen transport. Hyperoxia may increase the turnover of bone matrix components with a net effect of accelerated bone growth. Although hyperoxia was claimed could increase osteoblast activity, but expression level in possible genes which play role in proliferation is still unclear. This research aims to prove the differences of expression level of transferrin receptor gene and iron regulated transporter and other genes of 7F2 under 24 h normoxia, 24 h hyperoxia, and 48 h hyperoxia and the effect of hyperoxia by using osteoblast cell culture 7F 2 . Methods Reverse transcriptase, real time Polymerase Chain Reaction (PCR), and microarray is used to qualitatively detect gene expression. The computer softwares such as National Center for Biotechnology Information (NCBI) data base, Software Affymetrix, DNA Strider program, Genomatix – DiAlign program, Oligo 5.0 program (Software primer design) from Wojciech & Piotr Rychlik, and Genetyx-Mac version 8.0 have been used to analyze the PCR result. Results Under 24 h hyperoxia, there were 3,884 copies of transferrin receptor mRNA per 1,000,000 copies of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) mRNA. After 24 h hyperoxia, 8,325 copies of transferrin receptor mRNA per 1,000,000 GAPDH mRNA copies were found showing 2.1-fold up regulation. After 48 h hyperoxia, there was no significant increase at the level of expression of

transferrin receptor mRNA, 8,079 mRNA copies per 1,000,000 copies of mRNA were found (2.0-fold up regulation compared with 24 h normoxia). Conclusions It can be concluded that hyperoxia might have an effect on upregulating the expression of some osteoblast genes which might have an impact on osteoblast activity.

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 Budiatin, Ilham Bagus Sagitaras, Ika Putri Nurhayati, Nismatun Khairah, Khoirotin Nisak, Imam Susilo, Junaidi Khotib

Page range: 497–504

Abstract

Objectives This study was designed to evaluate the potential of Andrographis paniculata ethanolic extract to inhibit the increase in proliferation and induction of abnormal cell death. Methods The hyperplasia stage as an early stage of cancer development was induced by oral administration of 20 mg/Kg BW DMBA to SD rats twice a week for 5 weeks. There were five groups in this study include negative control, positive control, and treatment groups of DMBA induction followed by administration of A. paniculata ethanolic extract in doses equivalent to 10, 30 or 100 mg/Kg BW andrographolide once per day for 6 consecutive weeks. On the last day, rats were sacrificed, lung and colon tissues were collected. Histological examination by HE staining and immunohistochemistry using p53, telomerase, and caspase-3 antibodies were aimed at observing hyperplasia state in these tissues. Results DMBA induction to SD rats was able to produce hyperplasia in lung parenchymal and colon epithelial tissue. This can be showed by the increasing number of proliferated cells and as indicated by the number of brown-colored nuclei with sharper intensity. As well telomerase appears to be overexpressed strongly, while p53 and caspase-3 show low intensity. The administration of A. paniculata extract for 6 weeks showed a decrease in the number of cells that actively proliferate, a decrease in telomerase activity, and an increase in caspase-3 levels which indicate cellular death activity. Conclusions A. paniculata ethanolic extract can inhibit the development of cancer at the hyperplasia stage by reducing telomerase activity and increasing apoptosis, marked by an increase of caspase-3 expressions.

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

Abstract

Objectives For designing early treatment for liver cancer, it is important to prepare an animal model to evaluate cancer prevention treatment by using inflammation disease. The hepatocarcinogenic N-Nitrosodiethylamine (NDEA) has been reportedly able to produce free radicals that cause liver inflammation leading to liver carcinoma. This study aimed to evaluate the inflammation disease model of mice induced with hepatocarcinogenic NDEA for five weeks induction. Methods The BALB-c mice were induced with NDEA 25 mg/kg of body weight once a week for five weeks intraperitonially and it was then evaluated for the body weight during study periods. The mice were then sacrificed and excised for evaluating their organs including physical and morphological appearances and histopathology evaluations. Results The results showed a significant decrease of body weight of mice after five times induction of 25 mg NDEA/kgBW per week intraperitonially. Different morphological appearances and weight of mice organs specifically for liver and spleen had also been observed. The histopathology examination showed that there were hepatic lipidosis and steatohepatitis observed in liver and spleen, respectively that might indicate the hepatocellular injury. Conclusions It can be concluded that inducing mice with NDEA intraperitonially resulted in fatty liver disease leading to progress of cancer disease.

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

Page range: 511–516

Abstract

Objectives Echinometra mathaei was known to have potential antioxidant activities because it contains of polyhydroxy-naphthoquinone (echinochrome and spinochromes). The antioxidant properties contributed to the hepatoprotective effect by binding to free radicals compound that

causes oxidative stress and necrosis in the hepatocytes. The research aimed to determine the hepatorepair effects of the E. mathaei ethanol extract on high-dose paracetamol-induced hepatic damage in Wistar rats. Methods This research used a true experimental method. Thirty white male rats were divided into sixth groups, i.e., normal control group, group II–VI was induced paracetamol 2,000 mg/kg BW for three days. After paracetamol-induced, group III–VI was treated with curcumin 800 mg/kg BW, E. mathaei extract 400, 800, and 1,200 mg/kg BW for seven days. The hepatorepair parameter was obtained from AST/ALT, MDA tissue levels, and the number of hepatocyte necrosis cells. The data results were analyzed using the ANOVA test, followed by the LSD test to determine the difference between each treatment. Results The results showed that E. mathaei significantly ($p<0.05$) decreased the AST levels, MDA levels and the number of hepatocyte necrosis cells at a dose of 800 mg/kg BW per orally treatment. Conclusions The E. mathaei ethanol extract repaired the hepatic damage induced by paracetamol.

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

Page range: 517–525

Abstract

Objectives This study aims to develop coenzyme Q10 nanostructured lipid carriers (NLCs) using tristearin and stearyl alcohol as well as isopropyl palmitate (IPP) as solid and liquid lipid respectively for the dermal delivery system. Methods The coenzyme Q10 NLCs were optimized using tristearin, and stearyl alcohol in different concentrations and further characterized by dynamic light scattering (DLS) for particle size, polydispersity index (PDI), zeta potential, differential scanning calorimetry (DSC) and X-ray diffractometry for crystallinity behavior, Fourier transform infrared spectroscopy (FT-IR) for drug-lipid interaction, scanning electron microscopy (SEM) for particle shape, viscometer for viscosity, and pH meter for pH value. Furthermore, entrapment efficiency (EE), drug loading (DL), and skin penetration in vivo were also evaluated while molecular docking was conducted to examine the interaction between coenzyme Q10 and the lipids. Results The coenzyme Q10 NLCs with tristearin-IPP and stearyl alcohol-IPP as lipid matrix had <1,000 nm particle size, <0.3 PDI, less negative than −30 mV zeta potential, about 41% crystallinity index, and about six as the pH value. Moreover, the EE, DL,

viscosity, and in vivo skin penetration of the NLCs using tristearin were higher compared to stearyl alcohol, however, the skin penetration depths for both NLCs were not significantly different. Furthermore, the in silico binding energy of coenzyme Q10-tristearin was lower compared to coenzyme Q10-stearyl alcohol. Both of them showed hydrophobic and van der Waals interaction. Conclusions The NLCs of coenzyme Q10 were formulated successfully using tristearin-IPP and stearyl alcohol-IPP for dermal delivery.

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

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.

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

Abstract

Objectives The sugarcane leaf is rich inphytochemical content. It is rarely used because it is a waste although it has potential activity as antimutation, anti inflammation, and antioxidation. There is no study about its hepatoprotective activity yet. This study was conducted to determine the hepatoprotection of sugarcane leaves in tested animals with liver acute injury induced by carbon tetrachloride (CCl 4). Methods Twenty-four Wistar strain rats were divided into three groups of experimental animals (dose 300, 400, and 500 mg/kg) and three control groups (normal, positive, and negative). The ethanol extract of sugarcane leaves obtained from Panti, Jember, was made using the maceration method. The animals were treated for 14 days by giving the extract to the treatment group. One hour after treatment on the last day, the test animals were given CCl 4 intraperitoneally except for the normal group. On the 15th day, the blood of the test animal was taken to be tested for the biochemical value of the liver (aspartate transaminase (AST), alanine aminotransferase (ALT), alanine phosphatase (ALP), and bilirubin) and examined for its liver to be made histological preparations. Results The results showed that the treatment with a dose of 500 mg/kg was able to decrease AST, ALT, ALP, and bilirubin parameters compared to the negative control. The extract also provided improvements in liver tissue histology compared to the negative control. Conclusions Sugarcane leaf ethanol extract (SCLE) has a potential hepatoprotective effect.

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 Zulkarnain, Nadhifa Zahra

Page range: 541-545

Abstract

Objectives Computer vision syndrome (CVS) is a group of various eye and vision-related problems from prolonged use of mobile devices. Symptoms include dry eyes, blurred vision, eye strain, headache, and also neck and

shoulder pain. This study was carried out to analyze the correlation between the exposure time of High Energy Visible (HEV) from mobile devices' use and the prevalence of evaporative dry eyes in young age. Methods An observational cross-sectional study was done using quota sampling method for 100 High School students. Data collection was performed using questionnaire to identify daily use of mobile devices (hours) and duration for using mobile devices (years). A classification was determined as mild, moderate, and heavy HEV exposure. Evaporative dry eyes were diagnosed using tear break-up time test (TBUT) of less than 10 s for both eyes. Results Ninety-four students participated in this study. A total of 82 students (87.2%) experienced evaporative dry eyes. There were 11 students (11.7%) who had dry eyes with mild exposure, 18 students (19.1%) had dry eyes with moderate exposure, and 53 students (56.4%) had dry eyes with heavy exposure. A chi square analysis showed all HEV exposures have similar risk to the prevalence of dry eyes among High School students ($p<0.05$). Conclusions The risk of developing evaporative dry eyes, as one of the symptoms of CVS in young age with normal tear production, could be induced even with minimal exposure to mobile devices.

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

Abstract

Objectives Nonalcoholic fatty liver disease (NAFLD) is exceptionally common around the world. The development of NAFLD is increasing rapidly in the world, along with changes in lifestyle. Excess lipid intake is one of the risk factors for NAFLD. The NAFLD model is induced by a high-fat diet contains SFA, MUFA, and ω-6 PUFA. This study aims to assess the effect of high-fat diet variation on liver histology in developing NAFLD models in mice. Methods Thirty-six male mice (Balb/c) were divided into six groups fed a high-fat diet containing beef tallow 60%, beef tallow 45%, vegetable ghee, animal ghee + corn oil, vegetable ghee + corn oil for 28 days and compared to a control group fed a chow diet. All of the mice were fed with a high-fat diet in the form of pellets ad libitum for 28 days. Bodyweight and food intake were measured every day. At the last day of treatment, animals were sacrificed and the Liver were taken for histological analysis. Results This study showed that NAFLD model development was achieved in all group mice fed

a high-fat diet with different degrees of NAFLD. Beef tallow 60% had the worst liver histology. Conclusions Thus, based on this study, we found that high-fat diet variations influenced the development of NAFLD models in mice, particularly concerning liver histology.

Unlicensed | June 25, 2021

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

Samirah, Aniek Setiya Budiatin, Ferdiansyah Mahyudin, Junaidi Khotib

Page range: 555-560

Abstract

Objectives Alendronate are widely used in the treatment of bone disorders characterized by inhibit osteoclast-mediated bone resorption such as Paget's disease, fibrous dysplasia, myeloma, bone metastases and osteoporosis. In recent studies alendronate improves proliferation and differentiation of osteoblasts, thereby facilitating for bone regeneration. The disadvantages of this class are their poor bioavailability and side effects on oral and intravenous application such as stomach irritation and osteonecrosis in jaw. Thus, local treatment of alendronate is needed in order to achieve high concentration of drug. Bovine hydroxyapatite-gelatin scaffold with alendronate was studied. Glutaraldehyde was used as cross-linking agent, increase the characteristics of this scaffold. The objectives of this study were to manufacture and characterize alendronate scaffold using bovine hydroxyapatite-gelatin and crosslinked by glutaraldehyde. Methods Preparation of cross-linked bovine hydroxyapatite-gelatin and alendronate scaffold with different concentration of glutaraldehyde (0.00, 0.50, 0.75, and 1.00%). The scaffolds were characterized for compressive strength, porosity, density, swelling ratio, in vitro degradation, and cytotoxicity (the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide assay, shorted as MTT assay). Results Bovine hydroxyapatite-gelatin-alendronate scaffold cross-linked with glutaraldehyde showed lower density than without glutaraldehyde. As glutaraldehyde concentration increased, porosity also increased. Eventually, it reduced compressive strength. Swelling ratio and in vitro degradation was negatively dependent on glutaraldehyde concentration. In addition, the scaffold has a good safety by MTT assay. Conclusions Bovine hydroxyapatite-gelatin-alendronate scaffold was fabricated with various concentrations of glutaraldehyde. The presence of glutaraldehyde on bovine hydroxyapatite-gelatin-alendronate is safe and suitable candidate scaffold for bone regeneration.

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

Abstract

Objectives Breast cancer (BC) in women could decrease health-related quality of life (HRQoL). HRQoL becomes important to be assessed to design a relevant treatment that could improve patient outcomes. Furthermore, assessing HRQoL by measuring health state utilities becomes pivotal for health economic evaluation. This study aimed to describe the HRQoL of postmenopausal women with hormone responsive (HR+) HER2− BC using the EQ5D5L instrument in Indonesia. Methods A cross-sectional study was conducted among 126 patients in Dr. Sardjito Hospital in Indonesia. The HRQoL was assessed by interviewing BC patients using the EQ5D5L questionnaire, and the utility index was calculated using the Indonesian value set. Information regarding clinical characteristic and socio-demographic were gained from patient medical records. One-way ANOVA and post-hoc Scheffe's test was performed to compare the utility score within the health state. Results Of the 126 patients, a mean ± SD for the age of 59.2 ± 6.1 years. The major problems of patients were pain/discomfort (75.4%) followed by anxiety/depression (54.8%). The mean (SD) of EQ5D VAS was 76.64 (14.91). Mean (SD) of utility score was 0.87 (0.10), 0.77 (0.19) and 0.58 (0.44) for free metastasis (FM), locoregional metastasis (LM) and distant metastasis (DM), respectively. Poor QoL was observed at DM health state ($p<0.05$). Conclusions HRQoL of postmenopausal women with HR+ HER2− BC was low. The major reported problems were pain/discomfort and anxiety/depression.

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, Suharjono, Christoper P. Alderman

Page range: 567-570

Abstract

Objectives Previous research suggests that there may be intergender differences in the profile of glycemic control achievable during the treatment

of type 2 diabetes mellitus. This preliminary study was conducted to determine differences in glycemic outcomes in type 2 diabetes mellitus patients amongst men and women in an Indonesian hospital. Methods The study was conducted at the outpatient internal medicine polyclinic of Universitas Airlangga Teaching Hospital Surabaya. This observational prospective cohort study examining outcomes for 64 patients (32 men and 32 women) treated with insulin therapy. The primary outcome measure was the extent to which subjects achieved concordance with the target blood glucose parameters based on the American Diabetes Association (ADA) guidance. Results After 3 months of combination basal-bolus insulin treatment, the proportion of subjects who had fasting blood glucose values in the target range did not increase for either gender. For women, there was a significantly higher proportion of subjects who achieved a postprandial glucose value within the target range (p=0.04) Conclusions In this study, patients achieved postprandial glycemic outcomes for women but not men. More research is required to elucidate the possible intergender difference in results for subjects treated with basal-bolus insulin for type 2 diabetes mellitus.

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

Abstract

Objectives National Baseline Health Research 2013 showed that there were 706,757 (0.4%) hyperthyroid patients in Indonesia. Hyperthyroidism is characterized by abnormal thyroid stimulating immunoglobulin (TSI) which causes low TSH and high FT4 levels. Hyperthyroid patients have a decrease of serum iron levels due to acute phase reactions of hyperthyroidism. This study aimed to analyze the correlation between dietary iron intake and serum iron with TSH and FT4 levels in adult hyperthyroid patients. Methods This study was conducted in February–July 2020 at the Clinic of Magelang Health Research and Development Center. Sampling of this cross sectional study was based on inclusion criteria in order to obtain 50 adult hyperthyroid patients. Dietary iron intake was collected with 2 × 24 h dietary recall, serum iron was measured with colorimetric analysis, the levels of TSH and FT4 were measured by ELISA. The collected data were analyzed using Spearman correlation and multivariate linear regression with 95% confidence level. Results Deficiencies of dietary iron intake was found in 20 hyperthyroid

patients (40%). Low serum iron levels were found in 10 hyperthyroid patients (20%). Spearman correlation analysis showed that dietary iron intake had a negative correlation with TSH (r=−0.294; p<0.05) but did not correlate with FT4 (r=−0.142; p>0.05), while serum iron didn't associated with both TSH (r=0.110; p>0.05) and FT4 (r=0.142; p>0.05). Furthermore, regression analysis showed that dietary iron intake, serum iron, phytate, and thyrozol intake correlate with TSH levels (R square=0.193; p<0.05) and FT4 levels (R square=0.341; p<0.05), but there were no independent association between dietary iron intake and serum iron with TSH and FT4 levels (p>0.05). Conclusions Intake and serum of iron didn't correlate with TSH and FT4 levels in adult hyperthyroid patients.

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

Abstract

Objectives Nonadherence to a long-term therapy, including diabetes mellitus, is one of the global problems that need to be overcome. This study aims to determine the effect of pillbox use and education by pharmacists toward medication adherence in patients with diabetes mellitus in a Primary Health Care Center in Mataram. Methods This research was an experimental research design with pretest-posttest with control group design. The study was conducted from October to December 2019 at Tanjung Karang Primary Health Care Center, Mataram. Measurement of adherence was done using the Adherence to Refill and Medication Scale questionnaire. The higher the score, the more nonadherence the patients. Patients were divided into three groups, which were the control group, educational intervention group, and pillbox and educational intervention group. Each group consisted of 11 patients. Results Patients' medication adherence increased from 19.54 (SD 4.37) to 15.18 (SD 2.64) in the education and pillbox intervention group (p=0.004). Whereas, in the education and control group, the adherence did not provide a significant change (p>0.05). Based on the difference in adherence scores, it was known that what contributed to changes in compliance was refilling medicine and intentional nonadherence in taking medicine subscale (p=0.024). Conclusions Providing education and pillbox done by pharmacists at the Primary Health Care Center can increase adherence to the therapy of diabetes mellitus patients. Pharmacists at the

Primary Health Care Center can use the intervention model to improve the level of adherence of patients with chronic illness.

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

Abstract

Objectives This study aimed to evaluate the variation concentration effect of propyleneglycol, glycerin, and polyethyleneglycol 400 as a nonvolatile solvent on the physical properties and dissolution rate of the loratadine liquisolid tablet. Methods The tablet was formulated into 10 formulas, where nine were liquisolid and one was conventional (CT). The concentration of propyleneglycol, glycerin, and polyethyleneglycol used in liquisolid tablets were 14, 15, and 16%. Furthermore, the mixture was evaluated based on flow properties and compressibility index. The tablet was evaluated based on hardness, friability, disintegration time, and dissolution, and the data obtained was evaluated with ANOVA or Kruskal–Wallis statistic program. Results The result showed that flow properties, disintegration time, and dissolution have a significant value less than 0.05. The tablet friability for all concentration solvents, hardness at 14 and 15% solvent concentration, and compressibility index at 15 and 16% have significant value more than 0.05. The 16% propyleneglycol type solvent concentration tablet has the physical properties and contains the best solution Conclusions From the result, it is reasonable to conclude that F7 is the tablet with all the physical properties and the best dissolution.

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

Abstract

Objectives Batik dyes contain irritant chemicals that increase the risk of skin barrier disruption. This study aims to determine the effect of Centella asiatica and ceramide in transepidermal water loss (TEWL), hydration of the stratum corneum and skin acidity (pH). Methods This was a double blind clinical trial

of 30 Indonesian batik workers who suffered from skin dryness, but had no clinical manifestation of contact dermatitis. Subjects were given cream containing C. asiatica or ceramide that formulated and randomly labeled by manufacturer (PT Paragon Technology and Innovation). Both subjects and researchers were blinded to the type of the cream. Cream was applied to the hands and arms twice a day. Biological function of the skin (TEWL, stratum corneum hydration level, and skin acidity) was examined by Cutometer dual MP-580. Baseline was recorded in the first examination, followed by second and third examinations at two and four weeks after treatment. Results After four weeks treatment, there were significant improvement of C. asiatica application in evaluation of corneometer palmar (p=0.007; CI 95%), corneometer dorsum (p=0.001; CI 95%), and skin acidity dorsum (p=0.017; CI 95%). Ceramide application also gave significant improvement of corneometer palmar (0.038; CI 95%), skin acidity palmar (p=0.001; CI 95%), TEWL dorsum (p=0.023; CI 95%), corneometer dorsum (p=0.002; CI 95%) and skin acidity dorsum (p=0.011; CI 95%). There were no significant differences of C. asiatica effectiveness compared to ceramide in skin barrier improvement. Conclusions C. asiatica and ceramide can improve skin barrier hydration in order to prevent the risk of contact dermatitis in batik workers.

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

Abstract

Objectives Fever is a condition when the body experiences an increase in average body temperature above normal level. Maja fruit (Crescentia cujete L.) contains chemical compounds including alkaloid, flavonoid, saponin, and terpenoid, suspected as potential antipyretics. Methods The study aimed to determine the antipyretic activity of ethanol extract of Maja fruit. A total of 25 male white mice of the DDY strain (20–30 g). These treatments divided into three groups with a dose extract of 125, 250, 500 mg/kg BW, standard groups of ibuprofen 400 mg/kg BW, and control groups of CMC-Na 1%. Mice were injected intraperitoneally with 0.1 cc of DPT vaccine-induced. Observations were made by measuring the rectal temperatures of mice using a digital thermometer before DPT vaccine injected or average temperatures, at 0 min (after DPT vaccine injected), 60, 120, 180, and 240 min after administering the test material. The differences between the positive control group, test group, and the negative control group were compared using statistical analysis

using one-way variance analysis (ANOVA). The results were considered statistically when the value is ($p<0.05$). Results The above phytochemical screening results showed that alkaloids, flavonoids, and saponins were present in the Maja fruit powder and extract (C. cujete L.). Based on the results of the statistical analysis obtained, i.e., Group II was not significantly different from Group III and Group IV ($p\leq0.05$) and was significantly different from Group I and Group V. Group I was significantly different from Group II, Group III and Group IV and was not significantly different from Group V ($p\geq0.05$). Conclusions The study showed that Maja fruit mice's antipyretic behavior at doses of 125, 250, and 500 mg/kg BW was confirmed as a result in reducing the body temperature of male mice. The 500 mg/kg BW dosage of Maja fruit extract (C. cujete L) effectively reduced fever.

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

Abstract

Objectives Tumor lysis syndrome (TLS) is a life-threatening oncology emergency disorder, which may cause acute kidney injury (AKI), arrhythmias, seizures, and sudden death. Hydration is used to prevent TLS in medium-high risk patients, and treatment in TLS patients. According to the pediatric protocol in Dr. Soetomo District General and Teaching Hospital, close monitoring is required to prevent the progression of hematological malignancy towards TLS. The study aimed to analyze the hydration effect on potassium, calcium, and phosphate levels; serum creatinine (sCr); and blood urea nitrogen (BUN) level. Methods This was an observational and prospective study conducted at Dr. Soetomo District General and Teaching Hospital for four months on 15 pediatric hemato–oncology patients who got TLS and in risk of TLS. Laboratory parameters were observed in 11 days, pre and post hydration. Results Among the 15 patients who met the inclusion criteria, there were eight TLS patients and seven TLS risk patients. After hydration administration 67% of TLS patients achieved normal potassium level, 75% achieved normal phosphate level, 0% achieved normal calcium level, and 50% achieved normal sCr and BUN levels. Meanwhile, TLS risk patients reached normal level in all parameters. This difference in performance is caused by disease progression. Conclusions Hydration can maintain serum electrolytes and renal function in a normal range, preventing

TLS in TLS risk patients. In TLS patients, hydration only tends slow the progression of the disease.

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

Abstract

Objectives The main therapy of β-thalassemia major are blood transfusion and iron chelation drugs. However, those therapies also have some adverse effects and problems such as iron overload, transfusion reactions, nutritional deficiencies, and patient compliance problems. Those arising problems also have an impact on therapy cost. Hence, this study was designed to analyze drug utilization study and cost of therapy in β-thalassemia major adult patients at Dr. Soetomo General Hospital Surabaya. Methods This research was conducted in descriptive observational-retrospective design using secondary data obtained from patient's medical records and billing registrations from January 1–December 31, 2019. Results There were 18 patients out of 233 patients that were analyzed. Deferasirox was the most administered drug with doses between 500 mg/day–1,500 mg/day while deferiprone was ranged between 1,500 and 4,500 mg/day. Patients also received transfusion reaction drugs with dexamethasone injection 5 mg/ml which was administered the most. The most administered supplement was folic acid 1 mg. Patients had an increase in serum ferritin due to low compliance. Deferasirox had the most adherence number of patients with decrease of serum ferritin. The two highest costs of direct medical components were top-up medicines and consumable medical supplies. Overall, the hospital gained profit from national health insurance claims. Conclusions The most administered chelating agent was deferasirox. Deferasirox also had the most adherence number of patients with decreased number of serum ferritin. However, deferasirox also yielded the highest cost. Yet, overall, the hospital gained profit from national health insurance claims.

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

Abstract

Objectives Hyperglycemia in diabetes mellitus (DM) could cause rheological disorder, such as platelet aggregation and blood hyperviscosity. Hyperbaric oxygen (HBO) could decrease collagen as platelet aggregation agonist. This study aimed to explore the effect of HBO treatment to platelet aggregation parameters (latency time(LT), aggregation speed, aggregation index, and aggregation percentage) with the collagen aggregator in the noninsulin dependent diabetes mellitus (NIDDM). Methods The number of subjects in this study were 16 for each group normoxia normobaric (NONB) and HBO. NIDDM patients from DM polyclinic in Rumah Sakit Angkatan Laut (RSAL) Dr Ramelan Surabaya which was fulfilled inclusion criteria would receive HBO Therapy. Control Group/NONB were treated with NONB condition (20% O 2 1 ATA) for 90 min and treatment group/HBO were treated with hyperoxia hyperbaric condition (100% O 2 2.4 ATA) for 3 × 30 min with interval of 2 × 5 min for inhaling fresh air. Subject has been blood taken for platelet aggregation test before and after HBO Therapy. The length of treatment was 5 days for both condition (NONB and HBO). Results The data from both groups, NONB and HBO were tested first by normality test, homogenity test, correlation test, analysis of covariance, and paired t-test. Based on paired t-test, the decrease on platelet aggregation speed, aggregation index, and aggregation percentage after HBO treatment was showed significant difference on the LT and aggregation index while in aggregation speed and aggregation percentage was not significant. NONB group after 5 days was showed a significant difference on the aggregation speed and aggregation index while in LT and aggregation percentage was not significant. Conclusions The utilization of HBO 2.4 ATA 100% O 2 3 × 30 min, once a day, for 5 days could decrease the platelet aggregation parameters (LT, aggregation speed, aggregation index, and aggregation percentage) in patients with NIDDM.

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

Abstract

Objectives Loratadine belongs to Class II compound of biopharmaceutics classification system (BCS) due its low solubility and high membrane permeability. Cocrystal is a system of multicomponent crystalline that mostly

employed to improve solubility. Succinic acid is one of common coformer in cocrystal modification. This research aims to investigate cocrystal formation between loratadine and succinic acid and its effect on solubility property of loratadine. Methods Cocrystal of loratadine-succinic acid was prepared by solution method using methanol as the solvent. Cocrystal formation was identified under observation of polarization microscope and analysis of the binary phase diagram. The cocrystal phase was characterized by differential thermal analysis (DTA), powder X-ray diffraction (PXRD), Fourier transform infrared (FTIR), and scanning electron microscopy (SEM). Solubility study was conducted in phosphate-citrate buffer pH 7.0 ± 0.5 at 30 ± 0.5 °C. Results Loratadine is known to form cocrystal with succinic acid in 1:1 M ratio. Cocrystal phase has lower melting point at 110.9 °C. Powder diffractograms exhibited new diffraction peaks at 2 θ of 5.28, 10.09, 12.06, 15.74, 21.89, and 28.59° for cocrystal phase. IR spectra showed that there was a shift in C=O and O–H vibration, indicating intermolecular hydrogen bond between loratadine and succinic acid. SEM microphotographs showed different morphology for cocrystal phase. Loratadine solubility in cocrystal phase was increased up to 2-fold compared to loratadine alone. Conclusions Cocrystal of loratadine and succinic acid is formed by stoichiometry of 1:1 via C=O and H–O interaction. Cocrystal phase shows different physicochemical properties and responding to those properties, it shows improved loratadine solubility as well.

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

Abstract

Objectives The function of bone is to protect the vital organs of the body. Mechanical strength, especially compressive strength, plays an important role in fulfilling its function. Fracture healing depends on several substances, such as collagen, glucosaminoglycane and proteoglycan. Chondroitin sulfate as part of proteoglycane is an important component in the formation of callus in fracture healing. The aim of this study is to prove chondroitin sulfate role in supporting fracture healing. Methods The in vivo experiment has been performed to Rattus novergicus which met the inclusion criteria (age 3 months, 200–300 g weight), 18 males of R. norvegicus, Wistar strain, were divided into three equal groups of six rats each. After being anesthetized, fracturation was performed in a sterile manner to get simple fracture. The

area of dissection is in half length of tibial bone and the fracture incision is about 1 cm. Then it followed by immobilization of the lower leg bone on one side with a cast. The first group was given chondroitin sulfate 7 mg in 2 mL distilled water/200 g weight for 2 weeks. The second group was given chondroitin sulfate 7 mg in 2 mL distilled water/200 g weight for 4 weeks. The third group was given distilled water. This research was focused on treatment of cartilage. The callus position is in half length of tibial bone. Results There were significant differences in the increase of TGF-β, the number of osteoblasts and callus compressive strength in the groups with chondroitin sulfate treatment for 2 and 4 weeks, compared to the control group ($p<0.01$). Conclusions Administering chondroitin sulfate in a dose of 7 mg in 2 mL distilled water for 2 and 4 weeks may increase production of TGF-β, the osteoblast numbers and the callus compressive strength in fracture healing.

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

Abstract

Objectives The study aimed to determine the effect of quercetin on the expression of primary regulator gene involved in lipogenesis and triglycerides synthesis in the liver, and the sterol regulatory binding protein-1c (SREBP-1c) mRNA in non-alcoholic fatty liver disease (NAFLD) with a high-fat diet (HFD) model. Methods Fifty-six Balb/c mice were divided into seven groups: standard feed; HFD; HFD and quercetin 50 mg/kg for 28 days; HFD and quercetin 100 mg/kg BW for 28 days; HFD and quercetin 50 mg/kg for 14 days; HFD and quercetin 100 mg/kg for 14 days; HFD and repaired fed for 14 days. Quercetin was administered intraperitoneally. The animals were sacrificed 24 h after the last treatment; the liver was taken for macroscopic, histopathological staining using hematoxylin–eosin and reverse transcription-PCR analysis sample. Results HFD significantly increased the expression of SREBP-1c mRNA; meanwhile, quercetin and repaired feed significantly reduced the expression of SREBP-1c mRNA in the liver. Quercetin at a dose of 50 mg/kg and 100 mg/kg also improved liver cells' pathological profile in high-fat diet NAFLD. Conclusions The present study suggests that quercetin has an inhibitory effect on SREBP-1c expression and improved liver pathology in NAFLD mice.

June 25, 2021

Analysis of stress ulcer prophylaxis drug regimentation in surgical patients

Dhani Wijaya, Suharjono, Fendy Matulatan, Elfri Padolo

Page range: 645-649

Abstract

Objectives The World Health Organization (WHO) estimated that more than 50% of drugs were prescribed incorrectly, including stress ulcer prophylaxis (SUP) drugs. Prescribing SUP drugs in incorrect doses and frequencies are considered irrational, and may affects to the effectivity of the therapy. This research aimed to assess the appropriateness of the SUP drugs regimentation in the inpatient surgery room at Dr. Soetomo Hospital, Surabaya, Indonesia. Methods This research was cross-sectional study and conducted for 4 weeks in 2019 in the inpatient surgery room of Dr. Soetomo Hospital. The population was SUP drugs that were prescribed in inpatient surgery room. Those SUP drugs with indications for the prevention of stress-induced ulcers that complied to the terms listed on the American Society of Health-System Pharmacists (ASHP) were included as the samples, and vice versa. The samples then assessed for their regimentation appropriateness

using the dose and frequency standard of ASHP. Results There were 224 dose units taken as sample, from the total population of 1,404 SUP drugs. The result showed that as much as 48.2% of SUP medications were given to the patients in inappropriate regimentation. Of that number, all ranitidine injection were inappropriately regimented. On the contrary all omeprazole injection dose units were appropriately regimented, meanwhile the amount of appropriate regimentation of sucralfate suspension were 74.6%. Conclusions According to ASHP standard, the SUP drugs in the inpatient surgery room at Dr. Soetomo Hospital were mostly given in inappropriate regimentation. Further research is needed to explore how will those inappropriate regimentation affect on the efficacy of therapy in the patients.

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

Abstract

Objectives Chitosan is a natural polysaccharide widely used in various clinical applications including regeneration of skin tissue. Aloe vera has properties in healing burns on the skin, anti-inflammatory effect, and leaves a protective layer on the skin after drying so it provides protection to the wound. The spray gel of chitosan– A. vera was developed as a wound healing that has combined of effect of both component and easy to use. The purpose of this study was to determine the physical stability and irritability of chitosan–A. vera spray gel. Methods The spray gel stability test was conducted using thermal cycling and centrifugation methods. The organoleptic, viscosity, and pH of the spray were evaluated. The irritation test was performed by Draize Rabbit Test method. Results Chitosan (0.5%)– A. vera (1%) spray gel characteristics has a weak yellow color, clear, and a strong A. vera odor. The pH of the spray gel was 4.88 ± 0.01; and the viscosity was 36.50 ± 0.23 cps. The result from the chitosan (0.5%)– A. vera (1%) spray gel stability test using thermal cycling method showed a decrease of viscosity, but remained stable when evaluated using centrifugation method. There was no difference in the pH and organoleptic observation from both tests. Based on the scoring and analysis of the reaction in rabbit skin, the Primary Irritation Index (PII) obtained was 0.56. Conclusions The spray gel of chitosan (0.5%)– A. vera (1%) was stable and according to response category from the acute dermal irritation test, it can be concluded that chitosan (0.5%)– A. vera (1%) spray gel had a slightly irritating effect.

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

Abstract

Objectives Amblyopia is a decrease of visual acuity that cannot be attributed to any structural abnormality of the eye or visual system, causing a partial or complete loss of vision due to inadequate stimulation in early life. Citicoline has been reported to improve visual acuity in amblyopic eyes as adjuvant treatment. This study was aimed to determine the effectiveness of citicoline in pediatric patients with refractive amblyopia in ophthalmology daily practices. Methods This was a retrospective–descriptive study with a time limited sampling method. This study was conducted at Surabaya Eye Clinic,

East Java, Indonesia, by reviewing medical records for the period of January 2018 to December 2019. Results A total of 34 eyes were included in the study with the majority aged five years (41.2%) and six years (35.3%). The severity of amblyopia varied among patients, 21 eyes (61.76%) had mild amblyopia, seven eyes (20.59%) had moderate amblyopia, and two eyes (5.88%) had severe amblyopia. The duration of given therapy also varied, 18 eyes (52.94%) were given 3 months therapy, two eyes were given 4 months therapy, 12 eyes were given 6 months therapy, and two eyes were given 8 months therapy. Citicoline was found effective in mild and moderate amblyopia and for the duration of 3 and 6 months ($p<0.05$). In others group who did not showed statistically significant improvement was due to inadequate samples but clinically significant improvement was noted. Conclusions Citicoline therapy resulted in a clinically and statistically improvement in refractive amblyopia patients.

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

Abstract

Objectives Cyclodextrin's ability to form an inclusion complex with a guest molecule is a function of two factors. The first is steric and depends on the relative size of cyclodextrin cavity to the guest molecule, while the second is the thermodynamic interaction between the different system components. This study therefore aims to determine the effect of β-cyclodextrin and hydroxypropyl-β-cyclodextrin as complex formers, on thermodynamic parameter values (Δ H , Δ G , and Δ S) in the formation of inclusion complex with p -methoxycinnamic acid (p MCA). Methods The p MCA complex formation with β-cyclodextrin or hydroxypropyl-β-cyclodextrin was determined in 0.02 pH 4.0 M acetate buffer and 0.02 M pH 7.0 phosphate buffer, with a 0.2 μ value at 32, 37, and 42 ± 0.5 °C. This experiment was carried out in a waterbath shaker until a saturated solution was obtained. Subsequently, p MCA concentration was determined using UV spectrophotometer at the maximum p MCA wavelength, at each pH. Results The result showed p MCA formed inclusion complex with β-cyclodextrin or hydroxypropyl-β-cyclodextrin and exhibited increased solubility with increase in β-cyclodextrin or hydroxypropyl-β-cyclodextrin concentration. This temperature rise led to a decrease in the complex's constant stability (K).

Furthermore, the interaction showed a negative enthalpy (Δ H <0) and is a spontaneous processes (Δ G <0). At pH 4.0, an increase in the system's entropy occurred (Δ S >0), however, at pH 7.0, the system's entropy decreased (Δ S <0). Conclusions The rise in p MCA solubility with increase in cyclodextrin solution concentration indicates an inclusion complex has been formed, and is supported by thermodynamic data.

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

Abstract

Objectives In order to minimize gastrointestinal irritation and to extend the absorption of ketoprofen, microparticles prepared with chitosan have been developed. In this study, chitosan type and drug-chitosan ratio were investigated to prepare microparticles of ketoprofen and evaluated for physical characteristics and drug release profiles. Methods Microparticles were prepared by using ionic gelation methods with chitosan, which has two different viscosities i.e., 19 and 50 cPs, cross-linked with tripolyphosphate, and dried by spray drying method. The microparticles were made with a drug-chitosan ratio of 5:15 and 6:15. Results The results showed that the microparticles had spherical shapes. Increasing the amount of ketoprofen improved the drug content and entrapment efficiency. Evaluation of drug release in simulated intestinal fluid (pH 6.8) showed that the microparticles prepared with chitosan 19 cPs had the slowest release rate than those of chitosan 50 cPs, while that of the microparticles prepared with chitosan 50 cPs with the ratio of drug/polymer 6:15 was the fastest, as shown by its slope value. The release rate of microparticles with chitosan 19 cPs was slower than those microparticles with chitosan 50 cPs. Conclusions It could be suggested that by increasing the amount of ketoprofen, it improved the entrapment efficiency and the release rate of microparticles.

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

Abstract

Objectives One of the treatments for rheumatoid arthritis (RA) was methotrexate which a disease modifying antirheumatic drug therapy. The use of methotrexate required the right dose and length of therapy to achieve remission. The effectivity of methotrexate could be accounted by disease activity score 28 (DAS28) as a tool has been used clinically with a combination number of tender joints, swollen joints, erythrocyte sedimentation rate, and global clinical assessment by the patient. The aim of this study was to determine the effective dose and length of therapy methotrexate was measured by DAS28 score. Methods This research was a cross-sectional study and data was collected from patient medical records in Saiful Anwar Hospital, Malang, from February to July 2018. The research has been given ethical clearance. The inclusion criteria for the 88 subjects were men and women, over 20 years of age, usage of only methotrexate for at least three months, an erythrocyte sedimentation rate score, uncomplicated inflammatory bowel disease, cancer, and systemic lupus erythematosus. All data obtained was entered in formula DAS28. The Statistic analysis used both Pearson and Spearman's rank correlation. Results Only 16 patients achieved remission. There were not significant correlation in statistical analysis between DAS score and cumulative dose (r=−0.091; p=0.400), average dose (r=0.043; p = 0.692), maximum dose (r=0.074; p=0.492), and length of therapy (r=−0.075; p = 0.489). The initial dose of therapy methotrexate was different and the length of therapy was adjusted to the patient's health condition. Conclusions The maximum dose and length of therapy methotrexate was required to achieve remission in RA.

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, Elida Zairina

Page range: 681–686

Abstract

Objectives Pakistan has taken unprecedented measures to control the spread of COVID-19. Complete lockdown followed by smart lockdown and quarantine centres was established. Their awareness and attitude towards COVID-19 had an impact on the individual behaviour of the precautionary measures. The current study examined the knowledge, attitudes and practices of university students in Pakistan. Methods An online cross-sectional study was conducted among university students in Pakistan. A

questionnaire containing demographic and KAP information related to COVID-19 has been created. Results A total of 358 students responded to the survey, and 353 participants completed the study. Among the respondents, 61.5% were male, 76.8% were single, and 58.4% enrolled in a bachelor's degree. The results showed that most of the respondents (68%) had good knowledge about COVID-19, while the overall knowledge score was 8.78 ± 1.63 (range 1–10). The majority of the respondents (90.9%) were aware of COVID-19, 95.8% knew the sign and symptoms, and 83% of them knew about its transmission. We found a significant difference in knowledge scores across education and area of study $p<0.05$. More than half (53.5%) of the respondents were satisfied with the facilities provided by the government of Pakistan. The average practices score among the students was 5.08 ± 1.312. A significant difference was found among practice score and area of study $p<0.05$. Conclusions Most of the students have an adequate level of knowledge and are doing better preventive measures against COVID-19. Health education initiatives are required to ensure best practice among the high-risk groups.

June 25, 2021

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

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

Page range: 687-691

Abstract

Objectives Biomaterials are widely used as drug delivery systems targeting bone tissue, such as to treat bone infectious disease. However, the addition of drugs to biomaterials weakens their mechanical properties. Crosslinkers are compounds that improve the mechanical properties of biomaterials. This study aims to determine the effect of glutaraldehyde (GTA) as a crosslinker on the characteristics of bovine hydroxyapatite-gelatin-based bone scaffold with gentamicin as antibiotics (BHA-GEL-GEN-GTA). Methods BHA-GEL-GEN-GTA scaffold with GTA solid content ranging from 0.1 to 1.4 wt% was made by direct compression. The compressive strength test was carried out using autograph. Scaffold degradation test was carried out by dissolving the scaffolds in PBS. Scaffold toxicity was performed by MTT assay using BHK-21 fibroblast cells. Results There was a significant difference in the scaffolds' compressive strength due to differences in GTA volume. Scaffold crosslinked using GTA with solid content 0.1 and 0.2 wt% in 2 mL solution had higher compressive strength than those in 1 mL solution. Furthermore, GTA with

solid content 0.6, 1, 1.2, and 1.4 wt% showed higher compressive strength than those without GTA. Degradation test results showed that GTA increased the percentage of weight loss and swelling of the scaffold. The scaffold exhibited a nontoxic profile in MTT assay. Conclusions GTA with optimum solid content shows great compressive strength, stable swelling profile with low percentage of scaffold's weight loss, and is considered as nontoxic.

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

Abstract

Objectives The incision method operation with a high risk of infection in a clean and clean-contaminated operation requires the use of prophylactic antibiotics to minimize the risk of infection. This study was designed to analyze the effectiveness of prophylactic antibiotics in patients with digestive and oncology surgeries. Methods The statistical method used was chi-square to determine the risk factors for infection at surgical site infections (SSI) in patients with digestive and oncology surgeries. This study had received ethical approval from the Ethics Committee of Dr. H. Slamet Martodirdjo Hospital, Pamekasan. Results There were 67 patients consisted of 48 digestive surgeries (71.6%) and 19 oncology surgeries (28.4%). The criteria of observation on day 30 showed that as 1 (1.5%) SSI patient experienced purulence, inflammation, and erythema around the surgical wound so an analysis of $p>0.05$ was carried out so that there was no association with the incidence of SSI during hospitalization, but other factors originating from the patient, such as a lack of personal hygiene at home and lack of nutritious food intake was measured in temperature, pulse, respiration, and white blood cells examination before surgery and 24 h after surgery, all within normal ranges. The qualitative analysis of prophylactic antibiotics using the Gyssen method showed that 31 (46.3%) rationales needed an improvement process. Conclusions The widely used prophylactic antibiotics, namely cefazolin and cefuroxime are recommended antibiotics used in incision surgery and rationale used.

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 Hastutiek

Page range: 701-705

Abstract

Objectives The purpose of this study is to use the second internal transcribed spacer (ITS-2) to determine the molecular characteristics of Sarcoptes scabiei in rabbits from several areas of East Java. Methods Collecting S. scabiei mites from rabbits with clinical signs of scabies; DNA extraction with minikit QIAamp DNA; polymerase chain reaction amplification; nucleotide sequence analysis; homology and phylogenetic tree using the Neighbor-Joining method in the program molecular evolutionary genetics analysis-7 (MEGA-7). Results Sequence analysis of ITS-2 S. scabiei from five regions in East Java showed an identity >91.23% with isolates from China (KX695125.1). The phylogenetic analysis of ITS-2 S. scabiei from Mojokerto rabbits has a close relationship with AB82977.1; Surabaya and Nganjuk rabbits are closely related to KX695125.1; while Sidoarjo and Pasuruan rabbits are closely related to EF514469.2. and AB369384.1. Conclusions The homology analysis of all samples showed identity of more than 91.23% with isolate China (KX695125.1). The sequences of ITS-2 gen of S. scabiei from rabbits in several areas were relatively close to S. scabiei obtain various hosts from National Centre for Biotechnology Information (NCBI) data.

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

Abstract

Objectives This study was purposed to design gossypetin derivatives which have higher activity than the parent compound found in Hibiscus sabdariffa and to find the most potent compound as the antibacterial agent. Methods Twenty-five gossypetin derivatives were designed by conjugation the molecular structure of gossypetin with acyl group from some natural phenolic acids. The antibacterial activity was predicted by docking simulation on Escherischia coli DNA gyrase (PDB. 1KZN) which was performed by

Molegro Virtual Docker. Potency as an antibacterial agent was evaluated based on binding affinity, hydrogen bond, and similarity of binding pattern with reference ligand Clorobiocin. Results Almost all derivatives showed higher binding affinity than gossypetin (docking score −113.43 kcal/mol). The most active compound was 3G19 with docking score −167.42 kcal/mol which was comparable to clorobiocin (docking score −167.75 kcal/mol). The compounds displaying higher activity than gossypetin were belonged to 7,4'-dimethyl and 3,7,4'-trimethylgossypetin of coumaric acid, caffeic acid, and also ferulic acid. The compounds showed similar binding mode with clorobiocin especially in interaction with Asn46. Conclusions Gossypetin derivatives designed by conjugating the gossypetin with phenolic acyl increased in silico antibacterial activity of the parent compound. The 3,7,4'-trimethylgossypetin of coumaric acid was selected as the most potent compound for antibacterial agents.

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

Abstract

Objectives Tuberculosis (TB) remains a public health concern due to the emergence and evolution of multidrug-resistant strains. To overcome this issue, reinforcing the effectiveness of first line antituberculosis agents using targeted drug delivery approach is an option. Glyceraldehyde-3-Phosphate Dehydrogenase (GADPH), a common virulence factor found in the pathogenic microorganisms has recently been discovered on the cell-surface of Mycobacterium tuberculosis , allowing it to be used as a drug target for TB. This study aims to discover active small molecule(s) that target GAPDH and eventually enhance the delivery of antituberculosis drugs. Methods Ten ligands with reported in vitro and/or in vivo activities against GAPDH were evaluated for their binding interactions through molecular docking studies using AutoDock 4.2 program. The ligand with the best binding energy was then modified to produce 10 derivatives, which were redocked against GAPDH using previous protocols. BIOVIA Discovery Studio Visualizer 2019 was used to explore the ligand-receptor interactions between the derivatives and GAPDH. Results Among the 10 ligands, curcumin, koningic acid and folic acid showed the best binding energies. Further analysis on the docking of two folic acid derivatives, F7 (γ-{[tert-butyl-N-(6-aminohexyl)]carbamate}folic acid)

and F8 (folic acid N-hydroxysuccinimide ester) showed that the addition of a bulky substituent at the carboxyl group of the glutamic acid subcomponent resulted in improved binding energy. Conclusions Folic acid and the two derivatives F7 and F8 have huge potentials to be developed as targeting agents against the GAPDH receptor. Further study is currently on-going to evaluate the effectiveness of these molecules in vitro .

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

Abstract

Objectives The purpose of this study is to determine the effect of fermentation techniques on the inhibitory activity of red passion fruit (Passiflora edulis Sims.) fermentation filtrate in De Man Rogosa Sharpe-broth (MRS-B) media against Extended Strain Methicillin-Resistant (ESBL) Escherichia coli and Methicillin-Resistant Staphylococcus aureus (MRSA). Methods The fruit pulp was wrapped in banana leaves before compared to direct fermentation processes. This study was divided into three treatment groups. Group 1 was the fruit pulp (5 g) fermented in 45 mL of MRS-B medium for 24 h. Group 2 was the fruit pulp wrapped in banana leaves for 3 days before fermented in MRS-B for 24 h. Group 3 was the fruit pulp wrapped in banana leaves for 3 days before fermentation in MRS-B for 48 h. Fermentation broth of each condition was taken and then filtered using millipore (0.2 µm). As many as 50 µL of filtrates was tested for its inhibitory activity against E. coli ESBL and MRSA using the Kirby Bauer method. Results Group 2 showed the best antibacterial activity against E. coli ESBL and MRSA with the average zone of inhibition of 38.3 and 37.6 mm respectively. These values were higher than the first and group 3s activities. Conclusions The inhibitory activity of group 1s against ESBL and MRSA is categorized as a moderate potency with a diameter of growth inhibition zone of 16–20 mm, whereas the other groups are categorized as strong potency with a diameter higher than 20 mm.

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 Liestya Wardani, Suharjono, Kuntaman, Agus Widjaja

Page range: 729-735

Abstract

Objectives Acute respiratory tract infection (ARTI) nonpneumonia and nonspecific diarrhea are the most common cases in primary health care centre (PHCC) in Indonesia with the enormous use of antibiotics. The aims of this study were to analyze the antibiotic use and factors affected to the quality of antibiotic use in PHCC in Banjarbaru City, South Kalimantan, Indonesia. Methods The study was conducted in four PHCCs, two in urban and two in rural areas. All of the patients visited these PHCCs since March to April 2018 were recruited as samples after signing informed consent. Data were analyzed using SPSS version 18. Results There were no significant difference in antibiotic use between urban and rural PHCC, both on ARTI nonpneumonia and nonspecific diarrhea. The most prescribed antibiotics were amoxycillin and cephadroxil. Based on DDD/1,000 patients-day calculation, the quantity of antibiotics in urban PHCC was 3,544.4 and in rural PHCC was 3,478.6. Physicians with more than seven years of service, both in rural and urban PHCCs, were prescribe the antibiotics higher than who had been working for shorter period. There were no significant difference between physicians who had trained on rational drug use and had not trained yet in urban PHCC (p=0.874), while in rural PHCC there were a significant difference among them. Conclusions The quantitative analysis showed that the antibiotics use in DDD in urban PHCC was 3,544.416 and in rural PHCC was 3,478.693. Factors affected to the quality of antibiotic use were physician's years of service and rational drug use training's.

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 Widyawaruyanti, Nasronudin Nasronudin

Page range: 737-742

Abstract

Objectives Human immunodeficiency virus (HIV) infection is considered as a major immunosuppressive disease linked to malignancies and other

opportunistic infections. Recently, the high prevalence of HIV drug-resistant strains required a high demand for novel antiviral drug development, especially in herbal medicine approaches. The objective of this study was to evaluate the possibility of Ficus fistulosa leaves can inhibit HIV replication in ethanol extract form as well as its fractions using chloroform, ethyl acetate, and butanol solvents. Methods F. fistulosa leaves were extracted using ethanol as a solvent and further gradually fractionated in chloroform, ethyl acetate, and butanol solvents. The targeted persistently infected virus (MT4/HIV) cell lines were cocultured with ethanol extract and fractions at different time points. The syncytium formation and cytotoxicity assays were performed to evaluate the potential antiviral activity of F. fistulosa leaves. Results One of the four tested extract/fractions showed antiviral activity against HIV. The ethanol extract showed weak inhibition with a high level of toxicity (IC 50 = 8.96 μg/mL, CC 50 ≥50 μg/mL, and SI = 5.58). Meanwhile, chloroform fraction effectively inhibited the MT4/HIV cell proliferation while keeping the toxicity to a minimal level (IC 50 = 3.27 μg/mL, CC 50 = 29.30 μg/mL, and SI = 8.96). In contrast of ethyl acetate fraction and butanol fraction showed no anti HIV activity with a high level of toxicity (CC 50 ≥50 μg/mL) and low SI value (>2.17 μg/mL and >0.97 μg/mL). Conclusions Chloroform fraction of F. fistulosa leaves showed effectively as anti-viral activity against MT4/HIV cells.

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

Abstract

Objectives This study aims to determine the characteristics of Lactobacillus acidophilus and Lactobacillus reuteri from fermented soursop fruit juice and cow's milk, respectively as probiotic candidate based on exposure to pH, bile salts, pathogenic bacteria, and antibiotics. Methods In vitro studies were conducted to examine the resistance of Lactobacillus acidophilus and Lactobacillus reuteri in pH 2, 2.5, 3.2, and 7.2, resistance to bile salts, resistance to pathogenic bacteria (Escherichia coli, Staphylococcus aureus and Enterococcus faecalis) and antituberculosis antibiotics. Results Viability of Lactobacillus acidophilus and Lactobacillus reuteri isolates remained unchanged (6.3 × 10 7 CFU/mL and 5.03 × 10 7 CFU/mL) at various acidic pH, and had a low survival rate in Ox gall 0.3% (bile salts). These isolates also showed antibacterial properties against pathogens in the gastrointestinal

tract. Both of these bacteria are quite safe to be used together with ofloxacin, linezolid, moxifloxacin, and levofloxacin, antibiotic for tuberculosis therapy. Conclusions The results showed that Lactobacillus acidophilus and Lactobacillus reuteri from fermented soursop fruit juice and cow's milk respectively fulfilled the characteristics of probiotic and could potentially be used as adjunct therapy in tuberculosis drug-resistance.

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

Abstract

Objectives Escherichia coli is one of the pathogenic bacteria that caused a nosocomial infection. Levofloxacin is one of the fluoroquinolones group antibiotics which is a broad-spectrum antibiotic that works effectively against E. coli . The mutation can happen in the bacteria which caused a resistant effect in the use of antibacterial. This study aimed at identifying mutation in gene gyrA among E. coli that were resistant to levofloxacin. Methods The susceptibility of E . coli was determined by disk diffusion. PCR and sequencing were performed to identify the mutation in gyrA . Results A total of 10 isolates showed result resistance to levofloxacin and gyrA gene mutation in the amino acid changes. Nucleotide sequence analysis revealed a point mutation in QRDR (quinolone resistance determining region) of gyrA Ser83→Leu, Asp87→Asn. The silent mutation was also found at codon Val85, Arg91, Ser111, Thr123. Conclusions Mutation in the gyrA gene affect the occurrence of bacterial resistance of E. coli to levofloxacin.

June 25, 2021

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

Siti Mudaliana

Page range: 755–759

Abstract

Objectives Antibiotic treatments can create multi-drug resistance among several pathogens. There is a need for an antibiotic alternative to overcome this problem. In Indonesia, Centella asiatica (Asiatic pennywort) and Gigantochloa apus (string bamboo) are two common medicinal plants used to treat tuberculosis, diarrhea, and other symptoms. This study was done to

compare the antimicrobial activity of C. asiatica and G. apus against five pathogenic bacteria, i.e., Mycobacterium tuberculosis H37Rv strain, Escherichia coli , Staphylococcus aureus , Bacillus subtilis , and Salmonella typhi . Methods The ethanol extracts of C. asiatica , and G. apus shoot were obtained by using speed extractor, pressure, and temperature extraction. The phytochemical contents of each extract were screened. The ethanol extract's antimycobacterial activity was determined using Lowenstein Jensen (LJ) medium and antibacterial activity was determined using Kirby–Bauer methods on Mueller Hinton agar (MHA). Results The phytochemical analysis showed that G. apus extract contains alkaloids and tannins, whereas C. asiatica extract contains flavonoids, alkaloids, saponins, and tannins. This study showed that G. apus inhibited the growth of M. tuberculosis H37Rv strain and S. typhi . C. asiatica showed antimicrobial activity against all pathogenic bacteria tested, except B. subtilis . Conclusions Both medicinal plants extract can inhibit the growth of five pathogenic bacteria tested, thus, have the potential as an alternative treatment, or complementary, to treat the pathogenic bacterial infection.

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

Abstract

Objectives Gastroenteritis is a disease of digestive system commonly occur among the people. Some cases of gastroenteritis are caused by bacteria, so it is treated by using antibiotics. Inappropriate use of antibiotics can be associated to Drug-Related Problems (DRPs). This study aims to identify patterns of potential DRPs of antibiotic use and analyze the effect of potential DRPs of antibiotic use toward the patient's therapeutic outcomes and length of stay. Methods This is a retrospective cross-sectional study carried out by using patient's medical record. The study population was gastroenteritis patients at the inpatient ward of Universitas Gadjah Mada Hospital during January 2018–June 2019. Then, SPSS was employed to analyze the data and the effect of potential DRPs toward therapeutic outcomes was analyzed by utilizing the chi-square method. Results More than half of gastroenteritis patients in Universitas Gadjah Mada Hospital were identified to have potential DRPs of antibiotic use. The most identified of potential DRPs was problems related to drug selection. Based on the chi-square analysis, there was no relationship between potential DRPs of

antibiotic use and the therapeutic outcome. In addition, there was also no relationship between potential DRPs of antibiotic use and patient's length of stay. Conclusions The potential DRPs of antibiotics use do not have a significant effect on the therapeutic outcome and length of stay of the gastroenteritis patients in Universitas Gadjah Mada Hospital.

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

Abstract

Objectives Currently, respiratory infection is regarded as one of the most common infectious diseases. This study aims to find out the impact of appropriate use of empirical antibiotic on therapeutic outcomes of patients with respiratory infections at inpatient wards of UGM Academic Hospital. Methods This is a cross-sectional study that uses retrospective data through patient medical records. The population was all patients who received empirical antibiotic therapy for respiratory infections at inpatient ward from July 2018 to July 2019. The sample was collected using the purposive sampling method, and the total number of samples was 192. The appropriate use of empirical antibiotic including the correct type, dosage, route, duration, and frequency was evaluated according to the Antibiotic Guidelines of UGM Academic Hospital 2018, Drug Information Handbook, Frank Shann Drug Doses, Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) 2016 & 2019, Pharmacotherapy Handbook 2015, and Pharmaceutical Care for Respiratory Tract Infections 2005. The data was analyzed descriptively by using Chi-square bivariate analysis. Results The result shows that 47.9% of 192 patients have received antibiotics properly according to the type, route, dose, frequency, and duration. The results of empirical antibiotic therapy have improved the repair of vital signs in 37.5% of patients. Meanwhile, the result of Chi-square bivariate analysis between the suitability of empirical antibiotic use and the improvement of therapeutic outcome is p=0.478 (p>0.05), which means that it is not statically significant. Conclusions It can be concluded that there is no correlation between the suitability of empirical antibiotics use and the improvement of the therapy outcomes. Thus, the use of empirical antibiotics based on the guidelines does not always have an impact on the improvement of the treatment outcomes

of the patients with respiratory infection at inpatient wards of UGM Academic Hospital.

June 25, 2021

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

Risa Zulfiana, Suharjono, Kuntaman

Page range: 773–776

Abstract

Objectives Staphylococcus aureus is one of the bacteria which causes nosocomial infection. Methicillin-Resistant Staphylococcus Aureus eradication using antibiotics combined with rifampicin has shown good results, whereas, adjuvant rifampicin has long been hypothesized to improve the outcome of S. aureus infection treatment. Resistant-rifampicin S. aureus mutates in rpoB gene at some codons. This study was conducted to identify the mutation of rpoB gene in S. aureus which was resistant toward rifampicin. Methods In this study, isolates collected in the Microbiology Laboratory of Dr. Seotomo Surabaya Hospital during May–September 2019. Then, the dilution method was carried out to determine the minimum inhibition concentration for resistant-rifampicin and dilution to determine the inhibition zone diameter. After that, DNA extraction was carried out from rifampicin-susceptible isolates as a control and resistant-rifampicin isolates followed by identification of rpoB gene mutations by Polymerase Chain Reaction (PCR) and sequencing. Results There were nine isolates studied. They were four resistant-rifampicin isolates and four susceptible-rifampicin isolates. In four rifampicin-resistant isolates, the most frequent mutations that occurred was His-481 codon (75%) followed by the Ile-527 codon (25%). Rifampicin-susceptible isolates mutated in Pro-475 and Asn-474 codons. One rifampicin-resistant isolate had two mutations in codons Ile-527 and Asn-474. Conclusions The type of mutation that causes the most rifampicin resistance was a missense mutation. The susceptible-rifampicin isolate experienced silent mutations. There was a relation between the type of missense mutation of rpoB gene and rifampin resistance.

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

Abstract

Objectives This study aimed to estimate the prevalence and analyze the risk factors for linezolid-induced hematological side effects in multidrug-resistant tuberculosis (MDR-TB) patients. Methods Data were collected from medical records of MDR-TB patients who received linezolid between January 2018 and May 2020. Statistical significance analysis and multivariate analysis were performed with SPSS version 24 software. Results Hematological side effects were identified in 27 out of 93 patients (29.0%). The most prevalent effect was anemia (29.0%), while the less prevalent effects were thrombocytopenia (3.2%) and leukopenia (2.2%). These side effects were reported after 2 weeks of linezolid treatment. The drug dose was more than 11 mg/kgBW/day or patient weighing less than 54 kg was identified as an independent risk factor for anemia in multivariate analysis. Conclusions Anemia was the most prevalent of linezolid-induced hematological side effects in MDR-TB patients. Therefore, hemoglobin monitoring might be recommended in patients weighing less than 54 kg and after receiving linezolid therapy for at least 2 weeks.

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

Abstract

Objectives This study was conducted to assess adverse drug reactions and their management in MDR-TB patients. Indonesia is the fifth highest country with multidrug-resistant tuberculosis (MDR-TB) high burden around the world. The number of MDR-TB patients in Indonesia is increasing every year, but the data regarding ADRs are still limited. Therefore, more data on their characteristics and their management is very valuable for clinicians and pharmacists. Methods The study is a descriptive study, using retrospective data of MDR-TB patients who completed therapy from January 1st, 2015 to December 31st, 2015 at the Tuberculosis Outpatient unit at the Dr. Soetomo Teaching Hospital Indonesia. Each adverse effect was judged with standards of the clinic and was documented in patients' medical records. Results There were 40 patients included in this study. During therapy, 70% of patients developed at least one adverse drug reaction. The five most prevalent adverse effects found in this study were hyperuricemia (52.5%) followed by

gastrointestinal (GI) disturbances (40%), ototoxicity (37.5%), hypokalemia (27.5%), and athralgia (12.5%). Managements that were undertaken to overcome the adverse drug reactions were adding symptomatic drugs and/or modifying the treatment regimen. Conclusions Because of the small samples we cannot attain a general conclusion. However, the result of this study is very imperative as this data gives us insight regarding adverse effects in MDR-TB patients in Indonesia.

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

Abstract

Objectives The widespread use of inappropriate prophylactic antibiotics in urological surgery patients can increase the risk of resistance and development of postoperative infection. This study was aimed to analyze the quality of prophylactic antibiotics use and identify the risk factor of postoperative nosocomial infection in urological surgery patients. Methods Observational prospective data were obtained from patients' medical records. Data were the pattern of prophylactic antibiotic use in surgical patients' urology in Dr. H. Slamet Martodirdjo Hospital, Pamekasan, for the period of April–June 2020. Inclusion criteria included patients hospitalized with urological surgery and received prophylactic antibiotics before surgery. Exclusion criteria consisted of medical records that were incomplete, and the patient disagreed to participate in the research. Analysis qualitative antibiotic prophylactic used the Gyssens method and risk factor used Chi square. Results Seventeen patients were not administered for antibiotic prophylactic and nine patients with skin incision were observed to determine the incidence of surgical site infection (SSI) and 55 patients with urethral incision were observed to determine the incidence of urinary tract infection (UTI) postoperative. There was no incidence of SSI and there were three incidences of UTI. The qualitative analysis of the Gyssens method showed that category-0 was of 51 (79.7%) and category-I was of 13 (20.31%). Conclusions The quality of the use of prophylactic antibiotics with the Gyssens method shows that there is an appropriate category (category-0) and a few are in category-I (inappropriate administration time) and no incidence of surgical wound infection.

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 Budiatin, Siswandono Siswodihardjo, Junaidi Khotib

Page range: 795-802

Abstract

Objectives Histamine N -methyltransferase (HNMT) is an enzyme that plays a crucial role in the inactivation of histamine in central nervous system, kidneys and bronchi. Inhibition of HNMT is known to have a potential role in treating attention-deficit hyperactivity disorder, memory impairment, mental illness and neurodegenerative illnesses. Therefore, to find potential compounds that could be developed as novel HNMT inhibitors, this study conducted an in silico study of the secondary metabolites of Nigella sativa L and Curcuma xanthorrhiza Roxb . Methods In this study, we conducted a molecular docking study of 36 secondary metabolites of N. sativa L and 26 secondary metabolites of C. xanthorrhiza Roxb using an in silico approach targeting HNMT protein (PDB ID: 2AOT) using AutoDockVina software. The prediction of ADMET characteristics was done using the pkCSM Online Tool. Results This study obtained one metabolite from N. sativa L (longifolene) and seven metabolites from C. xanthorrhiza Roxb {(+)-beta-atlantone, humulene epoxide, (−)-beta-curcumene, (E)-caryophyllene, germacrone, (R)-(−)-xanthorrhizol, and (−)-beta-caryophyllene epoxide} which were predicted to have potential to be developed as HNMT inhibitors. Conclusions This study found several secondary metabolites of N. sativa L and C. xanthorrhiza Roxb which had activity as HNMT inhibitors. This research can likewise be utilized as a basis for further research, both in vitro , in vivo , and clinical trials related to the development of secondary metabolites from N. sativa L and C. xanthorrhiza Roxb as novel HNMT inhibitor compounds.

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

Abstract

Objectives Estrogen deficiency causes various health problems in postmenopausal women, including osteoporosis. Phytoestrogen emerged as a potential alternative of estrogen with minimum side effects. The aims of this study were to analyze the metabolite profiling results of various extract of Chyrsophyllum cainito L. leaves, which contain phytoestrogen, through in silico study against 3OLS protein, an X-ray protein of ERβ, so it can predict the types of the phytoestrogen contents which have antiosteoporosis property. Methods In silico analysis was carried out for the compounds from the metabolite profiling data of C. cainito leaves from our previous study. The structure compounds from metabolite profiling results of various extract of C. cainito leaves were prepared with Avogadro 1.0.1 software, molecular docking was done using PyRx 0.8 software, and Biovia Discovery Studio Visualizer 2016 software was used to visualize the structure of compounds against 3OLS protein. The physicochemical characteristics of the compounds were analyzed using the SwissADME web tool. Results From in silico studies, it was known that there were total 11 compounds in C. cainito leaves that predicted as phytoestrogens which have ERβ agonist properties against 3OLS protein. The ERβ agonist was a compound that has parameters similar to 17β-estradiol in its interaction with 3OLS protein, which has a pharmacophore distance of 10.862 Å, and binding to amino acids His 475 and Glu 305 or Arg 346 at receptor-ligand docking simulation. Conclusions C. cainito leaves contain 11 compounds that are predicted to be phytoestrogens with ERβ agonist properties, which is responsible for antiosteoporosis activity.

June 25, 2021

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

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

Page range: 809–815

Abstract

Objectives Phyllanthus niruri has been known as an immunomodulator and also reported to possess an antiviral activity against several RNA viruses, such as hepatitis B virus and hepatitis C virus by inhibiting viral entry and replication. Since the current situation of Coronavirus Disease 2019 (COVID-19) which infected among the world and caused severe disease and high morbidity, it urgently needed to find new agents against COVID-19. Therefore,

in silico screening against COVID-19 receptors is carried out as an initial stage of drug discovery by evaluating the activity of phyllanthin and hypophyllanthin, an isolated from Phyllanthus niruri , in inhibiting spike glycoprotein (6LZG) and main protease (5R7Y) which play as target receptors of COVID-19. Methods Molegro Virtual Docker 6.0 used to determine the best binding energy through the rerank score which shows the total energy bonds calculation. Results Phyllanthin and hypophyllanthin demonstrated to possess greater binding affinity toward the COVID-19 inhibition sites than their native ligand. The rerank score of phyllanthin and hypophyllanthin are lower than the native ligands 6LZG and 5R7Y. This result indicated that phyllanthin and hypophyllanthin have a stronger interaction than the native ligands both in spike glycoprotein (entry inhibitor) and main protease (translation and replication inhibitor). Conclusions In conclusion, phyllanthin and hypophyllanthin are predicted to have strong activity against COVID-19 through inhibiting spike glycoprotein and main protease under in silico study. Further research is needed to support the development of P. niruri as inhibitor agents of COVID-19 through bioassay studies.

June 25, 2021

***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

Abstract

Objectives The antimalarial drug resistance is an obstacle in the effort to overcome malaria. The new alternative antimalarial drug became in great attention of urgent need. Current antimalarial drugs were derived from plants. Therefore, the plant is considering a potential source of new drugs. Cratoxylum sumatranum belongs to the Hypericaceae family contain xanthones and phenolic compounds, which was reported for their antimalarial activities. This study aims to determine the antimalarial activities of C. sumatranum extracts and fractions. Methods Cratoxylum sumatranum stem bark (BP14-SB) collected from Balikpapan Botanical Garden in East Kalimantan, Indonesia, was extracted gradually with n-hexane, dichloromethane, and methanol by ultrasonic-assisted extraction method. All extracts were tested against Plasmodium falciparum 3D7 by lactate dehydrogenase (LDH) assay and followed by IC 50 determination. The most active extract was further separated and tested for their antimalarial activities. Results The results showed that dichloromethane stem bark

extract (BP14-SB-D) had the strongest inhibition of parasite growth with the IC 50 value of 0.44 ± 0.05 µg/mL and moderately toxic with the CC 50 value of 29.09 ± 0.05 µg/mL. Further fractionation of BP14-SB-D by open column chromatography using silica gel and gradient hexane–ethyl acetate obtained 12 fractions. LDH assay for these 12 fractions of BP14-SB-D showed that Fraction-6 (IC 50 value of 0.19 ± 0.03 µg/mL) was performed the strongest inhibition of parasite growth, compared to other fractions. TLC identification showed that BP14-SB-D contains xanthone. Conclusions The dichloromethane extract of C. sumatranum stem bark (BP14-SB-D) and Fraction-6 from this extract exhibited antimalarial activity and the potential to be developed an antimalarial substance.

June 25, 2021

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

Kartika Dyah Palupi, Muhammad Ilyas, Andria Agusta

Page range: 823-829

Abstract

Objectives Endophytic fungi are an essential source of biologically active compounds. They have the ability to synthesize secondary metabolites which are the same or have a high degree of similarity to their host plants. In this study, we aimed to explore the biodiversity and the bioactivities of active metabolites produced by 14 endophytic fungi isolated from the medicinal plant Physalis angulata L. (PA). Methods Fourteen endophytic fungi were isolated from the flowers, stems, leaves, and fruit husks of PA. The endophytic fungi were cultured and incubated in the PDB medium at room temperature. After three weeks, the cultures were extracted using ethyl acetate and dried using a rotary evaporator. The antioxidant activity was evaluated against DPPH while antibacterial activity was evaluated against Escherichia coli and Staphylococcus aureus using microdilution technique. TLC analysis was also done to profile the active compounds within the extract. Results Hyphomycetes fungus isolated from the flower of PA exhibited a moderate antioxidant activity with an antioxidant index value of 0.59 (IC 50 = 52.43 µg/mL). Six isolates have strong antibacterial activity against E. coli and S. aureus with minimum inhibitory concentration (MIC) value ranging from 8–64 µg/mL. These endophytic fungi are one Hyphomycetes fungus isolated from the flower, one Fusarium sp. isolated from the stem, and four Colletotrichum sp. isolated from leaf and fruit husk of PA. Conclusions Endophytic fungi isolated from PA are potential novel sources of active metabolites especially for antibacterial compounds.

June 25, 2021

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

Abstract

Objectives Osteoporosis is an ailment described by a skeletal degradation of bone skeletal dominating to increases the chance of fracture. In order to find out the bone formation agents from Baung Forest plants, this research analyzed the effects of 96% ethanol extract of several plants from Baung Forest on antioxidant activity and the effect of osteoblast differentiation-related to the bone formation on the most potent extract. Methods The antioxidant effect and osteoblast differentiation of 96% ethanol extracts were evaluated by measuring DPPH scavenging and alkaline phosphatase in p -

nitrophenyl phosphate effects by the enzyme-linked immunosorbent assay (ELISA) reader method, respectively. Results The 96% ethanol extract of Elaeocarpus serratus L. from Baung Forest had the strongest DPPH radical scavenging as anti oxidant (82.17%) and stimulated osteoblast differentiation (116%). Then, this extract had been fractionated based on polarity to become hexane, ethyl acetate, butanol, and aqueous fractions. All the fractions stimulated their alkaline phosphatase (ALP) activity to 138.11 ± 9.72%, 108 ± 5.05%, 148.56 ± 8.47, and 144.58 ± 1.04, respectively. Conclusions The extract and fractions of E. serratus L. can successfully inhibit DPPH radical scavenging value and increase ALP activities as markers of osteoblast functions.

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 Kemalahayati, Lidya Tumewu, Fendi Yoga Wardana, Suciati, Achmad Fuad Hafid, Aty Widyawaruyanti

Page range: 839-844

Abstract

Objectives The rapid spread of antimalarial drug resistance is becoming a problem in the treatment of malaria. The fact was indicated the importance of finding new antimalarial drugs. The genus Garcinia is well known to be a rich source of bioactive prenylated xanthones and triterpenes reported for their antimalarial activity. Garcinia parvifolia is one of the Garcinia genera that can be explored for the search of new antimalarial drugs. This study was aimed to determine the antimalarial activities of G. parvifolia extracts and fractions. Methods Garcinia parvifolia Miq. stem was collected from Balikpapan Botanical Garden in East Kalimantan, Indonesia, was extracted gradually with n-hexane, dichloromethane, and methanol by ultrasonic assisted method. The most active extract was further separated using the open column chromatography method. All extracts and fractions were tested against Plasmodium falciparum 3D7 using lactate dehydrogenase (LDH) assay and followed by IC 50 determination. Results The results showed that all extracts inhibit P. falciparum growth by LDH assay. The highest inhibition was showed by dichloromethane stem extract (BP12-S-D) with the IC 50 value of 6.61 ± 0.09 µg/mL. Further fractionation of BP12-S-D has obtained 10 fractions. All of them were identified by TLC, and a brownish-yellow spot (fraction-1) appears after spraying with 10% H 2 SO 4 . Fraction-1 (F1) performed the highest parasite growth inhibition with the IC 50 value of 6.00 ± 0.03 µg/mL compared with other fractions. This fraction

was classified as having a promising activity of antimalarial. The fraction-1 was identified using HPLC, and two major peaks were observed (A and B). The UV–Vis spectra showed the absorption at wavelengths 250 and 278 (A), 243, 281, and 317 nm (B). Based on the profile of TLC, HPLC, and UV–Vis spectra of F1, it was expected that the active compounds are flavonoid (A) and xanthone (B). Conclusions The fraction-1 of dichloromethane extract of G. parvifolia Miq. stem has the highest antimalarial activity. It might be a potential candidate for the new antimalarial drug.

June 25, 2021

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

Abstract

Objectives This study aims to evaluate the antioxidant and antiviral potency of n -hexane, ethyl acetate and, water fractions of Begonia medicinalis Ardi & D.C.Thomas as well as to identify the chemical constituents. Methods Assays for antioxidant and antiviral activity (HIV-1) were carried out on MT-4 cells infected with HIV using the DPPH method and the determination of the cytopathic effect. Meanwhile, GC-MS was used to identify the chemical compounds. Results The determination of antioxidants showed that all fractions possessed potent activity with the IC 50 ranging from 2.61 to 8.26 µg/mL. From the antiviral activity of MT-4 cells infected by HIV, the n -hexane fraction of B. medicinalis showed the most potency with the IC 50 of 0.04 ± 0.05 µg/mL. It has less cytotoxicity (11.08 ± 4.60 µg/mL) affording the high selectivity index of 238.80. Furthermore, GC-MS analysis of n-hexane fraction found the major compound of carboxylic acid derivate with the area percentage of 76.4% and the presence of phenolic compounds (8.38%). Meanwhile, in water fraction, terpenoids were found in a higher concentration (10.05%) than others. Conclusions Therefore, this study supports the application of B. medicinalis as a herbal medicine for antioxidant and antiviral.

June 25, 2021

Artocarpus sericicarpus* 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

Abstract

Objectives The finding of alternative medicine for malarial treatment still has become a substantial demand. The plant is one of the potential sources of drugs, among other natural sources. Artocarpus species showed great potential as the antimalarial source. This study aims to obtain active antimalarial fractions from Artocarpus sericicarpus stem bark. Methods Stem bark of A. sericicarpus was extracted by ultrasonic-assisted extraction method using n-hexane, dichloromethane, and methanol as solvents. Fractionation of dichloromethane extract was conducted by open column chromatography using octadecyl silica as a stationary phase and gradient acetonitrile-water as a mobile phase. The antimalarial activity was determined by lactate dehydrogenase (LDH) assay against Plasmodium falciparum 3D7 strain. Results A. sericicarpus n-hexane, dichloromethane, and methanol extracts were showed antimalarial activity with an IC 50 value of >4, 2.11, and >4 µg/mL, respectively. Fractionation of dichloromethane extract was obtained 13 fractions. Seven of the 13 fractions tested showed antimalarial activity. Fraction-6 performed the highest inhibition with an IC 50 value of 1.53 ± 0.04 µg/mL. Phytochemistry screening revealed that Fraction-6 contains flavonoid, polyphenol, and terpenoid compounds that can take a role in its antimalarial activity. Conclusions A. sericicarpus contains antimalarial substances mainly in Fraction-6, which strongly inhibited the growth of P. falciparum . The flavonoid, polyphenol, and terpenoid compounds were identified in Fraction-6, which need to be further isolated to obtain and elucidate the active antimalarial compounds.

June 25, 2021

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

Rahmi Annisa, Mochammad Yuwono, Esti Hendradi

Page range: 859–865

Abstract

Objectives This study aimed to determine the effect of different components and ratios of oil, surfactant, and cosurfactant on E. palmifolia extract-loaded SNEDDS. Methods E. palmifolia extract loaded SNEDDS was formulated from virgin coconut oil, Miglyol 812 as oil, using Tween 80 and Transcutol as surfactants, as well as propylene glycol and PEG 400 as cosurfactants. The optimization design formula consisted of eight design formulas in five ratio

formulas, thus a total of 40 formulas were optimized using different components and ratios of oil, surfactant, and cosurfactant. These ratios used were 1:1:1, 1:2:1, 1:3:1, 1:4:1, as well as 1:5:1, and the formula's components were determined based on the optimization results. Results The optimal formula of E. palmifolia extract loaded SNEDDS had the ratio 1:1:1 (formula A) of Miglyol 812:Tween 80:PEG 400 and 1:3:1 (formula E) of Miglyol 812:Tween 80:propylene glycol. Meanwhile, the optimal formulation characteristics showed a transmittance value above 90%, pH range of 5.10–5.20, 2.21–14.51 cP viscosity, emulsification time below 120 s, and particle size of 24.71–136.77 nm. Conclusions The optimal formula of E. palmifolia extract-loaded SNEDDS, were obtained using different components and ratios. These are Miglyol:Tween 80:PEG 400 at a component ratio of 1:1:1 (formula A) and Miglyol 812:Tween 80:propylene glycol at a component ratio of 1:3:1 (formula E).

June 25, 2021

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

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

Page range: 867-873

Abstract

Objectives Curcumin belongs to the family of curcuminoids, natural polyphenolic compounds that possesses neuroprotective properties, anti inflammatory and anticancer. Its entrapment in the developed casein-based micellar powder (CMP) and poloxamer-based micellar powder (PMP) was to enhance the solubility and improve the bioavailability. Henceforth, the present study aimed to acquire an efficient analytical method for the curcumin analysis in polymeric micellar formulations. Methods A fast and specific HPLC method was developed for analyzing curcumin in two different micellar matrices using casein and poloxamer. The HPLC was equipped with a C18 column (250 × 4 mm, 5 µm) and diode array detector. A designated isocratic elution of curcumin was employed using mobile phase with a composition of water (1%, v/v acetic acid) and acetonitrile in a ratio of 50:50 v/v. The employed flow rate was 1.0 mL/min and the analyte was examined at 421 nm. Results An effective analysis in HPLC was successfully achieved by the predetermined HPLC condition. A good resolution of peaks at the employed flow rate was achieved. The linearity was excellent in two different range of concentrations, 2–20 and 10–50 µg/mL. The selectivity, accuracy and precision fulfilled the acceptable requirements. Conclusions The developed

method was practically effective to qualitatively identified curcumin. In addition, the assay also effectively quantified the amount of curcumin in the polymeric entrapping matrices which demonstrates that it has great potential to be used in natural compound analysis.

June 25, 2021

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

Abstract

Objectives Community pharmacist has been widely known as a health professional who can be easily accessed to provide medicines and reliable medicine information. However, this was not always in the case of dispensing natural medicines. Several international studies revealed that community pharmacists were less likely to deliver natural medicines accompanied with detailed information. Therefore, this study aimed to investigate factors influencing Indonesian community pharmacists in the supply of, delivery of, and provision of information about natural medicines. Methods A qualitative study with purposively selected community pharmacists in four areas (district or municipality) in East Java Province was designed. In-depth, semi-structured interviewed were conducted using a Capability-Opportunity-Motivation-Behaviour approach. All interviews were audio-recorded, transcribed ad verbatim , and thematically analysed. Results Data saturation was reached after interviewing 14 community pharmacists. All informants reported dispensing non-prescribed natural medicines. Nine had experienced dispensing prescribed natural medicines, mainly fulfilling paediatricians' requests. The most common information given was about product usage, while information about safety (i.e. side effects, interaction) was rarely provided. Although numerous registered natural medicines have been available, informants had low motivation to supply a variety of types, primarily because little opportunity to receive requests from doctors and the community. Limited capability due to a lack reliable source of information about natural medicines was another reason. Conclusions Poor motivation to supply natural medicines was because community pharmacists had little opportunity for such requests and limited capability due to scarcity of information. This indicated support from natural medicine manufacturers, researchers, and the government is highly required.

June 25, 2021

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

Page range: 881–887

Abstract

Objectives Osteoporosis is the result of an imbalance in the rate of bone resorption and bone formation due to a decrease in estrogen. Phytoestrogens are plant compounds with structures and functions similar to estrogen. Phytoestrogens that bind to estrogen receptors in bone cells are able to modulate bone formation. Semanggi (Marsilea crenata Presl.) is a plant that contains phytoestrogens. The purpose of this study was to observe the expression of osteocalcin and predict the content of extract phytoestrogens through a computer simulation study to study the bone formation activity of the 96% ethanol extract of M. crenata leaves on hFOB 1.19 cells. Methods hFOB 1.19 cells were cultured in 24-well microplates, and 96% ethanol extract of M. crenata Presl. leaves was added at 62.5, 125 and 250 ppm. The expression of osteocalcin was analyzed using CLSM immunocytochemistry. Using PyRx 0.8 software and 1ERE protein for molecular docking, the compound was analyzed by computer. Results The 96% ethanol extract of M. crenata Presl. leaves can increase the expression of osteocalcin, the optimal dose is 125 ppm, and $p<0.05$ is 881.658 AU. In silico study was obtained six compounds that showed similar activity 17β-estradiol as ER-β agonists. Conclusions The 96% ethanol extract of M. crenata Presl. leaves contain six compounds that are thought to be phytoestrogens and ER-β agonists, and play a role in increasing bone formation activity and have the potential to be used as an oral drug.

June 25, 2021

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

Abstract

Objectives In food ingestion, alpha-glucosidase (α-glucosidase) and alpha-amylase (α-amylase) are enzymes that are responsible to convert a carbohydrate into glucose. Inhibition of both enzyme activities can prolong absorption of glucose in intestine and reduce post-prandial increase of blood

glucose concentration, thus, it is beneficial for type-2 diabetes treatment. Traditionally, Urena lobata (U. lobata) has been used to manage diabetes, but the scientific proof of this claim remains scarce. Therefore, the objective of this study to examine the anti-diabetic potential of U. lobata leaf extract through inhibition of α-amylase and α-glucosidase. Methods U. lobata leaf extract was obtained through extraction process using ethanol and the chemical compounds in the extract were analyzed by liquid chromatography–mass spectra (LC–MS). The inhibitory activity of U. lobata on α-glucosidase and α-amylase was evaluated by in silico using docking server, whereas in vitro enzymatic assays were using para- nitrophenyl-α- d -glucopyranoside (α-NPG) and starch as substrates. The data were presented as mean ± SD and the IC 50 value was calculated using SPSS. Results U. lobata leaf extract showed inhibitory activity on α-glucosidase and α-amylase with the IC 50 value was 43.73 and 83.73 µg/mL, respectively, meanwhile, acarbose as standard has IC 50 value at 1.14 and 0.08 µg/mL. Molecular docking study indicated β-sitosterol and stigmasterol from U. lobata extract have a huge inhibitory activity both on α-amylase and α-glucosidase based on inhibition constant (Ki) value. Conclusions Ethanolic extract of U. lobata showed inhibition activity on α-glucosidase stronger than on α-amylase as antidiabetic.

Case Report

June 25, 2021

Effect of hydrocortisone on hypocorticolism caused by pituitary adenoma

Niswah N. Qonita, Hanik B. Hidayati

Page range: 895–898

Abstract

Objectives Pituitary adenoma is a tumor that can cause hormonal secretion problems, including hypocortisolism. Hypocortisolism may result in negative impacts such as an increase in proinflammatory cytokine and immune system activation. Hypocortisolism therapy is performed by giving high-dose hydrocortisone. This case report presented a hypocortisolism therapy using hydrocortisone in a patient with pituitary adenoma. Case presentation A 17-year-old boy was admitted to a hospital due to right-eye vision loss, headache, and swallowing difficulty. During the treatment at the hospital, the patient had light depression. The brain Magnetic Resonance Imaging (MRI) scanning with contrast showed there was a supratentorial axial lesion enlarged from the intrasellar to the suprasellar. The anamnesis and physical

examination, as well as laboratory and supporting examinations, showed that the patient was diagnosed to suffer from pituitary macroadenoma. The laboratory examination showed that the size of hypocortisolism was at <0.5 μg/dL (reference value ranges from 4.30–22.40 μg/dL). The patient was treated with hydrocortisone IV therapy at 100 mg/dose administered in the morning and evening for 4 days. Then, the dose tapering off of 100 mg/dose was administered in the morning for 4 days. After that, the patient received hydrocortisone of 20 mg/dose peroral administration in the morning and evening until the patient was discharged from the hospital. Tapering off was performed to prevent the side effects of high-dose hydrocortisone. Besides, the patient was alsounder the Endoscopic Endonasal Transsphenoidal Hypophysectomy (EETH). The cortisol level in the pretreatment was at <0.5 and 5.3 μg/dL during the treatment. There were no side effects of the treatment when the patients were hospitalized. Conclusions The hydrocortisone IV therapy with 100 mg/do was administered in the morning and evening for 4 days, and then the dose tapering off of 100 mg/dose was done in the morning for 4 days. Then, the hydrocortisone therapy of 20 mg/dose peroral administration to the patient with pituitary macroadenoma in the morning and evening to improve the cortisol level. The cortisol level in the pretreatment was at 0.5 and 5.3 μg/dL in the post-treatment.

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

N-nitrosodiethylamine induces inflammation of liver in mice

https://doi.org/10.1515/jbcpp-2020-0475
Received November 29, 2020; accepted March 8, 2021

Abstract

Objectives: For designing early treatment for liver cancer, it is important to prepare an animal model to evaluate cancer prevention treatment by using inflammation disease. The hepatocarcinogenic N-Nitrosodiethylamine (NDEA) has been reportedly able to produce free radicals that cause liver inflammation leading to liver carcinoma. This study aimed to evaluate the inflammation disease model of mice induced with hepatocarcinogenic NDEA for five weeks induction.

Methods: The BALB-c mice were induced with NDEA 25 mg/kg of body weight once a week for five weeks intraperitonially and it was then evaluated for the body weight during study periods. The mice were then sacrificed and excised for evaluating their organs including physical and morphological appearances and histopathology evaluations.

Results: The results showed a significant decrease of body weight of mice after five times induction of 25 mg NDEA/kgBW per week intraperitonially. Different morphological appearances and weight of mice organs specifically for liver and spleen had also been observed. The histopathology examination showed that there were hepatic lipidosis and steatohepatitis observed in liver and spleen, respectively that might indicate the hepatocellular injury.

Conclusions: It can be concluded that inducing mice with NDEA intraperitonially resulted in fatty liver disease leading to progress of cancer disease.

***Corresponding author: Andang Miatmoko**, Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, 60115, Surabaya, Indonesia, Phone: +6231 5933150, E-mail: andang-m@ff.unair.ac.id

Devy Maulidya Cahyani, Berlian Sarasitha Hariawan and Retno Sari, Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

Kusuma Eko Purwantari, Department of Anatomy and Histology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Keywords: cancer; inflammation; liver; mice; n-nitrosodiethylamine.

Introduction

Cancer is the world's leading health problem and the second leading cause of death in United States [1]. Cancer continues to increase worldwide, primary liver cancer is the leading cause of cancer with case about 841,000 new patients and causing 782,000 deaths in 2018 [2, 3]. There are two types of liver cancer, first *Hepatocellular carcinoma* (HCC) which causes 75% of all liver cancer cases and *Intrahepatic Cholangiocarcinoma* (ICC) which causes 12–15% of incidence [4]. HCC comes from hepatocytes, in which it is caused due to oxidative stress, inflammation, and is based on liver disease. On the other hand, ICC appears on c*holangiocyte* which is an intrahepatic bile duct [4, 5]. The cancer progression includes initiation, inflammation, and cancer progression. Inflammation is a predisposing factor in cancer development and promotes the stage of tumorigenesis. Inflammation promotes the incidence of tumor initiation, growth, development, and metastasis [6]. Inflammation is considered as an important factor during cancer progression. Local inflammation in liver may be driven by infiltrating immune cells such as monocyte/macrophages, T lymphocytes, and neutrophils. Thus, inflammation is also caused by nonparenchymal cells such as kupffer cells, dendritic cells, liver sinusoidal cell, and hepatic stellate cells [7].

In cancer treatment, the early stage of cancer progression should determine the success of therapy. Inflammation in liver could highly lead to liver carcinoma. Chronic liver inflammation damages hepatic epithelial cells, including hepatocytes and biliaryepithelial cells. Because liver has a high regenerative capacity, this damage induces substantial cell proliferation. Simultaneously, inflammation induces reactive oxygen species (ROS) and deoxyribonucleic acid (DNA) damage, increasing the frequency of genomic DNA mutations. When the high rate of cell proliferation is coupled with DNA mutation, the incidence of malignant transformation increases. Further, chronic inflammation induces changes in the hepatic

immune system, allowing cancer cells to easily evade immune surveillance. In most cases, chronic liver inflammation and the resultant cirrhotic microenvironment promote the initiation and progression of HCC and CCA [8].

Local inflammation in hepatic tissue is driven by infiltrating immune cells (monocytes/macrophages, T lymphocytes, and neutrophils) and also by resident liver nonparenchymal cells [Kupffer cells, dendritic cells, liver sinusoidal cells, and hepatic stellate cells (HSCs)]. In a complex organ such as the liver, different cell types can secrete diverse cytokines/chemokines, and the resulting cocktail constitutes a "secretome" that leads to immunomodulation that manifests as an acute or chronic inflammatory response. Chronic inflammation acts as a favorable preneoplastic setting [7].

The acute inflammatory response occurs immediately or in minutes, hours, or days following injury. Normally, this is a physiologically beneficial response that helps in clearing injured hepatocytes and leads to wound healing. When this process fails, an overdrive of immune cells occurs that perpetuates as chronic inflammation [9]. As the name suggests, chronic inflammation is a prolonged progressive process lasting for months that tilts the homeostasis more toward damage than toward healing. In liver, chronic inflammation eventually sets the stage for progression toward cirrhosis and eventually to HCC.

Making animal models provides a great opportunity to study a disease as well as designing strategies for the treatment, whether it is preventive or curative actions [10]. Preventive care could highly help the disease into good prognosis and reducing the mortality rate. Moreover, the key success for cancer therapeutic highly depends on the early stage of cancer progression. The mice are often used for animal model, especially for cancer research [11]. This is because animals, especially rodents, have biological similarities both genetically and physiologically to humans. Therefore, the use of mice as experimental animal models is very suitable to identify the dangers caused by a xenobiotic or study the pathogenesis of a disease [12, 13].

The most common animal models of cancer are *xenograft* models [14]. However, the animals models using the *xenograft* model has a weakness, such as it can harm the immune system so it cannot represent cancer that occurs naturally in humans [11]. Another method of using mice as the inflammation disease model is the induction of hepatocarcinogen. Chemically, hepatocarcinogen can cause changes in the DNA structures and instability including N-Nitrosodiethylamine (NDEA), aflatoxine, carbon tetrachloride, dimethylnitrosamine, and thioacetamide. Inducing hepatocarcinogens using NDEA is a commonly used method for producing HCC animal model [11, 12].

In liver, NDEA can induce progressive, proliferative, and mutagenic metabolism of tumors, so it can cause a wide variety of tumors in all animal models by intraperitoneal injection for about 8 weeks or more [15]. NDEA can produce pro-mutagenic products namely O^6-ethyl deoxy guanosine and O^4 and O^6-ethyl dioxy thymidine in the liver which are responsible for its carcinogenic effects [16]. NDEA, which is a chemical hepatocarcinogen, is also known to induce the Transforming Growth Factor Alpha (TGF-α) expression, which is closely involved in hepatocarcinogenesis and transformation in humans and animals [17]. NDEA is known to induce damage to the liver. It is useful in the treatment of cancer since the early stages of cancer development are an essential stage in determining the success of therapy. Thus, this study aimed to evaluate the liver disease model observed in mice induced with hepatocarcinogenic NDEA for five weeks intraperitonal injection.

Materials and methods

Materials

N-Nitrosodiethylamine was purchased from Sigma-Aldrich (Tokyo, Japan). Normal saline was the product of PT. Widathra Bhakti (Pasuruan, Indonesia). This study used male Balb/c mice aged six weeks obtained from the animal laboratory, Faculty of Pharmacy, Universitas Airlangga.

Induction of NDEA in mice

All of the experimental procedures using animals had been approved by the Ethics Commission of Faculty of Veterinary, Universitas Airlangga. The mice were induced for liver disease by using NDEA diluted in normal saline. Mice were given NDEA intraperitonially at a dose of 25 mg/kgBW. The NDEA injection was given five times every seven days for five weeks. The disease progress induced by NDEA was evaluated by weighing the mice body weight every week.

Preparation of mice organs

At the end of NDEA induction, the mice were then sacrificed and excised for evaluating their organs (heart, lungs, liver, spleen, and kidneys) including physical and morphological appearances. The organs including liver and spleen were excised and stored at −20 °C for further analysis. The organs were evaluated for the weight and morphological appearances. Moreover, the histopathology evaluations were also performed by hematoxylin-eosin staining for liver and spleen tissues.

Data analysis

The results were presented as the mean ± SD. To determine the significant differences between data, a statistical analysis was carried out using the Oneway Analysis of Variance (ANOVA) method which was followed with the Honestly Significant Difference (HSD) post hoc test. The difference was statistically significant if the p-value was <0.05.

Results

Body weight evaluation of mice induced with NDEA

To evaluate the results of NDEA induction, the mice induced by NDEA 25 mg/kg per week were weighed every week and compared with mice injected with normal saline used as the control. The presence of weight loss in mice induced by hepatocarcinogens is one of parameters for cancer progress. The evaluation results of mice body weight can be seen in Figure 1. The NDEA-induced mice experienced weight loss while normal mice gained weight continuously. The results showed that there was a significant weight loss on the 29th day after five times NDEA induction. On the 31st day, the mice were then sacrificed and excised for evaluating their organs including physical and morphological appearances.

Physical appearances of mice organs

Based on observation of excised organs shown in Figure 2A–C, there were differences between organs specifically for liver and spleen of mice induced with normal saline and with NDEA for five weeks. In the control group, the morphological appearances of liver were shiny and bright red (Figure 2A). However, mice induced with NDEA had liver appearances with nodules and discoloration (Figure 2C). This suggests that NDEA induction for five weeks affects the liver cells, causes liver damage, and changes the external morphology of the liver of mice.

Evaluation weight of mice organ

The organ weights of mice in the control and NDEA-induction groups were evaluated to determine whether there were any significant differences on the physical weight during the induction. As it can be seen in Table 1, the liver in mice induced with NDEA was significantly relatively smaller than the control group ($p<0.01$), while the spleen were slightly smaller but no significant differences was observed ($p>0.05$).

Histopathological evaluations of liver tissue

According to the results as shown in Figure 3, the normal liver and spleen had regular architecture and cellular integrity with no fibrosis. After induction of NDEA, there were no malignancies observed in liver on spleen tissues in mice; however, there were single large fat droplets, alongside nuclei dislocation to the cell periphery that seemed to be macrovesicular steatosis. According to these results, there were lipidosis in liver and steatohepatitis observed for spleen tissue.

Discussion

Making the ideal of animal models of liver disease with pathological analogous to liver disease in humans,

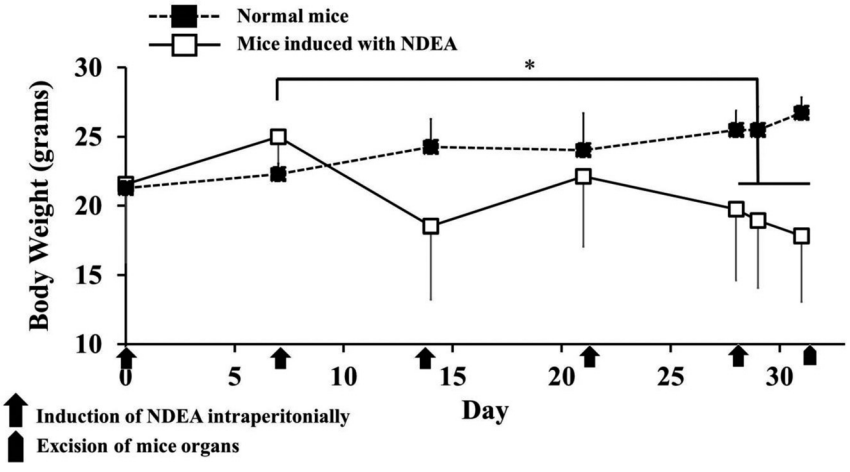


Figure 1: The mean of normal mice body weights (n=3) compared to mice induced with NDEA at a dose of 25 mg/kgBW intraperitonially once a week for five times and mice were then sacrificed at day 31 (n=7). **p<0.05.

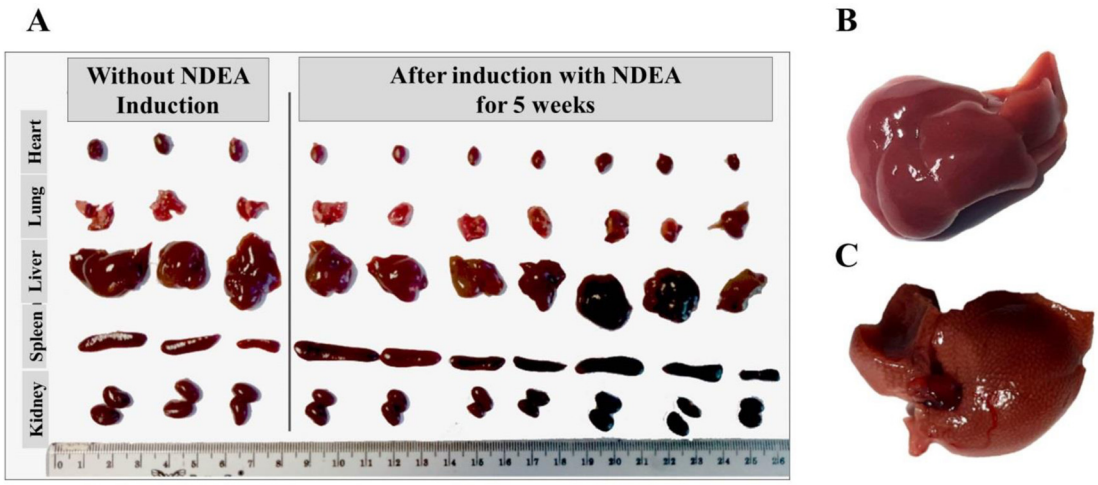


Figure 2: The physical appearances of mice organs including heart, lungs, liver, spleen, and kidneys from normal group treated with normal saline (n=3) and the NDEA-induced mice at a dose of 25 mg NDEA/kgBW once a week for five times, n=7.
(A) The visual observation of normal liver (B) and the liver after NDEA induction (C) of mice.

Table 1: Evaluation of mice organ weights in the control group (n=3) to the NDEA-induced group with a dose of 25 mg/kg five times then mice were sacrificed and excised for evaluating their organ (n=7).

Organ	Organ weights (mean ± SD)	
	Control	After NDEA induction
Heart	0.11 ± 0.01 g	0.08 ± 0.03 g
Lungs	0.20 ± 0.04 g	0.32 ± 0.05 g
Liver	1.86 ± 0.13 g	0.97 ± 0.27 g
Spleen	0.23 ± 0.12 g	0.20 ± 0.12 g
Kidneys	0.40 ± 0.05 g	0.25 ± 0.06 g

especially for HCC cancer formation model both pathologically and biochemically is a challenge for researchers [18]. NDEA is a compound that is generally known to be mutagenic, teratogenic, and carcinogenic. Recent study reports that the use of NDEA as a hepatocarcinogen is known to have a strong ability and is able to induce primary liver cancer such as HCC which is at various stages of liver cirrhosis, besides that it can greatly simulate the histopathological evolution of clinical liver cancer [19].

It has been reported previously that induction of NDEA for 8 weeks resulted in hepatocellular carcinoma as indicated by enlarged hyperchromatic nucleus and scattered

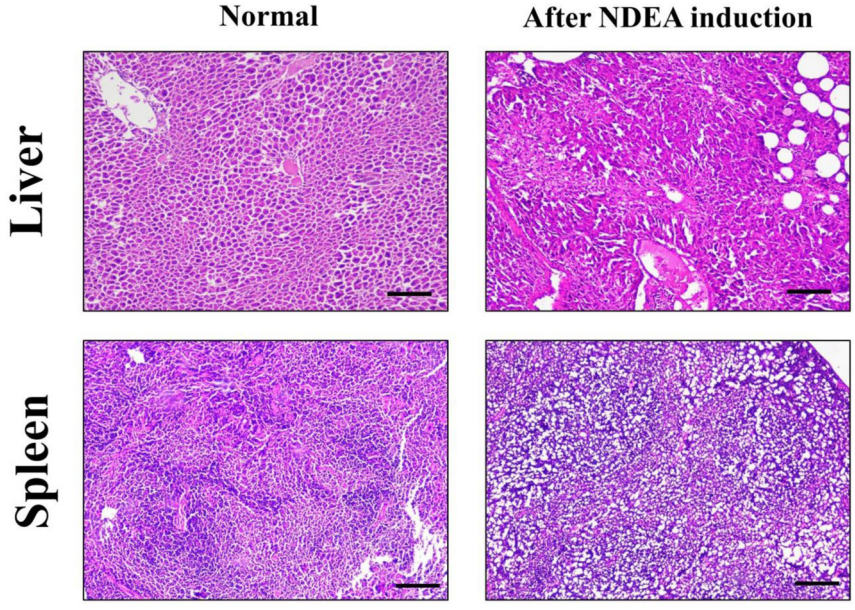


Figure 3: The histopathology photomicrographs of mice liver and spleen tissues stained with hematoxylin-eosin taken from specimens of normal mice and mice intraperitonially injected with NDEA at a dose of 25 mg NDEA/kgBW once a week for five times. Scale bar=100 µm.

mitosis in liver tissue [20]. In this study, NDEA was used to produce an animal model for inflammation liver disease as target for preventive cure of naticancer agents. NDEA induction at a dose of 25 mg/kgBW for five weeks showed that there were significant weight losses as shown in (Figure 1). In the previous study, administration of NDEA reduces the body weights in which the mice become lesser in food intake [21]. The weight loss observed during NDEA induction in mice is probably due to decreased liver function and nutritional deficiencies which may be due to reduced food intake [22]. However, in this study, there was no evaluation of food consumed by the mice during the experiments.

Based on the weight data for each organ shown in Table 1, it was known that the weight of liver organs in the treatment group decreased compared to control group. NDEA administration causes liver degeneration as evidenced by a significant reduction in liver weight index [23]. This relative liver weight assessment can be used as an evaluation in diagnosing liver disease characterized by changes in liver size. Liver weight loss generally reflects loss of function associated with atrophy or hepatocellular injury [24]. However, in this study, the mice induced with NDEA showed no differences in the lymph weight compared to control group.

NDEA induction for five weeks affects liver cells, causes liver damage, and changes the external morphology of the liver of mice. Previous studies report NDEA induction in mice causes a change in the structure of the liver in mice which is characterized by a reduction in size, discoloration, bleeding, scarring, and formation of nodule-like structures [25]. This is because NDEA is a toxic agent against the liver that can cause liver fibrosis [25, 26]. Fibrosis is formation of excess connective tissue, causing hardening and scar formation, in which about 20% of cancer cases are associated with chronic inflammation due to fibrosis, as found in liver cancer [27]. However, in this study, instead of malignancies, hepatic lipidosis and steatohepatitis were observed in mice liver and spleen after five weeks induction of NDEA. This indicates that the disease progress is still in the early stage of liver cancer diseases. It has been known that hepatic lipidosis is an early manifestation of some other underlying conditions related to cancer, pancreatitis, and other liver problems [28]. Another study reports that rats induced with NDEA will show the appearance of hepatocellular carcinoma with enlarged hyperchromatic nuclei and scattered mitosis after eight weeks of NDEA induction [20]. This early disease stage can be used for exploring preventive therapy of some drug compounds, such as for comparing the efficacy of drug delivery system. Lipid peroxidation and oxidative stress are dangerous to cells resulting in liver injury, which leads to liver fibrosis and cirrhosis or cancer. However, further biochemical investigation is required to definitely score the stage of liver disease after five weeks induction of NDEA.

Conclusion

Induction of NDEA in mice for five weeks results in hepatic lipidosis or fatty liver and steatohepatitis confirmed as the liver inflammation which may indicate the early stage of liver cancer disease, thus providing the potential use of NDEA for making animal models for the preventive cure of liver disease.

Acknowledgment: The author would like to thank to Alphania Rahniayu from Faculty of Medicine, Universitas Airlangga for her kind helps during the histopathology evaluation.

Research funding: This study was supported by a Preliminary Research on Excellence in Higher Education Institutions (Penelitian Dasar Unggulan Perguruan Tinggi, PDUPT) Grant Number AMD/E1/KP.PTNBH/2020 and 710/UN3/14/PT/2020 provided by the Ministry of Research and Technology-National Research and Innovation Agency of Republic of Indonesia.

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: The study protocol was approved by the Animal Care and Use Committee of the Faculty of Veterinary, Airlangga University with an Ethical Clearance No. 2.KE.022.02.2020.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA A Cancer J Clin 2020;70:7–30.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2018;68:394–424.
3. Dasgupta P, Henshaw C, Youlden DR, Clark PJ, Aitken JF, Baade PD. Global trends in incidence rates of primary adult liver cancers: a systematic review and meta-analysis. Front Oncol 2020;10:1–17.
4. Petrick JL, McGlynn KA. The changing epidemiology of primary liver cancer. Curr Epidemiol Rep 2019;6:104–11.
5. Ambade A, Mandrekar P. Oxidative stress and inflammation: essential partners in alcoholic liver disease. Int J Hepatol 2012; 2012:1–9.

6. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity 2019;51:27–41.
7. Gayatri R, Rastogi A, Trehanpati N, Sen B, Khosla R, Sarin SK. From cirrhosis to hepatocellular carcinoma: new molecular insights on inflammation and cellular senescence. Liver Canc 2012;2:367–83.
8. Yang YM, Kim SY, Seki E. Inflammation and liver cancer: molecular mechanisms and therapeutic targets. Semin Liver Dis 2019;39:26–42.
9. Mueller K. Inflammation's yin-yang. Science 2013;339:155.
10. Navale AM. Animal models of cancer: a review. Int J Pharmaceut Sci Res 2014;4:19–28.
11. Cekanova M, Rathore K. Animal models and therapeutic molecular targets of cancer: utility and limitations. Drug Des Dev Ther 2014;8:1911–22.
12. Khan AQ, Siveen KS, Prabhu KS, Kuttikrishnan S, Akhtar S, Shanmugakonar M, et al. Role of animal research in human malignancies. In: Azmi A, Mohammad RM, editors. Animal models in cancer drug discovery. New York: Academic Press; 2019:1–29 pp.
13. Ishida K, Tomita H, Nakashima T, Hirata A, Tanaka T, Shibata T, et al. Current mouse models of oral squamous cell carcinoma: genetic and chemically induced models. Oral Oncol 2017;73: 16–20.
14. Ruggeri BA, Camp F, Miknyoczki S. Animal models of disease: pre-clinical animal models of cancer and their applications and utility in drug discovery. Biochem Pharmacol 2014;87:150–61.
15. Velu P, Vijayalakshmi A, Iyappan P, Indumathi D. Evaluation of antioxidant and stabilizing lipid peroxidation nature of *Solanum xanthocarpum* leaves in experimentally diethylnitrosamine induced hepatocellular carcinogenesis. Biomed Pharmacother 2016;84:430–7.
16. Sivaramakrishnan V, Shilpa PNM, Praveen Kumar VR, Niranjali Devaraj S. Attenuation of N-nitrosodiethylamine-induced hepatocellular carcinogenesis by a novel flavonol-Morin. Chem Biol Interact 2008;171:79–88.
17. Kagawa M, Sano T, Ishibashi N. An acyclic retinoid, NIK-333, inhibits N-diethylnitrosamine-induced rat hepatocarcinogenesis through suppression of TGF-a expression and cell proliferation. Carcinogenesis 2004;25:979–85.
18. Santos NP, Colaço AA, Oliveira PA. Animal models as a tool in hepatocellular carcinoma research: a review. Tumor Biol 2017;39: 1010428317695923.
19. Liu Y, Yin T, Feng Y, Cona MM, Huang G, Liu J, et al. Mammalian models of chemically induced primary malignancies exploitable for imaging-based preclinical theragnostic research. Quant Imag Med Surg 2015;5:708–29.
20. Ali SA, Ibrahim NA, Mohammed MMD, El-Hawary S, Refaat EA. The potential chemo preventive effect of ursolic acid isolated from *Paulownia tomentosa*, against N-diethylnitrosamine: initiated and promoted hepatocarcinogenesis. Heliyon 2019;5: e01769.
21. Thomas NS, George K, Arivalagan S, Mani V, Siddique AI, Namasivayam N. The in vivo antineoplastic and therapeutic efficacy of troxerutin on rat preneoplastic liver: biochemical, histological and cellular aspects. Eur J Nutr 2016;56: 2353–66.
22. Rajesh V, Perumal P. Chemopreventive and antioxidant activity by *Smilax zeylanica* leaf extract against N-nitrosodiethylamine induced hepatocarcinogenesis in wistar albino rats. Orient Pharm Exp Med 2014;14:111–26.
23. Mittal G, Brar APS, Soni G. Impact of hypercholesterolemia on toxicity of N-nitrosodiethylamine: biochemical and histopathological effects. Pharmacol Rep 2006;58:413–9.
24. Cattley RC, Cullen JM. Liver and gall bladder. In: Haschek WM, Rousseaux CG, Wallig MA, Bolon B, Ochoa R, Wahler BM, editors. Haschek & Rouseaux's handbook of toxicology pathology (3rd). Boston: Academic Press; 2013.
25. Latief U, Husain H, Mukherjee D, Ahmad R. Hepatoprotective efficacy of gallic acid during Nitrosodiethylamine-induced liver inflammation in Wistar rats. J Basic Appl Zool 2016;76: 31–41.
26. Wills PJ, Suresh V, Arun M, Asha VV. Antiangiogenic effect of *Lygodium flexuosum* against N-nitrosodiethylamine-induced hepatotoxicity in rats. Chem Biol Interact 2016;164: 25–38.
27. Chandler C, Liu T, Buckanovich R, Coffman LG. The double edge sword of fibrosis in cancer. Transl Res 2019;209:55–67.
28. Brunt EM, Tiniakos DG. Histopathology of nonalcoholic fatty liver disease. World J Gastroenterol 2010;16:5286–96.

Journal of Basic and Clinical Physiology and Pharmacology

COUNTRY

Germany

Universities and research institutions in Germany

SUBJECT AREA AND CATEGORY

Biochemistry, Genetics and Molecular Biology
Physiology

Medicine
Medicine (miscellaneous)

Pharmacology, Toxicology and Pharmaceutics
Drug Discovery
Pharmacology

PUBLISHER

Walter de Gruyter GmbH

H-INDEX

36

PUBLICATION TYPE

Journals

ISSN

07926855, 21910286

COVERAGE

1985-1988, 1990-2021

INFORMATION

Homepage

How to publish in this journal

m.horowitz@mail.huji.ac.il

SCOPE

descriptive or behavioral studies with cellular and molecular mechanisms underlying the integrative processes. Topics: Behavior and Neuroprotection, Reproduction, Genotoxicity and Cytotoxicity, Vascular Conditions, Cardiovascular Function, Cardiovascular-Pulmonary Interactions, Oxidative Stress, Metabolism, Immune Response, Hematological Profile, Inflammation, Infection, Phytotherapy.

Join the conversation about this journal

Quartiles

FIND SIMILAR JOURNALS

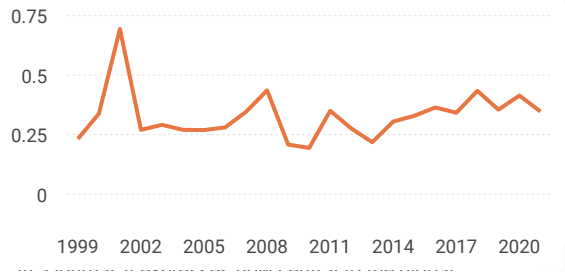
1
Archives of Physiology and Biochemistry
GBR
65%
similarity

2
International Journal of Pharmacology
PAK
62%
similarity

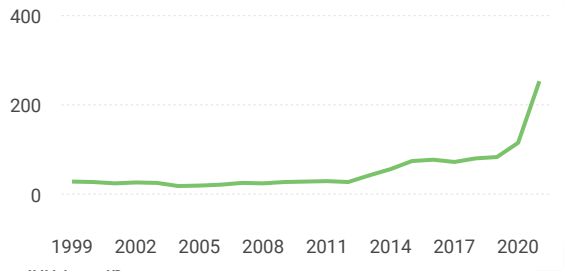
3
Pathophysiology
CHE
60%
similarity

4
Tropical Journal Pharmaceutical
NGA
60
simila

SJR



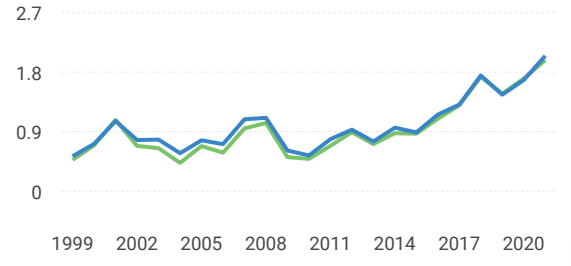
Total Documents

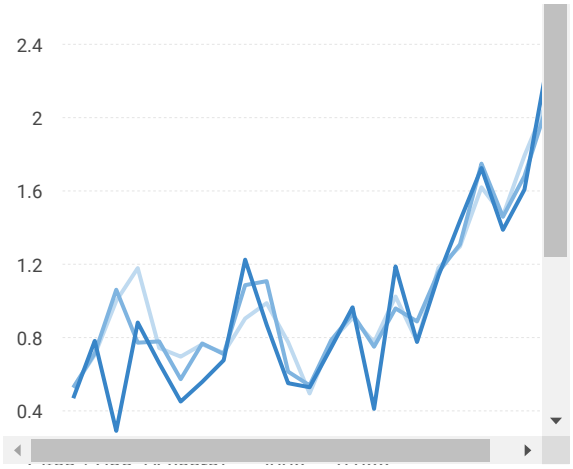


Total Cites Self-Cites

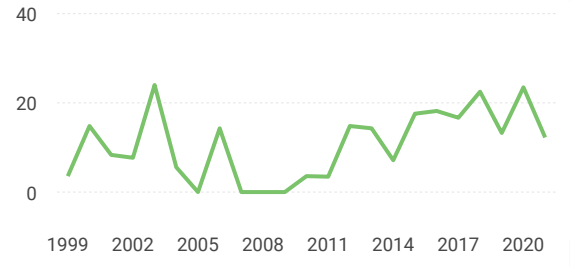
Citations per document

External Cites per Doc Cites per Doc

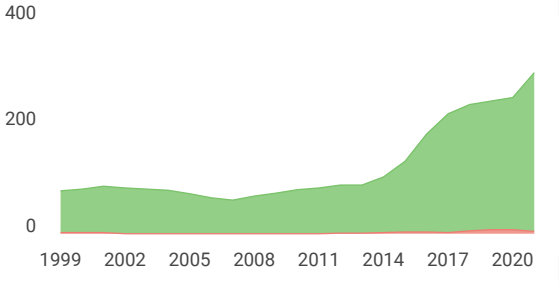




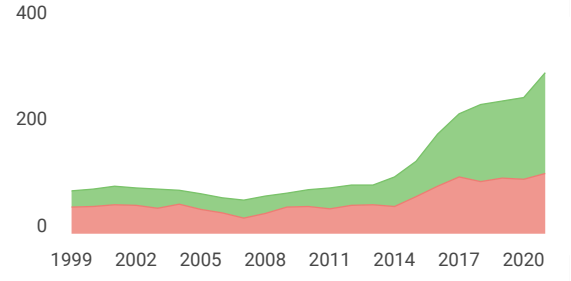
% International Collaboration



Citable documents Non-citable documents



Cited documents Uncited documents



← Show this widget in your own website

Just copy the code below and paste within your html code:

```
<a href="https://www.scimag
```

SCImago Graphica

Explore, visually communicate and make sense of data with our **new data visualization tool**.

Metrics based on Scopus® data as of April 2022

Source details

Journal of Basic and Clinical Physiology and Pharmacology

Formerly known as: Reviews in Clinical and Basic Pharmacology

Scopus coverage years: from 1985 to 1988, from 1990 to Present

Publisher: Walter de Gruyter

ISSN: 0792-6855 E-ISSN: 2191-0286

Subject area: Pharmacology, Toxicology and Pharmaceutics: Pharmacology

Pharmacology, Toxicology and Pharmaceutics: Drug Discovery

Biochemistry, Genetics and Molecular Biology: Physiology

Source type: Journal

CiteScore 2021
2.5

SJR 2021
0.347

SNIP 2021
0.728

View all documents > | Set document alert | Save to source list | Source Homepage

CiteScore | CiteScore rank & trend | Scopus content coverage

Improved CiteScore methodology

CiteScore 2021 counts the citations received in 2018-2021 to articles, reviews, conference papers, book chapters and data papers published in 2018-2021, and divides this by the number of publications published in 2018-2021. Learn more >

CiteScore 2021

$$2.5 = \frac{1{,}062 \text{ Citations } 2018 - 2021}{421 \text{ Documents } 2018 - 2021}$$

Calculated on 05 May, 2022

CiteScoreTracker 2022

$$3.5 = \frac{1{,}521 \text{ Citations to date}}{429 \text{ Documents to date}}$$

Last updated on 05 March, 2023 • Updated monthly

CiteScore rank 2021

Category	Rank	Percentile
Pharmacology, Toxicology and Pharmaceutics — Pharmacology	#203/303	33rd
Pharmacology, Toxicology and Pharmaceutics — Drug Discovery	#109/154	29th

View CiteScore methodology > | CiteScore FAQ > | Add CiteScore to your site

About Scopus

What is Scopus

Content coverage

Scopus blog

Scopus API

Privacy matters

Language

日本語版を表示する

查看简体中文版本

查看繁體中文版本

Просмотр версии на русском языке

Customer Service

Help

Tutorials

Contact us