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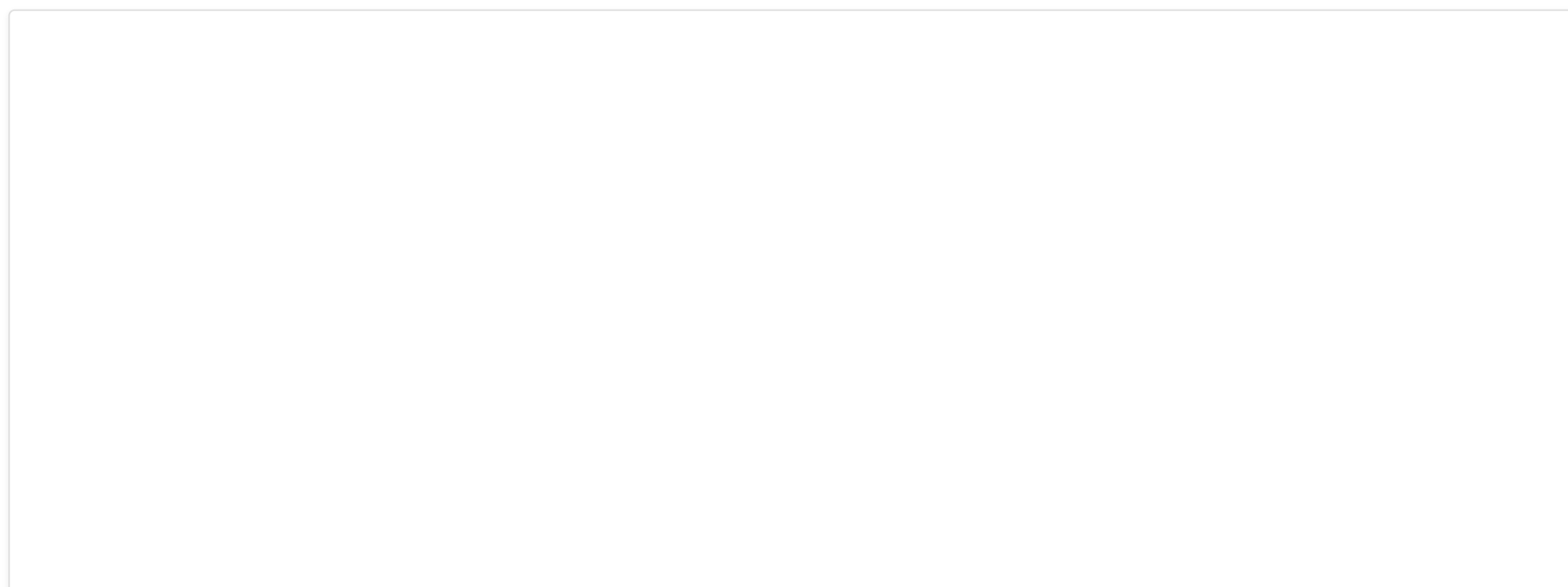
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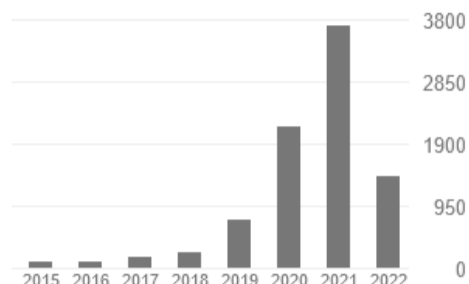
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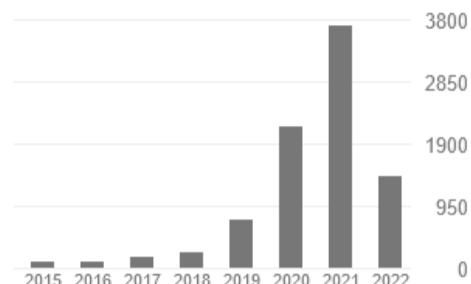
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👤 Agus Purnomo, Arya Pradana Wicaksono, Dodit Hendrawan, Muhammad Thohawi Elziyad Purnama.

SRP. 2020; 11(5): 464 - 468

» Abstract » PDF DOI: 10.31838/srp.2020.5.64

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[Regulatory-Adaptive Capabilities of the Organism after Radical Prostatectomy with Prostate Cancer of the I-II Degree](#)

👤 Artyom Grigorievich Penzhoyan, Grigory Artemovich Penzhoyan, Vladimir Mikhailovich Pokrovsky, Valery Gordeevich Abushkevich

SRP. 2020; 11(5): 29 - 32

» Abstract » PDF DOI: 10.31838/srp.2020.5.05

Review Article

[Prioritizing Well-being of Patients through Consideration of Ethical Principles in Healthcare Settings: Concepts and Practices](#)

👤 Ahmed Ahmed, Heyam Saad Ali, Mansour A. Mahmoud.

SRP. 2020; 11(5): 643 - 648

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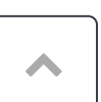
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[Accuracy of Otoacoustic Emission in Comparison to Diagnostic Test of Auditory Brainstem Response in Hearing Screening for Children in Vietnam](#)

👤 Tuyet Xuong Nguyen.

SRP. 2020; 11(5): 469 - 471

» Abstract » PDF DOI: 10.31838/srp.2020.5.65



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[The Genus *Asarum* L.: A Phytochemical and Ethnopharmacological Review](#)

Antsyshkina A.M., Ars Yu.V., Bokov D.O., Pozdnyakova N.A., Prosdusheva T.V., Zaichikova S.G..

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[The Solution to the Problem of a Heart Rhythm Recovery with Modern Methods](#)

Gradskaya Anastasia Igorevna, Vitaliy Alekseevich Solovyov, Maksimova Irina Valeryevna, Egorova Anastasia Yurievna, Grishachkina Nadezhda Igorevna.

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[Assessment the linking of Insulin-like growth factor 1 hormone and their gene polymorphism with excess adiposity](#)

Amera Kamal Mohammed, Chow Ahmed Khurshid, Heman Burhanalden Abdulrahman.

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[In Vitro Antioxidant and Anti-Mycobacterial Activities of Roselle \(*Hibiscus sabdariffa* L.\) Calyx Extract against Clinical Isolate of Multidrug Resistant *Mycobacterium tuberculosis*](#)

Sartini Sartini, M Natsir Djide, Gemini Alam, Andi Arjuna, Nana Juniarti N Djide

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[» Abstract](#) [» PDF](#) DOI: 10.31838/srp.2020.5.07

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[Relation of Access Information with Satisfaction and Loyalty in Medical \(Dental\) Tourism: Systematic Review](#)

Fuad Husain Akbar, Fridawati Rivai, Andi Zulkifli Abdullah, Abdul Hair Awang, Nurul Faizah, Syahrir A. Pasinringi, Lalu Muhammad Saleh, Irwandy.

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[Organization Decisions in Clinical Oncology Based on the Statistics of Malignant Neoplasms](#)

Vladimir Yu. Startsev, Roman E. Sen kov, Gleb V. Kondratiev, Vasyli I. Oriol, Vladimir S. Luchkevich.

SRP. 2020; 11(5): 503 - 510

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[Therapeutic Efficacy of Bone Marrow- Derived Mesenchymal Stem Cells Plus Zinc Oxide Nanoparticles Against Streptozotocin- Induced Type 2 Diabetes in Albino Rats](#)

Khabat Anwar Ali


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[Inhibition of Oral Bacterial Growth \(Streptococcus Mutans and Porphyromonas Gingivalis\) using Black Rice Bran Ethanol Extract \(Oryza Sativa L.\) as A Natural Mouthwash](#)

 Marhamah, Harun Achmad, Hendrastuti Handayani, Sherly Horax, Fajriani, Nurhaedah H. Galib B, Sasmita M. Arief.

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[Automatic Reminder for Fluids Management on Confidence and Compliance with Fluid Restrictions in Hemodialysis Patients](#)


 Nursalam Nursalam, Ninuk Dian Kurniawati, Inda Rian Patma Putri, Diah Priyantini

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[The Influence of Uric Acid Levels on Blood Pressure and Chronic Hypertension towards Hypertension Patient Proteinuria Levels \(Overview of the Banjar Ethnic at the Cempaka Banjarmasin Health Center\)](#)


 Huldani, Mohammad Rudiansyah, Fauzie Rahman, Adelgrit Trisia, Sri Ramadhany, Siti Kaidah, Harun Achmad, Bayu Indra Sukmana, Dhea M Swengly, Shelsy Marippi, Wafa Ahdiya, Muhammad Hasan Ridhoni, Amalia Rahman, Zhasifa Khoirunnisa Suwanto, Gandhi Mahesa Priambodo, Muhammad Rafagih, Abdullah Zuhair

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[Toxicity Test of Bioactive Red Alga Extract Eucheuma spinosum on Shrimp Artemia Salina Leach](#)

 Nurlindah Hamrun, Teiza Nabilah, Rafikah Hasyim, Muhammad Ruslin, Irfan Dammar, Muhammad Anugrah As Arianto

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[Effectiveness of Boiled Water of Breadfruit Leaf \(Artocarpus Altilis\) on Reducing Cholesterol Levels in The Blood of Mice \(Mus Musculus\)](#)

 Y Astuti, T Wahyudi, Siswoko

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[Factors Associated with the Use of Contraception among Women Age 15-24 Years in Indonesia](#)

 Fandy Euricky Petrus Mola, Dewi Elizadiani Suza, Ferry Efendi, Setho Hadisuyatmana, Erni Astutik, Ika Adelia Susanti.

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[The Influence of Zinc Supplement in Feeding Patterns on the Incidence of Stunted in the Toddler](#)

Erni Nuryanti, Cipto, Ajeng Titah Normawati.

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[A Review: Knowledge and Attitude of Society toward Tuberculosis Disease in Soppeng District](#)

Sri Ramadhany, Harun Achmad, Marhamah F. Singgih, Yunita Feby Ramadhany, Nur Hildah Inayah, Nurul Mutmainnah

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T Wahyudi, W Warijan, S Suyanta.

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[Determinants of Adolescent First Births in Indonesia](#)

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[Prevalence Of Cigarette Smoking Phenomenon In Iraqi University Students And Factors Affecting Its Cessation An Observational Epidemiologic Study](#)

Wael Waleed Mustafa and Samer Shukur Mohammed

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[Minimally Invasive Surgical Treatment of Open Ductus Arteriosus in Premature Infants](#)

KEMELBEKOV KANATZHAN, ZHUMABEKOV ZHARYLKAP, BEKTENOVA GULMIRA, BAIMAKHANOVA BAKHTYGUL, ASKAMBAY KULZINA, OSPANOVA ELMIRA, KUANDYKOV YERLAN, NAZIPIA BEKTIBAYEVA, VENERA MAKHATOVA, ARKADY KOTLYAR.

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[Morphological Condition of the Large Intestine in Chronic Intoxication with Pesticides Against the Background of Diabetes Mellitus](#)

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[Family Empowerment Model Based on Belief and Health-Related Quality of Life among Housewives With HIV/AIDS](#)

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[Effective Implementation of Marketing Management of Hospital Pharmacy: A Study on the Impact of Hospital Service Quality Improvement in Enhancing the of Patients' Satisfaction and Loyalty](#)

👤 Chairun Nasirin, Andries Lionardo.

SRP. 2020; 11(5): 705 - 712

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[Community Health Worker-Based Empowerment Against Stigmatization of People Living with HIV/AIDS: A Meta-Synthesis](#)

👤 Ernawati, Nursalam, Shrimarti Rukmini Devy.

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[Prevalence of Rheumatological Manifestations Among Diabetes Mellitus](#)

👤 Yaqoob Yousif Al-Kufi and Mohammad Abd Abdul-Hussain

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[Four-Dimensional Echocardiographic Volumetric and Functional Assessment of the Left Atrium in Healthy Male Subjects in Relation to Age](#)

👤 Asaad Hasan Noaman Al-Aboodi, Hamid Mohammed Hussein Abbas, Falah Mahdi Dananah

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[The effect of use of Dexmedetomidine hydrochloride as an adjuvant in general anesthesia on rate of awareness](#)

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[Medical Tourism Association as an Instrument of Managing Health Industry Competitivity](#)

 Nelli A. Saveleva, Tatyana A. Yudina, Elena E. Sinyavskaya, Viktor A. Yanyushkin, Violetta V. Rokotyanskaya.

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[The Relationship between Socio-Economic Factors and Parenting Styles with the Incidence of Stunting in Children](#)

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[Solid Lipid Nanoparticles \(SLN\) as a Novel Drug Delivery System: A Theoretical Review](#)


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[The Autophagy Inhibitor Hydroxychloroquine Enhances Sensitivity of Osteosarcoma Cell Line MG-63 to Doxorubicin Treatment](#)

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[Validity And Reliability Of The Indonesian Version Of The Conduct Disorder Rating Scale \(CDRS\)- Parent And Teacher As An Initial Screening For Conduct Disorders In Elementary School Children](#)

 Yunias Setiawati, I Gusti Ayu Indah Ardani, Sasanti Yuniar, Atika Atika, Zain Budi Syulthoni.

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 Era Catur Prasetya, Nalini Muhdi, Atika Atika

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[Impact of Omega-3 on Hypercholesteremia Induced Male Rabbits](#)

 *Fadhil A. Rizij, Ali M. Janabi, Ayad A. Ameen, Najah R. Hadi*

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[The Effect of Immersion of 12,5% Basil Leaves and 25% Mauli Banana Stem Mixture Extracts on Surface Hardness, Surface Roughness and Discoloration of Acrylic Resin](#)

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[Phytochemical Screening, Antioxidant Activity, Functional Groups and Chemical Element Characterization Analysis of \(-\)-Epigallocatechin-3-Gallate \(EGCG\) in East Javanese Green Tea Methanolic Extract: An Experimental In Vitro Study](#)

 *Ida Bagus Narmada, Andari Sarasati, Satutya Wicaksono, Fianza Rezkita, Kadek Gede Putra Wibawa, Suhailah Hayaza, Alexander Patera Nugraha.*

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[Immunohistochemical Study of Adenomatous Polyposis Coli Protein in Colorectal Carcinoma and its Precursor Lesions in Iraq](#)

 *Kaswer Musa Jaafar Altoriah, A Alaa Salah Jumaah, Adeen Abdulally Abdulhussein, Asaad Abdul Hamza Aljanabi, Hawraa Sahib Al-Haddad, Aseel Al-Quzweni, Najah R. Hadi*

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👤 Purwati, Andang Miatmoko, Nasronudin, Deya Karsari, Aristika Dinaryanti, Eryk Hendrianto, Igo Syaiful Ihsan, Nora Ertanti, Disca Sandyakala Purnama, Tri Pudy Asmarawati, Erika Marfiani, Zamrotul Izzah, Alfian Nur Rosyid, Prastuti Asta Wulaningrum, Herley Windo Setiawan.

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[Prevalence of Toxic Shock Syndrome Toxin-1 \(TSST-1\) Produced by Staphylococcus aureus Isolated from Patient Combined Psoriasis with Urinary Tract Infections \(UTIs\) and Gastroenteritis in Age Groups Between 8-18 Years](#)

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[Studies on the Photostability of Polystyrene Films with New Metals Complex of 1, 2, 4-triazole-3-thione Derivate](#)

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[Synthesis, Characterization and Spectroscopic Study of New Metal Complexes form Heterocyclic Compounds for Photostability Study](#)

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[The Promising Barrier: Theoretical Investigation](#)

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[A Reviews on Use of Sea Cucumber as a Treatment for Oral Cancer](#)

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[Cytomegalovirus UL83 Gene as Diagnostic Marker for Preliminary Infection in Pregnant Women in AL-Najaf City](#)

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[Intravitreal Implantable Film Containing Ketorolac Tromethamine Microsponges ? In Vitro/In Vivo Correlation](#)

👤 Wid F. Neamah, Nidhal K. Maraie, Hameed A. Al-Timmemi.

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[Amino Acid Profile and Content in Crude Herbal Drugs \(Fruits\) of Rosaceae Species](#)

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[Human resource orchestration in partnership companies: a multiple case study](#)

 *Juliani Dyah Trisnawati, Indrianawati Usman, Dwi Ratmawati.*

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[The Effect of Topical Curcumin Extract on Fibroblast Count and Collagen Density as an Indicator on Accelerating Clean Wound Healing Process: A Study on Wistar Rats](#)

 *Erick Berto Yahya, Ariandi Setiawan, Marjono Dwi Wibowo, Edwin Danardono.*

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[Indonesia-South Korea Extradition Agreement as a Form of Cooperation in Efforts to Eradicate International-Scale Crimes](#)

 *Lynda Asiana, Supanto, Hari Purwadi*

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[Comparison of Anti-Oxidant Activity of Different Brands of Esomeprazole Available in Iraqi Pharmacies](#)

 *M. Alfahad, M. E. Qazzaz, M. N. Abed, F. A. Alassaf, M. H. M. Jasim.*

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[To Consider The Organogel Of Span 40 And Span 60 In Sesame Oil As A New Member In The Gastro Retentive Drug Delivery Systems](#)


 *Zainab Saad Kaddoori, Masar Basim Mohsin Mohamed, Wesam R. Kadhum, Nawfal Am. Numan*

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[Hematological changes among Corona virus -19 patients: a longitudinal study](#)

 *Nasser Ghaly Yousif, Ahmed N. Altimimi, Fadhil G. Al-amran, Lee, J Adrienne, Samar Muayad Al-Fadhel, Salwa Riyadh Hussien, Najah R. Hadi, Maitham G. Yousif, Mohammad AG. Alfawaz, Kareem G. Mohammed*

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[Determination and Evaluation of Doses of Metronidazole in Different Quantities and Formulations with Multiple Spectroscopic-Methods](#)

 *Khawla Salman Abd-Alrassol, H. N. K. AL-Salman, Ekhlās Qanber Jasim, Hussein H. Hussein*

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[Effect of Aloe vera Extracts towards the Fibroblast Number and Collagen Thickness on Clean Skin Wound Healing on Rattus Novergicus](#)

👤 *Rezky Sagita Girsang, Marjono Dwi Wibowo, Ariandi Setiawan*, Edwin Danardono*

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[ENHANCEMENT MODEL FOR HOSPITAL QUALITY SERVICE WITH CONSIDERATION OF INTEGRATING PATIENTS HEALTH INSURANCE TO UTILIZE FINTECH](#)

👤 *Fauzi Arif Lubis, Nurlaila, Ismail Husein, Susilawati, Muhammad Lathief Ilhamy Nasution, Marischa Elveny, Afnaria, Nurlama Siregar.*

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[Comparative Characteristics of Osteofixators in Treatment of Dogs with Cranial Cruciate Ligament Rupture](#)

👤 *Sergey Pozyabin, Yury Vatnikov, Dmitry Kachalin, Evgeny Kulikov, Grigorii Kukovenko, Elena Piven, Olesya Petrikhina, Alexander Strachuk, Aleksandr Petrov, Irina Popova, Daria Lukina, Esam Almenshavi.*

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[Effect of Bovine Dried Amniotic Membranes as Prosthesis of Abdominal Fascial Defect Closure Reviewed from The Level of Density Collagen Type I and III in Rattus novergicus Wistar Strain](#)

👤 *Ahmad Jazlaniardi Primaditya Wardhana, Fendy Matulatan, Marjono Dwi Wibowo, Edwin Danardono*

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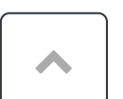
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[Top-Down Orientation on Fourth Industrial Revolution: A Literature Review](#)

👤 *Mansoor Ahmed Soomro, Mohd Hizam-Hanafiah, Nor Liza Abdullah*

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[Antibacterial and Phytochemical Analysis of Two Plants Menispermaceae Family](#)

👤 *Silvia Anitasari, Sjarif Ismail, Bayu Satria Wiratama, Hendrik Setia Budi*

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[Social, Environment and Economy: Community Empowerment in Utilizing Organic Waste as Batik Dyes through CSR](#)

👤 *Endah Nurhawaeny Kardiyati, Mahendra Wijaya, Suwarto Suwart, Supriyadi Supriyadi.*

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[The Relationships Among Service Quality, Emotional Satisfaction and Behavioural Intention In Childcare Provider Choice: Evidence From Malaysia](#)

👤 *Nik Syuhailah Nik Hussin, Safiek Mokhlis, Hayatul Safrah Salleh, Zuraimi Abdul Aziz*

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[Controlled Glycolysis as the Basis of Beer Technology with Specified Consumer Properties](#)

👤 *Lyudmila Tretyak, Maksim Rebezov, Nadezhda Kenijz, Mars Khayrullin, Vera Gribkova, Andrey Goncharov.*

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[Phase 2 Study Assessing the Bactericidal Effects of Electrolyzed Oxidized Water as an Antiseptic towards the Reduction of The Peristomal Germ Density Level in Child Colostomy in Dr. Soetomo Hospital, Surabaya](#)

👤 *Bonni Saptia Pratidina¹, Ariandi Setiawan, Maryono Dwi Wibowo³, Edwin Danardono⁴.*

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[The Barriers Of International Expansion: A Study On Education And Learning Centre Franchisors](#)

👤 *Nurul Ashykin Abd Aziz, Mohd Hizam Hanafiah, Hamizah Abd Hamid, Rosmah Mat Isa*

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[The Role of Lymph-vascular Space Invasion towards Disease of Free Survival and Overall Survival Cancer in High-Risk Endometrial Cancer Endometrioid Type Patients](#)

👤 *Brahmana Askandar Tjokropawiro, Trianggono Bagus Ariyanto, Indra Yuliati, Willy Sandhika.*

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[The Regulation of Independent Candidates in Organizing Regional Head Elections in Indonesia: A literature Review](#)

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[Characteristics of Suspected Malignant Ovarian Tumor Patients Who Performed Surgery at Tertiary Referral Hospital](#)

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[Differences of Dried Amniotic Membrane Effect on Healing of Gastric Tissue Post Penetrating Trauma Reviewed from Collagen Thickness and Fibroblast Count](#)

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[Advancements in development and characterization of Single Droplet Combustion: A review](#)

Adhes Gamayel, M.N. Mohammed, Salah Al-Zubaidi, Eddy Yusuf

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[Characterization and Physicochemical Properties of Biofuel from Mixed Crude Jatropha Oil and Clove Oil](#)

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[The Mechanism of Endoplasmic Reticulum Stress and the Cyclin D2 Expression on Ovarian Granulosa Cell Cycle in Infertile Women with Endometriosis](#)

Jimmy Yanuar Annas, Hendy Hendarto, Erry Gumilar Dachlan, Samsulhadi, Soegiharto Soebijanto, Eu Leong Yong.

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[Increasing Neoadjuvant Chemotherapy in Nasopharyngeal Carcinoma Patients](#)

Muhtarum Yusuf, Andri Foris.



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[Biocoenotic Diagnostics of Unfavorable Factors in the Cows Infection of Farms in the Moscow Region](#)

👤 Pavel Rudenko, Victoria Rudenko, Yury Vatnikov, Andrei Rudenko, Evgeny Kulikov, Nadezhda Sachivkina, Elena Sotnikova, Nikolai Sturov, Ekaterina Rusanova, Tatiana Mansur, Sergey Vyalov, Nikolay Sakhno, Stanislav Drukovsky.

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[High-Level of Notch 1/Jagged 1 Level up Regulated Chemo-Resistance of Cisplatin in NSCLC](#)

👤 Nasser Ghaly Yousifa, Alla Mohammed Sadiqueb, Laith Mohammad Abbas Al-Huseinic, Muntadher NoamanJassimd, Najah R. Hadie, Fadhil Al-Amranf

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[Assessment of Respiratory Rate in Dogs during the Sleep with Mitral Valve Endocardiosis, Complicated by Congestive Heart Failure Syndrome: the Degree of Adherence for this Test by Animal Owners and its Impact on Patient Survival](#)

👤 Andrei Rudenko, Pavel Rudenko, Igor Glamazdin, Yury Vatnikov, Evgeny Kulikov, Nadezhda Sachivkina, Victoria Rudenko, Nikolai Sturov, Nikolay Babichev, Elena Romanova, Ekaterina Rusanova, Daria Lukina.

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[Evaluation of Statin Therapy on Lipid Profile of Diabetic Dyslipidemia Patients](#)

👤 Soebagijo Adi Soelistijo, Wynne Widiarti, Bambang Hermanto.

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[Evaluate the fPSA for Discriminate between Prostate Cancer Patients \(PCa\) and Benign Prostatic Hyperplasia \(BPH\) Depending on PSA Fucosylation by Using Nano-Lectin Immunoassay.](#)

👤 Aamer M. Ali*, Omar F. Abdul-Rasheed, Ahmed Turki Obaid.

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[Phenolic Compounds and Biological Activity of Badan \(*Bergenia crassifolia* \(L.\) Fritsch\) Leaves Growing in Russia](#)

👤 Kovaleva T.Yu., Ermakova V.A., Dorovskih E.A., Trashchenkova D.A., Bokov D.O., Shilova I.V., Samylina I.A..

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[Outcome and Radiotherapy Side Effects of High-Risk Endometrial Cancer](#)

👤 *Brahmana Askandar Tjokroprawiro, Lulus Handayani, M. Dimas Abdi Putra.*

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[The Effect of Il-6 Enhancement Due to Oral Cavity Infection on Skeletal Muscle](#)

👤 *Risma Aprianda Kristanti, Aulia Ramadhani, R Darmawan Setijanto*

SRP. 2020; 11(5): 597 - 602

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[Repellent Activity of Bintaro Leaf Extract \(Cerbera manghas\) against Spodoptera litura](#)

👤 *Achmadi Susilo, Dwi Haryanta, Tatuk Tojibatus Sa'adah.*

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[Association of Additive Risk of Pioglitazone Use with the Presence of CYP1A1 Polymorphisms in the Occurrence of Bladder Cancer](#)

👤 *Zainab Nizar Jawad, Kamal A.R, Weaam awad.*

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[The Relationship of Knowledge and Motivation with Anti Tuberculosis Drugs Compliance in Tuberculosis Patients](#)

👤 *Tintin Sukartini, Tri Retno Widianingrum, Deni Yasmara.*

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[Modern Therapeutic Approaches to the Treatment of Anal Fissure](#)

👤 *Aleksandra Savosina, Simon Lazar, Svetlana Suslina, Rimma Abramovich, Olga Potanina, Oleg Novikov*

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The Potency of Hematopoietic Stem Cells (HSCs) and Natural Killer (NK) Cells as A Therapeutic of SARS-CoV-2 Indonesia Isolates Infection by Viral Inactivation (In Vitro Study)

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ABSTRACT

Background: The prevalence of COVID-19 cases in Indonesia as of June 9, 2020, has been confirmed 32,076 positive cases, with 1,923 death cases. The total number of deaths reached 92,941 cases. There has been a recent update on stem cell-based biological, medical therapy as an optional treatment to handling COVID-19 due to its potential viability besides using the prevalent conventional chemical drug therapy.

Methods: In this study, in vitro research was conducted to determine the potential of hematopoietic stem cells (HSCs) and natural killer cells (NK cells) against SARS-CoV-2 viruses, which virus isolates were collected in Indonesia. The SARS-CoV-2 virus was planted in rat kidney cells and Vero cells. The cells that had been planted with the virus were given HSCs and NK cells, followed by being evaluated at intervals of 24, 48, and 72 hours. The evaluation was done by collecting cells and supernatant from the cell plate and then determining the viral load using a Polymerase Chain Reaction (PCR) machine.

Results: The results showed that the addition of HSCs and NK on cells that had been infected by SARS-CoV-2 resulted in a decrease in viral load within 24 to 72 hours in all variations of Multiples of Infection (Moi) values.

Conclusions: The administration of HSCs and NK cells has the potential to eliminate the SARS-CoV-2 virus. Although this study is only an in vitro study, it could be the basis for the development of alternative stem cell-based therapies to tackle COVID-19 cases.

Keywords: COVID-19, SARS-CoV-2, hematopoietic stem cells, natural killer cells

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INTRODUCTION

This year, our attention is focused a lot on the outbreak of Coronavirus Disease (hereafter, COVID-19), which was officially designated as a global pandemic in April 2020 by WHO.[1,2] The viral spread is increasing dramatically within a short period.[3] According to data collection from 213 countries who are currently battling COVID-19, the total positive number of COVID-19 stood at 1,524,161 cases, and the number of deaths reached 92,941 cases.[1] The prevalence of COVID-19 cases in Indonesia as of June 9, 2020, furthermore, has been confirmed 32,076 positive cases, with 1,923 death cases.[4]

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus.[5,6] Like a zoonotic virus, SARS-CoV-2 was transmitted from animals to humans.[7] On its viral infection mechanism, the virus infiltrates to the cells and begins to replicate/reproduce itself using a host cell machine, while causing damages to the host cell.[8] The respiratory system, moreover, is the target of the SARS-CoV-2 virus, which further infects the alveoli cells in the lungs.[6]

In patients with mild infection of COVID-19, there was no increase in chemokine and proinflammatory cytokines, similar results were found even in patients who showed symptoms.[5] On the other hand, a higher neutrophil-

lymphocyte ratio, lower leukocytes, and lymphocyte count, and a lower percentage of eosinophils, basophils, and monocytes are observed in patients with severe symptoms, as well as a high level of pro-inflammatory cytokines.[5,9] Acute Respiratory Distress Syndrome (ARDS) is the main cause of death in COVID-19 cases caused by an uncontrolled systemic inflammatory response due to pro-inflammatory cytokines and chemokines that are released in large amounts, which also called as the cytokine storm.[5,10,11] Functional disability will be inevitable due to lung deterioration and fibrosis if this enormous immune response continues to happen.[10,12]

Antiviral therapy, thus, is chosen to treat COVID-19 by referring to therapies used during the previous pandemics, namely MERS and SARS pandemics.[8,13,14] The Republic of China National Health Commission (NHC) has included antiviral therapy as an experimental treatment for COVID-19 in the latest version of the Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia.[15] Antibiotic therapy, moreover, is also used in conjunction with antiviral therapy.[16] Recently, stem cell-based biological, medical therapy is selected as an optional treatment for handling COVID-19 due to its potential viability.[17]

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Hematopoietic stem cells (HSCs) as a multipotent progenitor cell that can be derived into various types of blood cells.[18] HSCs are found in peripheral blood mononuclear cells (PBMCs), bone marrow, or umbilical cord blood.[18,19] HSCs isolation and culture derived from PBMCs and bone marrow must express CD73, CD90, and/or CD105 markers, and not express CD14, CD34, CD45 markers.[18] HSCs further change the profile of cytokine secretion from NK cells, dendritic cells, and naive and effector T cells to induce a more progressive phenotype and anti-inflammatory.[19] The secretion of Tumor Necrosis Factor-alpha (TNF- α) and Interferon-gamma (IFN- γ) as pro-inflammatory cytokines are decreased, while Interleukin-4 (IL-4) and Interleukin-10 (IL-10) are more suppressive stimulated.[18] The other factors, nonetheless, may also be involved, including Interleukin-6 (IL-6), Interleukin-10 (IL-10), Transforming Growth Factor-beta1 (TGF- β 1), hepatocyte growth factor, nitric oxide, prostaglandin E2, and possible indoleamine 2, 3-dioxygenase.[19] Numerous evidence claims that HSCs are anti-inflammatory, immunosuppressive, and can be transplanted to incompatible individuals, even though the specific mechanism has not been clarified yet.[20] Another cell, Natural killer (NK), is inborn lymphocytes that serve as the first defense line against tumor cells and viral infections.[21,22] NK cells have numerous mechanisms to kill cells infected by the virus, including cytolytic granules exocytosis and the potency of extracellular death receptors.[23,24] While the main work describes their antitumor activities, NK cells also play an important role in controlling certain infections, especially viral infections.[25] Granulocyte-macrophage colony-stimulating factor (GM-CSF), also known as a multifunctional cytokine, plays a role as generation and cytotoxicity of NK cells and stimulates macrophages to be antitumor and antimicrobial action.[26] IL-2, furthermore, is needed for the activation and proliferation of many different types of cells, such as NK and T lymphocytes.[27] After being activated by IL-2, NK cells get an increased cytotoxic function (namely lymphokine-activated killer cell, also known as LAK cell), knowing a wider range of targets and killing with heightened lytic potential.[24,27] From the description above, therefore, the authors aim to conduct an in vitro study concerning the potency of hematopoietic stem cells (HSCs) and natural killer (NK) cells in handling COVID-19 (SARS-CoV-2 virus) using Indonesian virus isolates.

MATERIALS AND METHODS

Materials

α -Minimum Essential Media (α -MEM), Fetal Bovine Serum (FBS), Penicillin-Streptomycin, L-Glutamine, NaHCO₃, and HEPES Medium from Gibco®-ThermoFisher Scientific, USA; Amphotericin B solution and Phosphate Buffer Saline (PBS) from Sigma-Aldrich®, USA; Collagenase type IV from Worthington®, USA; culture dishes, CO₂ incubator, centrifuge, microscope fluorescence, and polymerase chain reaction (qPCR) machine.

Sample Collection

The SARS-CoV-2 isolates were collected from three confirmed patients with informed consent and ethical approval clearance at Universitas Airlangga Hospital – Tropical Infectious Disease Hospital, Surabaya. Viral Transport Medium (VTM) consisting of Gentamycin

sulfate (100 μ g/ml) and Amphotericin B (0,5 μ g/ml) were used to collect the patient's sputum. Once samples were collected, the virus isolates were then stored at Biosafety Level 3 (BSL-3) Laboratory in the Institute of Tropical Disease, Universitas Airlangga, Surabaya. Samples were transferred into the new falcon tube, followed by vortexed for 5 minutes and centrifuged at 13.000 rpm for 10 minutes. Each sample was labeled as P1, P2, and P3. After that, the supernatant of each sample was aliquoted in cryotubes and preserved in -80°C deep freezer for long-term use.

Hematopoietic Stem Cells (HSCs) Isolation

The HSCs were obtained from peripheral blood mononuclear cells (PBMCs) of a healthy person and cultured at the Stem Cell Research and Development Center, Universitas Airlangga, Surabaya. The cell culture process took two weeks with changing new medium every three days and adding mitogen GM-CSF (20ng/ml) and IL-2 (100IU/ml). After two weeks of cell culture, hematopoietic stem cells were confirmed with a CD34 marker using immunocytochemistry and seeded 5x10⁵ in 12 multi well-plate each well.

Natural Killer (NK) Cells Isolation

The NK cells were accumulated from peripheral blood mononuclear cells (PBMCs) of a healthy person and cultured at the Stem Cell Research and Development Center, Universitas Airlangga, Surabaya. The cell culture process took two weeks with changing new medium every three days and adding mitogen GM-CSF (20ng/ml) and IL-2 (100IU/ml). After two weeks of cell culture, hematopoietic stem cells were confirmed with a CD56 marker using immunocytochemistry and seeded 5x10⁵ in 12 multi well-plate each well.

Co-cultivation of HSC, NK cell and SARS-CoV-2 in Vitro

Co-cultivation of HSCs, NK cells, and SARS-CoV-2 isolates were performed at Biosafety Level 3. Each sample of P1, P2, and P3 measuring as much as 200 μ l was incubated for 72 hours in the CO₂ incubator. The collected-supernatant was centrifuged at 5000 rpm for 5 minutes; then, the supernatant and the cell pellet was separated. After that, each sample was extracted with GENE AID RNA extraction kit, and followed by proceeding to check the amount of copy DNA with qRT-PCR.

Pro-viral Load determination

SEEGENE COVID-19 detection kit was used to determine the pro-viral load, which detected three target genes, which are N gene, E gene, and RdRP gene. ABI Prism 7500 Sequence Detector System from Applied Biosystems®, USA, moreover, was used to perform amplification and data acquisition.

RESULTS

The confirmations of HSCs with the CD34 marker and NK cells with the CD56 marker are shown in Figure 1 (a,b), emitting green fluorescence.

A group of Figure 2 displayed the co-cultivation of HSCs and 50 μ l, 100 μ l, 150 μ l, and 200 μ l of each sample after 72 hours when the viral load was then determined with qRT-PCR.

A group of Figure 3 presents the co-cultivation of NK cells and 200 μ l of each sample P1, P2, and P3 after 72 hours the viral load was then determined with qRT-PCR.

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Once the virus planted on HSCs and NK cells, cells and supernatants were taken from existing cell plates, and the viral load was calculated from all plates using Polymerase

Chain Reaction (PCR) machine, as shown in Table 1 and Figure 4.

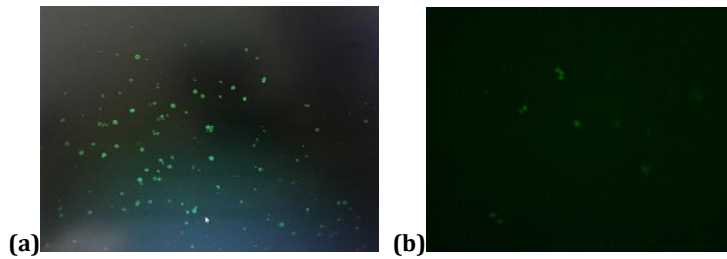


Figure 1. (a) HSCs confirmed with the CD34 marker, (b) NK cells confirmed with the CD56 marker

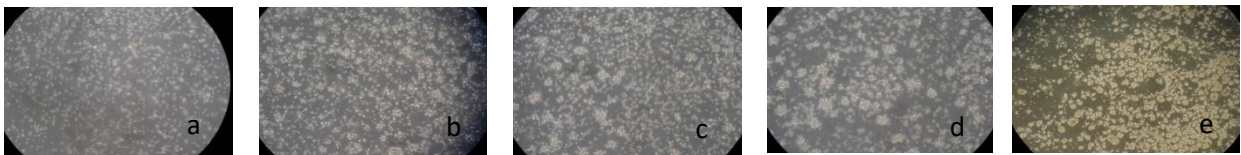


Figure 2. Microscopic Images of HSCs after Planting Viruses after 72 hours (a) Control HSCs, (b) HSC with 50µl viruses, (c) HSCs with 100µl viruses, (d) HSCs with 150µl viruses, (e) HSCs with 200µl viruses

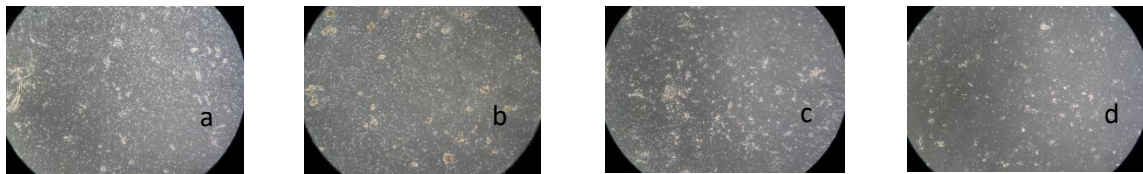


Figure 3. (a) Control cells of NK, (b) 72 hours after co-cultivation of P1 sample, (c) 72 hours after co-cultivation of P2 sample, (d) 72 hours after co-cultivation of P3 sample

Table 1. Data of the viral load on cells and supernatants after augmentation of HSCs

No.	Virus Dosage		Mol	Period	Viral Load
1.	100µl		0.00416	0 hours	20.8 Copy/µl
				24 hours	0 Copy/µl
				48 hours	0 Copy/µl
				72 hours	0 Copy/µl
1.	150µl		0.00624	0 hours	20.8 Copy/µl
				24 hours	0 Copy/µl
				48 hours	0 Copy/µl
				72 hours	0 Copy/µl
2.	200µl		0.00832	0 hours	20.8 Copy/µl
				24 hours	0 Copy/µl
				48 hours	0 Copy/µl
				72 hours	0 Copy/µl

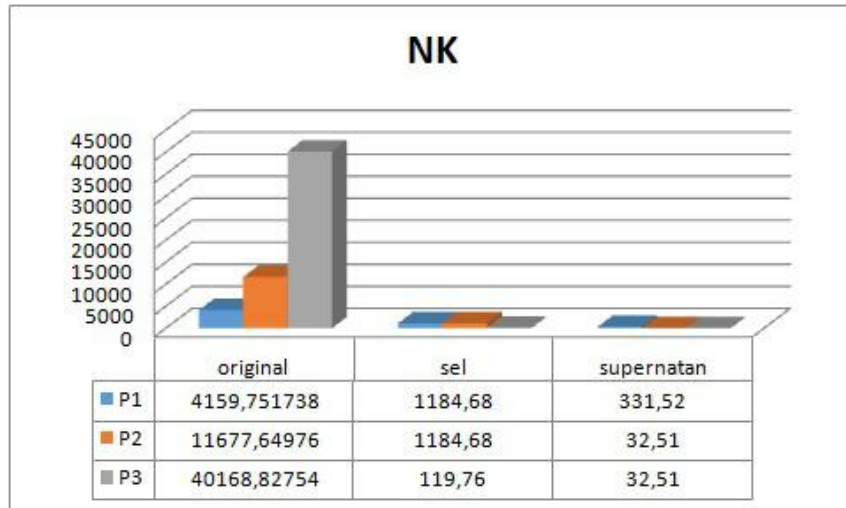


Figure 4. Viral Load of samples after 72 hours co-cultivation NK cells and Indonesian SARS-CoV-2 isolates

DISCUSSION

The immune response against viral infections depends on the effector mechanisms from the innate and adaptive immune responses.[28] The cytotoxicity mediated by cytotoxic CD8+ T cells and NK cells is responsible for executing infected cells.[22] Moreover, NK cells are the potential to mediate antibody-dependent cellular cytotoxicity (ADCC) over the receptor CD16 by binding to antibodies opsonizing infected cells that lead to apoptosis. NCAM-1 (CD56) is expressed by classical NK cells on its membranes in high or low intensity or not express CD16 and lacks express CD3.[25]

Reverse transcription loop-mediated isothermal amplification (RT-LAMP), reverse-transcription polymerase chain reaction (RT-PCR), and real-time RT-PCR (rRT-PCR) are the current gold standards of diagnostic tests to identify the presence of coronavirus.[1,13] Two one-step quantitative RT-PCR (qRT-PCR) is developed to detect two different regions (ORF1b and N) of the SARS-CoV-2 genome to identify patients earlier. Three novel RT-PCR are developed to target the nucleocapsid (N) genes, spike (S), and RNA-dependent RNA polymerase (RdRp)/helicase (Hel). From these three novel assays, the COVID-19-RdRp/Hel has the lowest limit of detection in vitro, and strongly sensitive and specific assays may improve the laboratory diagnosis of COVID-19. The RdRp gene assay, together with the one-step RT-PCR system, is not more sensitive than the SARS-CoV E gene assay.[13]

HSCs as multipotent progenitor cells can rearrange, renew, and differentiate into many various types of blood cells, so it is probably the best type of stem cell with a large-scale of application for the treatment of numerous diseases.[18,19] HSCs change the profile of cytokine secretion from NK cells, dendritic cells, naive and effector T cells to induce a more progressive phenotype and anti-inflammatory, decrease the secretion of TNF- α and IFN- γ as pro-inflammatory cytokines, whereas IL-4 and IL-10 more suppressive stimulated.[19] Other factors may also be involved, such as IL-6, IL-10, TGF- β 1, hepatocyte growth factor, nitric oxide, prostaglandin E2, and possible indoleamine 2, 3-dioxygenase. The evidence further claims that HSCs are anti-inflammatory and

immunoregulatory, even though the specific mechanism has not been clarified yet.[20]

An increase in IL-10 levels and decreases in TNF- α levels and IL-2 levels in all-time variations and multiplicity of infection (MoI) on the cytokines examination are further discovered. As presented in Table 1, the value of the viral load was decreased. The amount of viral load at the initial administration of HSCs was 20.8 copies/ μ l in all variants of MoI. After the administration of HSCs, the viral load became 0 copies μ l in all-time variants: 24 hours, 48 hours, and 72 hours. The findings further indicate that HSCs can eliminate viruses in cells and supernatants after 24 hours of inoculation. The virus binding to the plasma membrane of the cells is a crucial step in viral infection. The susceptibility of cells to infections depends on the different surface receptor expression. Specifically, the integrin adhesion receptor plays a vital role in mediating the binding and internalization of some viruses. Different integrin receptors expression on early HSC even were noted. Hence, it can be conceived that these receptors mediate the interaction between HSCs and some viruses.[19]

The increase in anti-inflammatory cytokines and the strong decrease in inflammatory cytokines, thereby the virus becomes inactive, are the other mechanisms of HSCs in terminating viruses.[20] HSCs differentiate into the immune cell lineage that leads to virus phagocytosis, and the damaged virus is discharged from the cell.[19,20] From the results, therefore, it is suggested for HSCs to be given to COVID-19 patients in combination with other therapeutic regimens.

As Figure 3 displayed, after 72 hours of co-cultivation of both supernatant and the cell pellet confirmed with qRT-PCR to determine the viral load, the amount of viral load each sample had decreased from the original amount and each showed a decrease of more than 50%. Besides, there was no reduction in the number of NK cells that had been co-cultivated. On the contrary, there was a significant increase in the number of viruses, although the addition of NK cells has inactivated the virus. The result is probably caused by the functions of NK cells, which are related to NCR (NKp46, 44, and 30) that can bind glycoprotein from the virus so that the virus becomes inactive, besides the release of cytokines that cause the virus to be inactivated.

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Natural killer (NK) cells, as the critical effector in immunity, play an essential role in the first line of host defense against viral infection by eliminating the infected cells without early antigen stimulation.[25] NK cells have a complex receptor repertoire in inactivating and inhibitory form.[23] After NK cells stimulation, the activating signaling leads to a downstream cascade of kinase activation with the final exocytosis of cytotoxic granules and resulting in the terminating of target cells.[24] The balance of inhibitory and activating receptors and some costimulatory molecules are controlling the cytotoxicity of NK cells.[25] For NK cells to reach a productive response, a critical threshold of signaling must be achieved.[30] Furthermore, virus-infected respiratory epithelial cells release inflammatory chemokines that recruit NK cells to the site of infection.[13]

NK cells demonstrate cytotoxic effects because of direct or indirect target recognition.[24] In the direct target recognition, the identification happens over a general signal from surface receptors of NK cells that receive activating and inhibiting environmental signals.[30] Surface glycoproteins present on all nucleated cells, including major histocompatibility complex I (MHC I) or viral antigens can be molecules recognized by NK cells.[25] The effect of precise target recognition is the killing mechanisms activation, in NK cells: exocytosis of cytotoxic granules or death receptor-mediated cytotoxicity.[21,22,31] Cytotoxic granules contain pore-forming protein, granzymes-serine proteases, and perforin. Perforin produces pores in the target cell membrane, which allows granzymes to get in the cell and begin the apoptosis.[30]

CONCLUSION

The administration of HSCs in patients with COVID-19 can terminate the SARS-CoV-2 virus. During viral infections, the SARS-CoV-2 virus and NK cells are in a constant state of battle. NK cells react to terminate the invading viruses through the increased activating signals or recognition of the missing self. Nevertheless, many viruses have developed different strategies to modulate NK cell activities. Still, this study has shown that NK cells play a critical role in decreasing the viral load of the SARS-CoV-2 virus. Even though this study is an in vitro, it could be the theoretical basis to develop other alternative stem cell-based therapies in handling COVID-19 in Indonesia, particularly and in the globe generally.

Abbreviations

HSCs	: Hematopoietic Stem Cell
NK	: Natural Killer
Mol	: Multiple of Infection
PCR	: Polymerase Chain Reaction
SARS	: Severe Acute Respiratory Syndrome
MERS	: Middle East Respiratory Syndrome
IFN	: Interferon
TNF	: Tumor Necrosis Factor
IL	: Interleukin
ARDS	: Acute Respiratory Distress Syndrome
TGF	: Transforming Growth Factor
CD	: Cluster of Differentiation
PBMCs	: Peripheal Blood Mononuclear Cells
BSL-3	: Bio Safety Level 3
RNA	: Ribonucleic acid

DNA	: Deoxyribonucleic acid
CPE	: Cytopathic Effect
Alpha MEM	: Alpha Minimum Essential Medium
GM-CSF	: Granulocyte-Macrophage Colony Stimulating Factor
HEPES	: (N-2-hydroxyethyl piperazine-N-2-ethane sulfonic acid) Medium
NaHCO ₃	: Natrium bicarbonate

Declarations

Ethics approval

The patient's sputum sampling requires an ethical test that was submitted to the Universitas Airlangga Hospital Ethics Commission and has been approved, as evidenced by the issuance of the ethics-worthy certificate number 136/KEP/2020 on April 20, 2020, following the regulatory guidelines of the country.

Consent to publication

Not applicable.

Availability of data and material

Availability of data and materials.

Competing interests

The authors report no conflicts of interest in this work.

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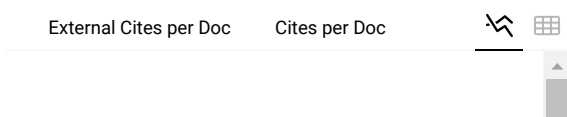
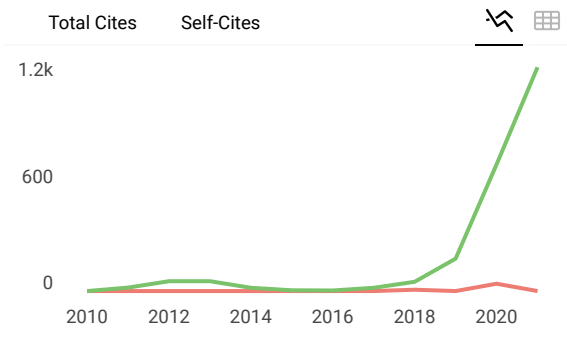
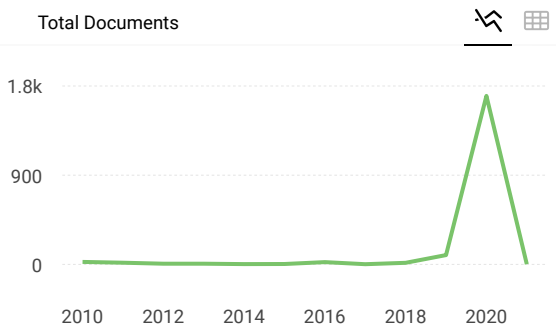
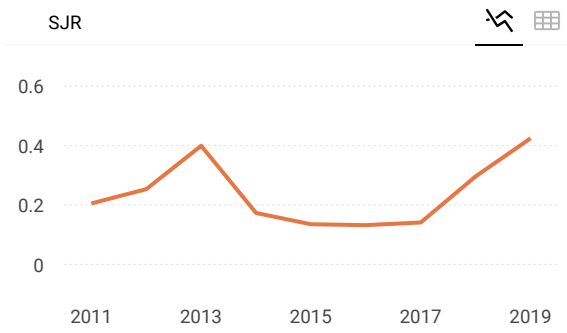
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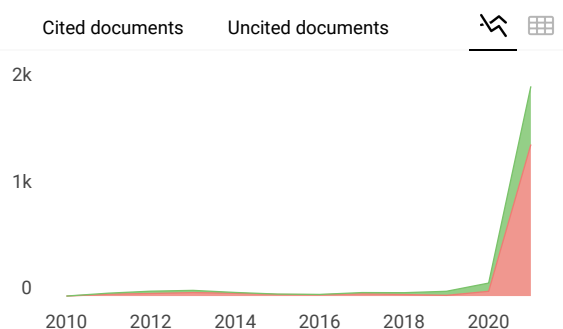
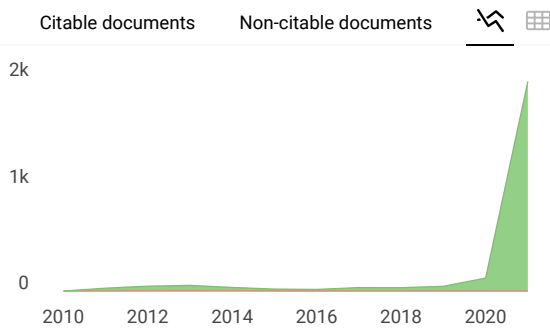
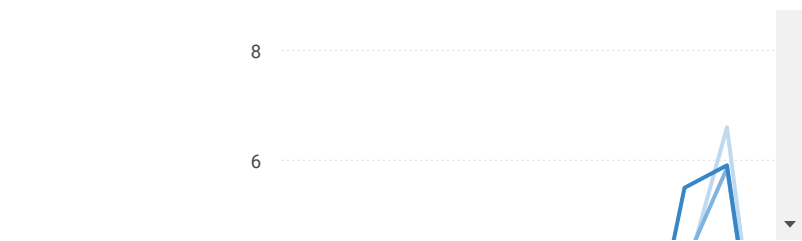
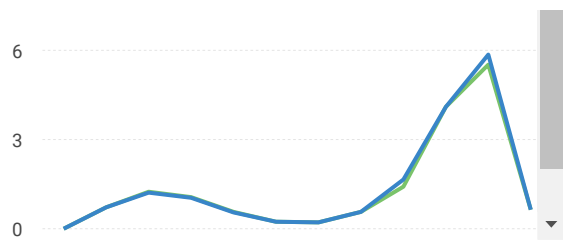
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