

 BMC Series

BMC
Complementary
Medicine and
Therapies

Part of Springer Nature

BMC Complementary Medicine and Therapies

[Home](#) [About](#) [Articles](#) [Submission Guidelines](#)

[Contact](#)

[Editorial Board](#)

Editorial Board

Editor

[Anne Menard](#), *BioMed Central, UK*

Assistant Editors

[Esther Fagelson](#), *BioMed Central, UK*

[Kate Gaines](#), *BioMed Central, USA*

Senior Editorial Board Members

[Victor Kuete](#), *University of Dschang, Cameroon*

[Insop Shim](#), *Kyung Hee University, South Korea*

[Jianping Liu](#), *Beijing University of Chinese Medicine, China*

Jenny Wilkinson, *Charles Sturt University, Australia*

Amie Steel, *University of Technology Sydney, Australia*

Associate Editors

Basic research

Siti Salwa Abd Gani, *Universiti Putra Malaysia, Malaysia*

Wonder Kofi Mensah Abotsi, *Kwame Nkrumah University of Science & Technology (KNUST), Ghana*

Oluyomi Adeyemi, *Landmark University, Nigeria*

Bulus Adzu, *National Institute of Pharmaceutical Research, Nigeria*

Fatma Afifi, *University of Jordan, Jordan*

Dildar Ahmed, *Forman Christian College Lahore, Pakistan*

Peter Akah, *University of Nigeria, Nigeria*

Niaz Ali, *Khyber Medical University, Pakistan*

Angel Josabad Alonso-Castro, *Affiliation University of Guanajuato, Mexico*

Mohammed Alshawsh, *University of Malaya, Malaysia*

Amr Amin, *University of Chicago, USA*

Patrick Amoateng, *University of Ghana, Ghana*

Stephen Amoo, *University of KwaZulu-Natal, South Africa*

Sheetal Anandjiwala, *National Institute of Pharmaceutical Education and Research (NIPER), India*

Adeyemi Aremu, *North West University, South Africa*

Karuppusamy Arunachalam, *Federal University of Mato Grosso, Brazil*

Sylvin Benjamin Ateba, *University of Yaoundé, Cameroon*

Maurice D Awouafack, *University of Dschang, Cameroon*

Muhammad Ayaz, *University of Malakand, Pakistan*

Gamal Badr, *Assiut University, Egypt*

Enitome Bafor, *University of Benin*, Nigeria
Prasanta Bag, *University of Calcutta*, India
Vivek K Bajpai, *Yeungnam University*, South Korea
Matthew Gavino Donadu, *University of Sassari*, Italy
Mohd Fadzelly Abu Bakar, *Universiti Tun Hussein Onn Malaysia*, Malaysia
Maruthaiveeran P Balasubramanian, *University of Madras*, India
Manjeshwar S Baliga, *Father Muller Medical College*, India
Parveen Bansal, *Baba Farid University of Health Sciences*, India
Sanaa Bardaweel, *The University of Jordan*, Jordan
Deepak Bhatia, *Shenandoah University*, USA
Tannaz Birdi, *The Foundation for Medical Research*, India
Anupam Bishayee, *California Northstate University*, USA
Cornelia Braicu, *Iuliu Hațieganu University of Medicine and Pharmacy*, Romania
Bruno Bueno-Silva, *Guarulhos University - Praca Tereza Cristina*, Brazil
Prosper Cabral, *University of Dschang*, Cameroon
Esperanza Carcache de Blanco, *Ohio State University*, USA
Maria Carpinella, *Catholic University of Cordoba*, Argentina
Chanpen Chanchao, *Chulalongkorn University*, Thailand
Hsiu-Mei Chiang, *China Medical University*, Taiwan
Meng-Tsan Chiang, *National Taiwan Ocean University*, Taiwan
Jae Youl Cho, *Sungkyunkwan University*, South Korea
William CS Cho, *Queen Elizabeth Hospital*, Hong Kong
Anderly Chueh, *University of Melbourne*, Australia
Ooi Der Jiun, *MAHSA University*, Malaysia
Saikat Dewanjee, *Jadavpur University*, India
Abhijit Dey, *Presidency University*, India
Yavuz Dodurga, *Pamukkale University Medical Faculty Medical Biology and Genetics*, Turkey
Jean Paul Dzoyem, *University of Dschang*, Cameroon
María Celina Elissondo, *Facultad de Ciencias Veterinarias*, Argentina
Levent Elmas, *Pamukkale University School of Medicine*, Turkey
Agustina Endharti, *Brawijaya University*, Indonesia
Adaobi Chioma Ezike, *University of Nigeria*, Nigeria
Wissam Faour, *Lebanese American University*, Lebanon
Ammad Ahmad Farooqi, *Institute of Biomedical and Genetic Engineering (IBGE)*, Pakistan
Olaniyi Fawole, *Stellenbosch University*, South Africa
Yibin Feng, *The University of Hong Kong*, Hong Kong
Maria Leticia Miranda Fernandes Estevinho, *Instituto Politécnico de Bragança*, Portugal
Manuel Fernandes-Ferreira, *University of Porto*, Portugal
Caleb Firemping, *KNUST*, Ghana
Fenghua Fu, *Yantai University*, China
Mirutse Giday, *Addis Ababa University*, Ethiopia
Ahmad Reza Gohari, *Tehran University of Medical Sciences*, Iran
Ramakrishnan Gopalakrishnan, *University of Southern California*, USA
Vlasios Goulas, *Cyprus University of Technology*, Cyprus
Rohit Goyal, *Shoolini University*, India
Sebastian Granica, *Medical University of Warsaw*, Poland
Massimo Grilli, *University of Genova*, Italy

Jian-You Guo, *Institute of Psychology, Chinese Academy of Science, China*
Keisuke Hagihara, *Osaka University Graduate School of Medicine, Japan*
Raghavendra Hallur, *Wollega University, Ethiopia*
James Hamuel, *Federal University of Technology, Nigeria*
Da-Cheng Hao, *Dalian Jiaotong University, China*
Nicholas Heng, *University of Otago, New Zealand*
Seyed Jalal Hosseinimehr, *Mazandaran University of Medical Sciences, Iran*
Junguk Hur, *University of North Dakota, USA*
Dae Youn Hwang, *Pusan National University, Republic of Korea*
Jin Taek Hwang, *Korea Food Research Institute, South Korea*
Mustapha Imam, *Zhengzhou University, China*
Ai-Qun Jia, *Nanjing University of Science and Technology, China*
Jin Boo Jeong, *Andong National University, South Korea*
Zorica Juranic, *Institute of Oncology and Radiology of Serbia, Serbia*
Gaurav Kaithwas, *Baba Saheb Bhimrao Ambedkar University, India*
David Katerere, *Tshwane University of Technology, South Africa*
Gurcharan Kaur, *Guru Nanak Dev University, India*
Martin Kello, *University of P.J. Safarik, Slovakia*
Philip Kerr, *Charles Sturt University, Australia*
Imran Khan, *The Hormel Institute, USA*
Muhammad Rashid Khan, *Quaid-I-Azam University, Pakistan*
Chang-Eop Kim, *Gachon University, South Korea*
Sun Kwang Kim, *Kyung Hee University, South of Korea*
No Soo Kim, *Korea Institute of Oriental Medicine, South Korea*
Hee Young Kim, *Daegu Haany University, South of Korea*
Seong-Gyu Ko, *Kyung Hee University, South Korea*
Michal Kohout, *University of Chemistry and Technology Prague, Czech Republic*
Anna Krasowska, *Uniwersytet Wroclawski, Poland*
Yogesh Anant Kulkarni, *Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, India*
Pradeep Kumar, *North Eastern Regional Institute of Science & Technology, India*
Ho-Keun Kwon, *Harvard Medical School, USA*
Namrita Lall, *University of Pretoria, South Africa*
Bae Hwan Lee, *Yonsei University College of Medicine, South Korea*
Jung-Jin Lee, *Korea Institute of Oriental Medicine, South Korea*
Gerhard Litscher, *Medical University of Graz, Austria*
Jiawei Liu, *Guangzhou University of Chinese Medicine, China*
Richard Lobo, *Manipal College of Pharmaceutical Sciences, India*
Victor Lopez, *Universidad San Jorge, Spain*
Michel Machado, *Universidade Federal do Pampa, Brazil*
Nattaya Lourith, *Mae Fah Luang University, Thailand*
Xiao Ma, *Mayo Clinic, USA*
Vinesh Maharaj, *University of Pretoria, South Africa*
Kenneth Markowitz, *Rutgers School of Dental Medicine, USA*
Carlos Henrique Gomes Martins, *University of Franca, Brazil*
Peter Masoko, *University of Limpopo, South Africa*
Andrea Mastinu, *University of Brescia, Italy*

Armelle T Mbaveng, *University of Dschang*, Cameroon
Lyndy McGaw, *University of Pretoria*, South Africa
Natalizia Miceli, *University of Messina*, Italy
Przemysław Mikołajczak, *Poznan University of Medical Sciences*, Poland
Akansha Mishra, *Baylor College of Medicine*, USA
Chakrabhavi Dhananjaya Mohan, *University of Mysore*, India
Thomas Monsees, *University of the Western Cape*, South Africa
Mohamad Mroueh, *Lebanese American University*, Lebanon
Yogendra Nayak, *Manipal Academy of Higher Education*, India
Michele Navarra, *University of Messina*, Italy
Pradeep Negi, *CSIR-Central Food Technological Research Institute*, India
Wang Ning, *The University of Hong Kong*, China
Fidele Ntie-Kang, *University of Buea*, Cameroon
Oluwafemi Oguntibeju, *Cape Peninsula University of Technology*, South Africa
Seung Min Oh, *Hoseo University*, South Korea
Thiago Napoleão, *Universidade Federal de Pernambuco*, Brazil
Chidozie Nwabuisi Okoye, *University of Nigeria*, Nigeria
Javier Palacios, *Universidad Arturo Prat*, Chile
Abhay K Pandey, *University of Allahabad*, India
Yoon Jung Park, *Ewha Womans University*, South Korea
Jayanta Kumar Patra, *Dongguk University*, South Korea
Constant Anatole Pieme, *Faculty of Medicine and Biomedical Sciences, University of Yaounde I-Yaounde*, Cameroon
E. Sanmuga Priya, *Anna University*, India
Steven Qian, *North Dakota State University*, USA
Xinhua Qu, *Shanghai Ninth People's Hospital*, China
Matthias Rostock, *University Hospital Zurich*, Switzerland
Fraser Russell, *University of the Sunshine Coast*, Australia
Suna Sabuncuoglu, *Hacettepe University*, Turkey
Abdul Sadiq, *University of Malakand*, Pakistan
Nurdan Sarac, *Mugla Sitki Kocman University*, Turkey
Lidija Senerovic, *Institute of Molecular Genetics and Genetic Engineering*, Serbia
Gowhar Shafi, *Karolinska Institute*, Sweden
Ismail Shah, *Abdul Wali Khan University Mardan*, Pakistan
Naseer Ali Shah, *COMSATS Institute of Information Technology*, Pakistan
Javad Sharifi-Rad, *Shahid Beheshti University of Medical Sciences*, Iran
Shruti Shukla, *Dongguk University*, South Korea
Sahabjada Siddiqui, *Era University*, India
Brahmanand Singh, *CSIR-National Botanical Research Institute*, India
Antonella Smeriglio, *University of Messina*, Italy
Chang Gue Son, *Daejeon University*, South Korea
Tatjana Stanojković, *Institute of Oncology and Radiology of Serbia*, Serbia
Vanessa Steenkamp, *University of Pretoria*, South Africa
Rajasekaran Subbiah, *Anna University*, India
Sachiko Sugimoto, *Hiroshima University*, Japan
Ipek Suntar, *Gazi University*, Turkey
Deny Susanti, *International Islamic University Malaysia*, Malaysia

Jean-De-Dieu Tamokou, *University of Dschang*, Cameroon
Chanderdeep Tandon, *Amity Institute of Biotechnology*, India
Emmanuel Tshikalange, *University of Pretoria*, South Africa
Gaffari Türk, *Firat University*, Turkey
Sakthivel Vaiyapuri, *University of Reading*, UK
Sully Margot Cruz Velasquez, *Universidad de San Carlos de Guatemala*, Guatemala
Hui-Min David Wang, *National Chung Hsing University*, Taiwan
Kai Wang, *Chinese Academy of Agricultural Sciences*, China
Yong Wang, *Beijing University of Chinese Medicine*, China
Ramida Watanapokasin, *Srinakharinwirot University*, Thailand
Chi-Rei Wu, *Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources*, Taiwan
Suowen Xu, *University of Rochester*, USA
Arun Yadav, *North-Eastern Hill University*, India
Woong Mo Yang, *Kyung Hee University*, Republic of Korea
Lim Yau Yan, *Monash University Malaysia*, Malaysia
Yueh-Chiao Yeh, *Nanhua University*, Taiwan
Looi Chung Yeng, *Taylor's University*, Malaysia
Ho Wan Yong, *The University of Nottingham*, Malaysia
Zhiling Yu, *Hong Kong Baptist University*, Hong Kong
Cristiane Yumi Koga-Ito, *UNESP-Universidade Estadual Paulista*, Brazil
Zainul Amiruddin Zakaria, *Universiti Putra Malaysia*, Malaysia
Ramón E Robles Zepeda, *Universidad de Sonora*, Mexico
Denis Zofou, *University of Buea*, Cameroon

Clinical research

Lijun Bai, *Chinese Academy of Sciences*, China
Zhaoxiang Bian, *Hong Kong Baptist University*, Hong Kong
Younbyoung Chae, *Kyung Hee University*, South Korea
Seung-Hun Cho, *Kyung Hee University Medical Hospital*, South Korea
Lorenzo Cohen, *MD Anderson Cancer Center*, USA
Catherine Cook-Cottone, *State of University of New York*, USA
Meaghan Coyle, *RMIT University*, Australia
Ranjeet Dash, *Charles River Laboratories*, Ashland, USA
Gary Elkins, *Baylor University*, USA
Mohamed Essa, *Sultan Qaboos University*, Oman
Neha Gothe, *University of Illinois*, USA
Motjaba Heydari, *Research Center for Traditional Medicine and History of Medicine*, Iran
Markus Horneber, *Klinikum Nuernberg Nord*, Germany
Mohammad Hosein Farzaei, *Kermanshah University of Medical Sciences*, Iran
Alyson Huntley, *University of Bristol*, UK
Mohamed Imam, *Norfolk and Norwich University Hospitals*, UK
Jian Kong, *Harvard Medical School*, USA
Dieudonne Kuate, *University of Dschang*, Cameroon
Romy Lauche, *University of Technology Sydney*, Australia
Bong Hyo Lee, *Daegu Haany University*, South Korea
Hyangsook Lee, *Kyung Hee University*, South Korea

Ju Ah Lee, *Gachon University*, South Korea
Junhee Lee, *Kyung Hee University Korean Medicine Hospital*, South Korea
Ping-Chung Leung, *The Chinese University of Hong Kong*, Hong Kong
Filipe Carvalho Matheus, *Federal University of Santa Catarina*, Brazil
Norazlina Mohamed, *Universiti Kebangsaan Malaysia*, Malaysia
Vitaly Napadow, *Massachusetts General Hospital*, USA
Mohsen Naseri, *Shahed University*, Iran
Hi-Joon Park, *Kyung Hee University*, South Korea
Jung-Mi Park, *Kyung Hee University*, South Korea
Wenbo Peng, *University of Technology Sydney*, Australia
Karen Pilkington, *University of Westminster*, UK
Asser Sallam, *Suez Canal University Hospitals*, Egypt
Adelaida María Castro Sánchez, *Universidad de Almería*, Spain
Jiangang Shen, *University of Hong Kong*, Hong Kong
Genevieve Steiner, *Western Sydney University*, Australia
Tobias Sundberg, *Karolinska Institutet*, Sweden
Shirley Telles, *Patanjali Research Foundation*, India
Vijayabhaskar Veeravalli, *Johns Hopkins University*, USA
Luis Vitetta, *University of Queensland*, Australia
Gloria Yeh, *BIDMC*, USA
Anthony Zhang, *RMIT University*, Australia
Yan Zhang, *Texas Tech University Health Sciences Center*, USA
Guo-qing Zheng, *The 2nd Affiliated Hospital of Wenzhou Medical University*, China
Linda Zhong, *Jockey Club School of Chinese Medicine*, China

Integration into healthcare

Vincent Chung, *Chinese University of Hong Kong*, China
In-Hyuk Ha, *Jaseng Medical Foundation*, South Korea
Hao Hu, *University of Macau*, China
Yoon Jae Lee, *Jaseng Medical Foundation*, South Korea
Carolina Oi Lam Ung, *University of Macau*, China

Patterns of use, knowledge and attitudes

Jon Adams, *University of Technology*, Australia
Eran Ben-Arye, *Clalit Health Organization*, Israel
Moshe Frenkel, *The University of Texas Medical Branch*, USA
Corina Guthlin, *Institute of General Practice*, *Goethe University*, Germany
Dongwoon Han, *Hanyang University College of Medicine*, *Korea, Republic of (South Korea)*
Pengyu Hong, *Brandeis University*, USA
Nidal Jaradat, *An-Najah National University*, Palestine
Agnete Kristoffersen, *National Research Center in Complementary and Alternative Medicine*, Norway
Alfred Laengler, *Gemeinschaftskrankenhaus*, Germany
Olivia Lindly, *Massachusetts General Hospital*, USA
Sascha Meyer, *Great Ormond Street Hospital*, UK
Richard Nahin, *National Institutes of Health*, USA
Jeremy Y. Ng, *McMaster University*, Canada

Ramzi Shawahna, *An-Najah National University, Palestine*
Fuschia Sirois, *University of Sheffield, UK*
Jon Wardle, *University of Technology Sydney, Australia*

Research methodology

Scott Mist, *Oregon Health & Science University, USA*
Damien Ridge, *University of Westminster, UK*
Barbara Wider, *Peninsula Medical School, UK*

Editorial Advisors

David Aldridge, *Universitat Witten Herdecke, Germany*
Brian Berman, *University of Maryland, USA*
Edzard Ernst, *University of Exeter, UK*
Ronald Feise, *Institute of Evidence-Based Chiropractic, USA*
Sheila Greenfield, *University of Birmingham, UK*
Wayne Jonas, *Samueli Institute, USA*
Klaus Linde, *Technische Universität München, Germany*
Adam Perlman, *Saint Barnabas Health Care System, USA*

Statistical Advisors

Ioannis Hatzaras, *NYU Langone Health, USA*
Dominik Mertz, *Juravinski Hospital and Cancer Center, Canada*
Eric Steiner, *Gesundheits- und Pflegezentrum Russelsheim, Germany*
Zhijie Zhang, *Fudan University, China*

Systematic Review Editors

Jürgen Barth, *University Hospital Zurich, Switzerland*
Yutong Fei, *Beijing University of Chinese Medicine and Pharmacology, China*
Myeong Soo Lee, *Korea Institute of Oriental medicine, Republic of Korea*
L. Susan Wieland, *University of Maryland School of Medicine, USA*

 **BMC** Series

[Submit manuscript](#)





BMC Complementary Medicine and Therapies



Volumes and issues > Volume 23, issue 1

Search within journal

Volume 23, issue 1, December 2023

48 articles in this issue

[Keratitis following leech therapy for periocular eczematous dermatitis: a case report](#)

Dilek Özkaya

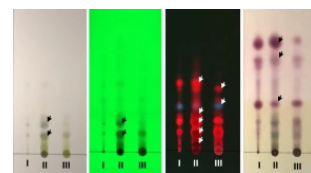
Case report | [Open Access](#) | Published: 02 January 2023 | Article: 124



[In vitro and in vivo antiplasmodial activities of leaf extracts from *Sonchus arvensis* L.](#)

Dwi Kusuma Wahyuni, Sumrit Wacharasindhu ... Sehanat Prasongsuk

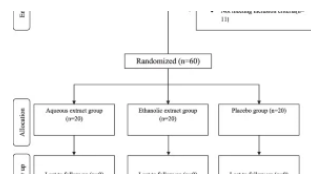
Research | [Open Access](#) | Published: 14 February 2023 | Article: 47



[The effects of aqueous and ethanolic extracts of *Rheum ribes* on insulin-resistance and apolipoproteins in patients with type 2 diabetes mellitus: a randomized controlled trial](#)

Atieh Ghafouri, Sahar Jafari Karegar ... Farzad Shidfar

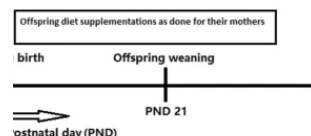
Research | [Open Access](#) | Published: 14 February 2023 | Article: 46



[In utero and postnatal exposure to *Foeniculum vulgare* and *Linum usitatissimum* seed extracts: modifications of key enzymes involved in epigenetic regulation and estrogen receptors expression in the offspring's ovaries of NMRI mice](#)

Fahimeh Pourjafari, Massood Ezzatabadipour ... Tahereh Haghpanah

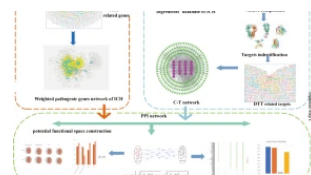
Research | [Open Access](#) | Published: 14 February 2023 | Article: 45



[Decoding the underlying mechanisms of Di-Tan-Decoction in treating intracerebral hemorrhage based on network pharmacology](#)

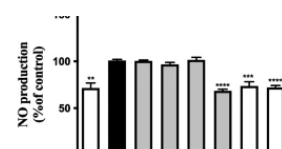
Zheng Zhen, Dao-jin Xue ... Tao Huang

Research | [Open Access](#) | Published: 10 February 2023 | Article: 44



[In vitro antioxidant, anti-inflammatory, and anticancer activities of mixture Thai medicinal plants](#)

Suchada Jongrungraungchok, Fameera Madaka ... Nalinee Pradubiyat



RESEARCH

Open Access



In vitro and in vivo antiplasmodial activities of leaf extracts from *Sonchus arvensis* L.

Dwi Kusuma Wahyuni^{1,2*}, Sumrit Wacharasindhu³, Wichanee Bankeeree¹, Sri Puji Astuti Wahyuningsih², Wiwied Ekasari⁴, Hery Purnobasuki², Hunsu Punnapayak¹ and Sehanat Prasongsuk^{1,2*}

Abstract

Background Malaria continues to be a global problem due to the limited efficacy of current drugs and the natural products are a potential source for discovering new antimalarial agents. Therefore, the aims of this study were to investigate phytochemical properties, cytotoxic effect, antioxidant, and antiplasmodial activities of *Sonchus arvensis* L. leaf extracts both in vitro and in vivo.

Methods The extracts from *S. arvensis* L. leaf were prepared by successive maceration with *n*-hexane, ethyl acetate, and ethanol, and then subjected to quantitative phytochemical analysis using standard methods. The antimalarial activities of crude extracts were tested in vitro against *Plasmodium falciparum* 3D7 strain while the Peter's 4-day suppressive test model with *P. berghei*-infected mice was used to evaluate the in vivo antiplasmodial, hepatoprotective, nephroprotective, and immunomodulatory activities. The cytotoxic tests were also carried out using human hepatic cell lines in [3(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) assay.

Result The *n*-hexane, ethyl acetate, and ethanolic extracts of *S. arvensis* L. leaf exhibited good in vitro antiplasmodial activity with IC₅₀ values 5.119 ± 3.27, 2.916 ± 2.34, and 8.026 ± 1.23 µg/mL, respectively. Each of the extracts also exhibited high antioxidant with low cytotoxic effects. Furthermore, the ethyl acetate extract showed in vivo antiplasmodial activity with ED₅₀ = 46.31 ± 9.36 mg/kg body weight, as well as hepatoprotective, nephroprotective, and immunomodulatory activities in mice infected with *P. berghei*.

Conclusion This study highlights the antiplasmodial activities of *S. arvensis* L. leaf ethyl acetate extract against *P. falciparum* and *P. berghei* as well as the antioxidant, nephroprotective, hepatoprotective, and immunomodulatory activities with low toxicity. These results indicate the potential of *Sonchus arvensis* L. to be developed into a new antimalarial drug candidate. However, the compounds and transmission-blocking strategies for malaria control of *S. arvensis* L. extracts are essential for further study.

Keywords Antioxidant, Antiplasmodial, Hepatoprotective, Immunomodulator, Nephroprotective, Malaria, *Plasmodium berghei*, *Plasmodium falciparum*, *Sonchus arvensis* L.

*Correspondence:

Dwi Kusuma Wahyuni
dwi-k-w@fst.ac.id
Sehanat Prasongsuk
Sehanat.p@chula.ac.th

¹ Plant Biomass Utilization Research Unit, Department of Botany, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand

² Department of Biology, Faculty of Science and Technology, Universitas Airlangga Surabaya, East Java 60115, Indonesia

³ Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand

⁴ Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, East Java 60115, Indonesia



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Malaria is an endemic disease in tropical areas of Asia, Africa, and Central and South America, and is known to spread even in vaccinated populations [1]. In 2020, malaria accounted for 241 million new infections and 627 thousand deaths worldwide in 87 endemic countries. There were 14 million more malaria cases and 47,000 more deaths compared to 2019 [2]. Therefore, one of the United Nations Millennium Development Goals (MDGs) is to reduce the incidence and subsequent morbidity and mortality associated with malaria [2]. The malaria elimination target in Indonesia is no high-endemic district by the end of 2024 [3]. However, the significant obstacles to the treatment and prognosis of malaria are its resistance to chloroquine [4, 5] and artemisinin-based combination therapy [2]. There is an urgent need to develop new antimalarial drugs and many researchers are currently exploring the efficacy of synthetic and natural products [6].

An estimated 80% of the global population uses natural products to treat various illnesses and diseases [7, 8]. In the case of malaria, 75% of patients have been reported to treat themselves with traditional medicines derived from various plant sources, including *Cinchona succirubra* L., as well as relatively newer medicines, such as artemisinin, which is produced from *Artemisia annua* L. [9]. In Indonesia, *Sonchus arvensis* L., a highly invasive species of the family Asteraceae, is used as a traditional medicinal plant for malaria treatment [10]. This plant contains various active compounds including flavonoids, saponins, and polyphenols [11], which have been reported for moderate to high antioxidant [12], hepatoprotective [13], nephroprotective [14], anti-inflammatory [15], and antibacterial activities [16–18]. Although *S. arvensis* L. has pharmaceutical benefits, it has never been evaluated for in vivo treatment of malaria.

The aim of the present study was to determine the in vitro and in vivo antiparasitocidal activities of crude extracts from *S. arvensis* L. leaf, as well as the in vitro toxicity, in vitro antioxidant activities, and whole blood analysis of mice infected with *Plasmodium berghei*. The study results provide useful information regarding the antiparasitocidal activity of a *S. arvensis* L. crude extract.

Materials and Methods

Plant collection and identification

S. arvensis L. was from Taman Husada Graha Famili (Medicinal Plant Garden of Graha Famili) Surabaya, East Java, Indonesia. The plant was cultivated in private field and harvested at 2–3 months before the generative stage. The leaves were green and healthy, with no indications of damage due to insects or microbes. The plant material used was confirmed by Mr. Dwi Narko, a botanist researcher

at Purwodadi Botanical Garden, Indonesian Institute of Sciences, Purwodadi, East Java, Indonesia (number of determination 1020/IPH.3.04/HM/X/2019). The voucher specimen was deposited in the Plant Systematics Laboratory, Department of Biology, Faculty of Science and Technology, Universitas Airlangga (No. SA.0110292021).

Plant extraction

The leaves of *S. arvensis* L. were air-dried and then ground into a powder (60-mesh size sieves). Each 1 kg of powder was separately macerated with different solvents including *n*-hexane, ethyl acetate, and ethanol for 24 h at room temperature (28 ± 2 °C) three times, filtered with filter paper (pore diameter 110 mm; Merck KGaA, Darmstadt, Germany), and then evaporated in a rotary evaporator at 60 °C to acquire crude extracts. The yields of the extracts (w/w) were measured prior to storage at 4 °C.

Phytochemical screening

The crude extracts of *S. arvensis* L. leaf was screened for phytochemical content by standard methods including the Wilstatter "cyanidin" test for flavonoids, Mayer's test for alkaloids, the ferric chloride test for tannins, the Liebermann–Burchard test for terpenoids, and the foam test for saponins [19].

Thin Layer Chromatography (TLC) Analysis

Five mg of each crude extract of *S. arvensis* L. leaf were dissolved in 100 μ L of *n*-hexane, ethyl acetate, and ethanol, respectively. Aliquots of samples (5 μ L; 250 μ g) were spotted and allowed to dry on a TLC plate (Silica gel GF254). The plate was developed with *n*-hexane: ethyl acetate (4:1v/v) as the mobile phase. Detection of compounds was achieved by spraying with ρ -anisaldehyde sulfuric acid reagent [18], then heating at 105 °C for 10 min or until the colored bands appeared.

Antioxidant assay

Antioxidant activity was evaluated by a method of 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) assay based on a stable and synthetic radical [20]. When DPPH reacts with an antioxidant compound, its free radical property is lost and its color changes from violet to yellow. In brief, 100 μ L of methanolic DPPH reagent (0.2 mM) was mixed with 100 μ L of each sample in methanol at different concentrations (1.75, 3.15, 6.25, 10, 12.5, 15, 25, 35, 50, 75, 100, 150, and 200 μ g/mL) and methanol as the control. The mixtures were incubated for 30 min in the dark at room temperature and the absorbance was measured at 517 nm. The assay was conducted in two independent wells for each sample and control for calculating the IC₅₀ value and replicated three times. The DPPH radical scavenging capacity was calculated using the following equation:

$$\text{DPPH radical scavenging capacity (\%)} = [(A_{\text{control}} - A_{\text{sample}}) / A_{\text{control}}] \times 100\% \tag{1}$$

where A_{sample} is the absorbance of the sample and A_{control} is the absorbance of the DPPH reagent at the wavelength of 517 nm. The results of DPPH radical scavenging capacity at different concentrations were then plotted and regressed linearly to obtain the IC_{50} values of samples. The IC_{50} value was calculated as the mean and standard deviation from triplicate samples.

In vitro antiplasmodial activity assay

In this study, the antiplasmodial activity of leaf extracts was investigated against the chloroquine-sensitive strain of *P. falciparum* (3D7). The parasite was cultured in human O^{Rh+} red blood cells according to the method of Trager and Jensen [21] using Roswell Park Memorial Institute 1640 (RPMI-1640) medium supplemented with 50 $\mu\text{g}/\text{mL}$ hypoxanthine, 2 mg/mL sodium bicarbonate (NaHCO_3), 5.94 g/L of N-2-hydroxyethyl piperazine-N-2-ethane sulfonic acid (HEPES) and 10% serum blood group O^{Rh+} . The parasitized culture suspension (1% parasitemia) was prepared in complete RPMI-1640 and 150- μL volume of this was dispensed in a 24-well microplate (5% hematocrit). The parasites were synchronized using 5% sorbitol to ring stage. The extracts and chloroquine diphosphate served as positive controls were dissolved in dimethyl sulfoxide (DMSO), diluted with medium to obtain the required concentrations (0.01, 0.1, 1, 10, and 100 $\mu\text{g}/\text{mL}$), and aliquoted [50 μL with final concentration at 0.5% (v/v) of DMSO] into each well of parasitized culture suspension. The parasitized cultures with 0.5% (v/v) of DMSO served as negative controls. The plates containing parasite cultures were incubated in an incubator (at 37 $^{\circ}\text{C}$, 5% CO_2 , 95% humidity) for 48 h. The antiplasmodial assay of each extract were carried out in three replicates (n=3). Afterward, the suspensions were collected, thinly smeared on glass slides, fixed with methanol, and stained with 10% Giemsa. The number of parasites was counted under a microscope and compared with the negative control to determine the extent of parasite growth inhibition in 5000 of total erythrocytes. The equation for calculating parasitemia, inhibition, and growth percentage used the equation method as described in a previous study [18].

The percentage of parasitemia was calculated using the formula:

$$\% \text{Parasitemia} = \frac{\sum \text{infected erythrocytes}}{5000 \text{ of total erythrocytes}} \times 100\% \tag{2}$$

The percentage of inhibition was counted using the equation:

$$\% \text{ Inhibition} = 100\% - \left[\frac{X_p}{X_k} \times 100\% \right] \tag{3}$$

The percentage of growth was calculated using the formula:

$$\% \text{ Growth} = \% \text{ parasitemia Un} - \% \text{ parasitemia Do} \tag{4}$$

Where:

X_p = Treatment parasitemia

X_k = Negative control parasitemia

U_n = % parasitemia in each concentration

D_o = % parasitemia at the start

\sum infected erythrocytes = the number of infected erythrocytes in 5000 of total erythrocytes

The probit analysis was conducted to calculate the IC_{50} values.

Cytotoxicity test

Cytotoxicity of extracts was assessed by the method of 3- [4, 5-dimethylthiazol-2-yl] 2, 5-diphenyl tetrazolium bromide (MTT) assay as described by Fosenca et al. [22]. MTT assay detect the mammalian cells survival based on the tetrazolium salt signal when the tetrazolium ring is cleaved in active mitochondria [23]. Dimethyl sulfoxide (DMSO) was used to dissolve the extracts, then they were diluted with medium to obtain the required concentrations (6.25, 12.5, 25, 50, 100, 200, 400, 600, 800, and 1000 $\mu\text{g}/\text{mL}$). Human hepatic cell lines (Huh7it-1 cells) from Institute Tropical Diseases, Universitas Airlangga, Surabaya, Indonesia, were cultured in complete Dulbecco's modified Eagle's medium (DMEM) supplemented with 1% (v/v) glutamine (200 mM) at 37 $^{\circ}\text{C}$ under an atmosphere of 5% of carbon dioxide atmosphere and 95% humidity. The culture was conducted three times. The cell numbers were determined by measuring the absorbance at 560 nm and 750 nm using multiplate reader and the viability were assessed. The viability of cells was calculated using the equation:

$$\% \text{ of viability} = (A_{\text{sample}} / A_{\text{control}}) \times 100\% \tag{5}$$

where A_{sample} was the absorbance sample at 560 nm-Absorbance sample at 750 nm and A_{control} was the absorbance DMEM medium. The percentage of cell viability was then plotted and regressed linearly to obtain the CC_{50} values. The selectivity index (SI) values were calculated based on the ratio between the CC_{50} value of

cytotoxicity and antiplasmodial activity *P. falciparum* 3D7 from each extract (IC₅₀).

In vivo antiplasmodial activity assay

The extract with the highest antiplasmodial activity against *P. falciparum* 3D7 was selected to subsequently analyze the antiplasmodial activity against *P. berghei* (the mice-infected Plasmodium) with Peter’s method [24]. The strain of *P. berghei* ANKA was obtained from the Eijkman Institute of Molecular Biology (Jakarta, Indonesia). Blood infected with *P. berghei* ANKA was taken from mice with 20% parasitemia and diluted with phosphate-buffered saline. Swiss mice *Mus musculus* of BALB/c strain (male; body weight 25 ± 3 g; 6–8 weeks old) were intraperitoneally injected with 0.2 mL blood (1 × 10⁶ ANKA parasitized erythrocytes) and randomly divided (n = 7 per group) into four experimental groups and three control groups (normal, negative, and positive control). The experimental groups were orally treated with 0.25 mL single dose of 1, 10, 100, or 200 mg/kg BW of leaf extract (in 0.5% sodium carboxymethyl cellulose (Na-CMC)) two times per day for four days for antiplasmodial assay and continued seven days for biochemical analysis. The negative and positive control groups were treated with 0.5% Na-CMC suspension and 10 mg/kg BW of chloroquine diphosphate, respectively. The normal control group was the uninfected and untreated mice group (Table 1). On each day, blood was collected from the tail vein of each mouse, thinly smeared on a glass slide, fixed with methanol, and then stained with Giemsa. The slides were then observed under a microscope to calculate the percentage of parasitemia, inhibition, and growth. The formula of them used as described in in vitro antiplasmodial activity against *P. falciparum* 3D7. The median effective dose or effective dose for 50% of the population (ED₅₀) was calculated with Probit analysis. The ED₅₀ was calculated from each

replication, and then averaged getting the mean and deviation standard.

Biochemical analysis

After seven-day treatments, blood samples (0.5–0.75 mL) were collected from the left ventricle of each mouse into 1.5-mL microtubes and left standing at room temperature for 2 h. Then, serum was isolated by centrifugation at 3000 rpm for 20 min. The levels of serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) in obtained serum were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (DiaSys Diagnostic System, Holzheim, Germany) to assess the hepatoprotective effects of the selected extract on infected mice. For analyzing nephroprotective effects, blood urea nitrogen (BUN) and creatinine levels were measured using commercial ELISA kits (DiaSys Diagnostic System, Holzheim, Germany). The level of tumor necrosis factor-alpha (TNF-α) and interleukin 10 (IL-10) in serum was also analyzed to investigate the immune response of treated/control mice using commercial ELISA kits (BioLegend, San Diego, CA, USA). The replication of samples was four to seven times (Table 1).

Data analysis

Data are expressed as the mean ± standard deviation (SD). The IC₅₀ of antioxidant and CC₅₀ of cytotoxicity were counted using regression linearly (Microsoft Excel). The Probit analysis was conducted to calculate the IC₅₀ and ED₅₀ values. Statistical significance was determined with the one-way analysis of variance (ANOVA) continued with Duncan Multiple Range Test (DMRT) for IL10 and TNFα, with a nonparametric independent t-test for SGOT and SGPT, and Kruskal–Wallis continued with Mann Whitney test for BUN and creatinine data. The level of significance was set at 0.05. All statistical analyses

Table 1 Experimental design of in vivo study for antiplasmodial activity and biochemical analysis

Experiment Group	<i>Plasmodium berghei</i> -infected mice	Treatment	Days	Replication
Normal Control (healthy/untreated)	-	Na-CMC	7	7
Positive Control	+	Chloroquine-phosphate	7	7
Negative Control	+	Na-CMC	7	7
T1	+	1 mg/kg BW	7	7
T2	+	10 mg/kg BW	7	7
T3	+	100 mg/kg BW	7	7
T4	+	200 mg/kg BW	7	7

Mice blood sample was analyzed for the percentage of parasitemia for 4 days except for the normal control and biochemical analysis on the seventh day for all treatment and control

Table 2 Extraction yield of *Sonchus arvensis* L. leaf

No	Extract	Yield (g/kg)
1	<i>n</i> -Hexane	25.90 ± 5.50
2	Ethyl acetate	10.00 ± 1.10
3	Ethanol	59.26 ± 2.04

The data were represented as mean ± standard deviation (SD), *n* = 3

Table 3 Phytochemical screening of *Sonchus arvensis* L. leaf extract

No	Phytochemical agent	<i>n</i> -Hexane	Ethyl acetate	Ethanol
1	Terpenoids	++	+++	+
2	Flavonoids	+	++	++
3	Alkaloids	+	+	+
4	Saponin	-	-	++
5	Polyphenol	-	+	++

++ , Strongly positive; + , Weakly positive; - , Not detected

were conducted using IBM SPSS Statistics for Windows, version 20.0. (IBM Corporation, Armonk, NY, USA).

Results

The extract yields and phytochemical screening

The dried leaf was successively macerated and each kilogram of dried leaf yielded 59.26 ± 2.04 g of ethanol extract, 10 ± 1.1 g of ethyl acetate extract, and 25.9 ± 5.5 g of *n*-hexane extract (Table 2).

Secondary metabolites including terpenoids, flavonoids, and alkaloids were present in all extracts. However, saponins and polyphenols were present only in the ethanol and ethyl acetate extracts respectively (Table 3).

Terpenoid screening of the extracts of *Sonchus arvensis* L. by thin-layer chromatography (TLC)

The *n*-hexane, ethyl acetate, and ethanol extracts of *Sonchus arvensis* L. were observed by TLC and there were two visible spots in daylight and under 254-nm UV light (*R_f* value = 0.12 and 0.18). Under 366-nm UV light, there were five separate spots with *R_f* values of 0.14, 0.19, 0.24, 0.35, and 0.53. After staining using *p*-anisaldehyde sulfuric acid, three separate purple stains were seen, with *R_f* values of 0.31, 0.59, and 0.71 (Fig. 1).

Antioxidant activities

The DPPH assay was conducted to assess antioxidant activities. The IC₅₀ values of all extracts are shown in Table 4. All extracts possessed antioxidant activities. From lowest to highest, the IC₅₀ values were 8.27 ± 4.93, 12.36 ± 10.40, 31.35 ± 3.27, and 108.59 ± 11.24 µg/mL for the ethyl acetate, ethanol, methanol, and *n*-hexane extracts, respectively. Furthermore, the IC₅₀ of ascorbic acid as standard was 22.63 ± 1.40 µg/mL.

In vitro antiplasmodial activity

The IC₅₀ values of all extracts (Table 5) of *Sonchus arvensis* L. leaf at various doses indicated that the ethyl acetate extract (IC₅₀ 2.92 ± 3.27 µg/mL) had the highest in vitro

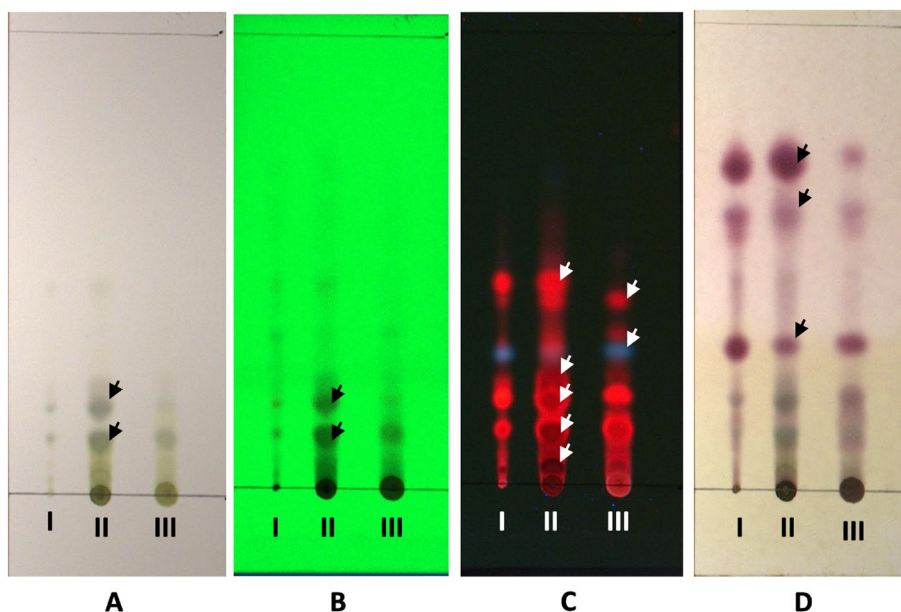


Fig. 1 Chromatogram of *Sonchus arvensis* L. extracts TLC. **A.** Day light, **B.** UV 254 nm, **C.** UV 366 nm, **D.** After spray with *p*-anisaldehyde sulfuric acid (the purple spot is terpenoid), I. *n*-Hexane extract, II. Ethyl acetate extract, III. Ethanol extract

Table 4 In vitro antioxidant activity of *Sonchus arvensis* L. leaf extract

No	Extract	Antioxidant activity (IC ₅₀ , µg/mL)
1	<i>n</i> -Hexane	108.59 ± 11.24
2	Ethyl acetate	8.27 ± 4.93
3	Ethanol	12.36 ± 10.40
4	Methanol	31.35 ± 3.27
5	Ascorbic acid	22.63 ± 1.40

The data were represented as mean ± standard deviation (SD), *n* = 3

antimalarial activity, followed by the *n*-hexane and ethanol extracts.

Toxicity and selectivity index (SI)

The toxicity of all *Sonchus arvensis* L. extracts to hepatocytes was determined. From highest to lowest, the CC₅₀ values of the extracts were 1420.88 ± 20.88, 437.39 ± 7.46, and 778.77 ± 10.53 µg/mL for *n*-hexane, ethanol, and ethyl acetate extract, respectively (Table 6). Then, the SI was calculated by comparing the toxicity and in vitro antimalarial activity. From highest to lowest, the SI values were 277.57 ± 5.77, 150.00 ± 3.62, and 97.03 ± 13.13 for *n*-hexane, ethanol, and ethyl acetate extract, respectively (Table 6).

In vivo antiplasmodial activity

The in vivo antimalarial activity of the ethyl acetate extract was also determined. As shown in Table 7, the parasitemia rates decreased with increasing doses. The inhibition of % parasitemia at doses at 1, 10, 100, and 200 mg/kg BW were 0%, 32.86 ± 7.50%, 56.32 ± 2.64% and 77.48 ± 2.93%, respectively. Probit analysis determined that the ED₅₀ value of the ethyl acetate extract was 46.31 ± 9.36 mg/kg BW. This result was significant as compared to the negative control.

Whole blood analysis of *P. berghei* infected mice

Mice infected with *P. berghei* were orally administered ethyl acetate extract of *S. arvensis* L. leaves two times per

day for 7 days. Afterward, blood samples were collected to determine the hepatoprotective (SGOT and SGPT), nephroprotective (BUN and creatinine), and immunomodulatory (IL-10 and TNFα) effects (Fig. 2).

SGOT and SGPT levels

The liver cells will spill the enzymes including aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) into the blood to respond with liver injury. Therefore, raising the enzyme levels in the blood is the signaling to indicate the damage of liver. As compared to the negative control (201.87 ± 91.73 U/g/mL), serum SGOT levels of mice infected with *P. berghei* were significantly decreased by treatment with ethyl acetate extract at 1, 10, 100, and 200 mg/kg BW (100.68 ± 2.98, 73.85 ± 10.41, 69.82 ± 7.10, and 33.11 ± 13.16 U/g/mL, respectively, *p* < 0.05). However, there was no different significant between normal control (40.76 ± 9.59 U/mL), positive control (32.92 ± 6.07 U/mL), and treatment groups (31.11 ± 13.16 U/mL at a concentration of 200 mg/kg BW) (Fig. 2.A.1).

Furthermore, as compared to negative control (24.13 ± 2.45 U/mL) and treatment with ethyl acetate extract at 1 mg/kg BW (32.37 ± 13.6 U/mL) and 10 mg/kg BW (22.74 ± 2.08 U/mL), serum SGPT levels were significantly decreased in the groups treated with 100 and 200 mg/kg BW (13.45 ± 3.4 and 2.75 ± 0.59 U/mL, respectively) as well as the positive and normal control groups (5.4 ± 2.73 and 12.4 ± 0.84 U/mL, respectively). Overall, the SGOT and SGPT levels significantly decreased in the treatment groups compared with the negative control group (*p* < 0.05) (Fig. 2.A.2).

BUN and creatinine levels

Relatively higher serum levels of BUN and creatinine are indicative of severe renal injury. As compared to the negative control (*Plasmodium berghei* infected mice that was given Na-CMC) group (7.00 ± 0.26 mg/mL), the serum BUN levels of the infected mice were significantly decreased by treatment with the ethyl acetate extract at 1, 10, 100, and 200 mg/kg BW (2.61 ± 1.62,

Table 5 In vitro antiplasmodial activity of *Sonchus arvensis* L. leaf extracts against *P. falciparum* strain 3D7

No	Extract	% Inhibition at each concentration (µg/mL)						IC ₅₀ (µg/mL)
		100	10	1	0.1	0.01	0.001	
1	<i>n</i> -Hexane	100.00 ± 0.00	53.81 ± 0.65	45.21 ± 1.94	35.79 ± 3.90	31.73 ± 3.73	-	5.12 ± 2.34
2	Ethyl acetate	100.00 ± 0.00	75.82 ± 1.93	65.68 ± 3.09	44.89 ± 9.73	34.84 ± 1.49	-	2.92 ± 3.27
3	Ethanol	93.60 ± 0.53	27.54 ± 2.51	23.50 ± 1.11	13.09 ± 1.49	6.94 ± 0.36	-	8.03 ± 1.23
4	Chloroquine diphosphate	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	79.76 ± 4.51	40.49 ± 5.29	17.17 ± 2.31	0.01 ± 0.00

Note: The data were represented as mean ± standard deviation (SD), *n* = 3

Table 6 In vitro toxicity and selectivity index (SI) of *Sonchus arvensis* L. leaf extract

No	Extract	In Vitro Toxicity, CC ₅₀ (µg/mL)	Selectivity Index (SI)
1	<i>n</i> -Hexane	1420.88 ± 20.88	277.57 ± 5.77
2	Ethyl Acetate	437.39 ± 7.46	150.00 ± 3.62
3	Ethanol	778.77 ± 10.53	97.03 ± 13.13

Note: The data were represented as mean ± standard deviation (SD), *n* = 3

2.95 ± 1.19, 4.75 ± 0.97, and 2.01 ± 1.33 mg/mL, respectively), *p* < 0.05 (Fig. 2.B.1). In addition, as compared to the negative control group (1.99 ± 0.29 mg/mL), serum creatinine levels were significantly decreased by treatment with the ethyl acetate extract at 1, 10, 100, and 200 mg/kg BW (0.14 ± 0.02, 0.37 ± 0.04, 0.27 ± 0.04, and 0.23 ± 0.06 mg/mL, respectively), *p* < 0.05 (Fig. 2 .B.2).

Cytokine production

Serum IL-10 and TNFα levels were significantly increased in the treatment groups as compared to the normal and negative control groups. As compared to the negative control group (88.00 ± 22.96 pg/mL), serum IL-10 levels were significantly increased in the positive control group (131.09 ± 8.13 pg/mL) and slightly increased in the groups treated with the ethyl acetate extract at 1, 10, 100, and 200 mg/kg BW (113.27 ± 13.21, 106.36 ± 11.32, 116.55 ± 6.95, and 119.64 ± 2.84 pg/mL, respectively, *p* < 0.05), while there was no significant difference as compared to the normal control group (Fig. 2 .C.1).

Moreover, as compared to treatment with the ethyl acetate extract at 1 mg/kg BW (387.93 ± 123.59 ng/mL), serum levels of TNFα were significantly increased by treatment with 10, 100, and 200 mg/kg BW (794.93 ± 427.89, 848.07 ± 216.86, and 729.64 ± 126.89 ng/mL, respectively, *p* < 0.05). There were also significant differences among the negative, normal control, and positive control groups (237.64 ± 113.123, 249.64 ± 99.97, and 257.93 ± 160.33 ng/

mL, respectively, *p* < 0.05). Collectively, these results suggest that ethyl acetate extract of *S. arvensis* L. enhances the immune response of mice against *P. berghei* infection (Fig. 2 .C.2).

Discussion

Management and accessibility of healthcare are important problems in Eastern Indonesia. Hence, home remedies with traditional medicines is the most common method for the treatment of malaria. The use of traditional medicine is safe, cost-effective, and efficient. According to the World Health Organization (WHO), the use of traditional medicines continues to increase worldwide. Traditional medicines are rooted in Indonesian culture and history, although many traditional treatments have not been scientifically validated. Among the strategic objectives proposed by the WHO, the safety and efficacy of traditional medicines are primary goals before integrating traditional drugs in modern healthcare [2].

S. arvensis L. is the seventh most popular medicinal plant for treating various diseases in Indonesia, especially in Java and Bali [12]. Although the extract of *S. arvensis* L. callus is reported to possess antiplasmodial activities [17, 18], the efficiency and safety for malaria treatment have not been registered. Hence, the aim of this study was to evaluate the antiplasmodial activity, toxicity, and antioxidant activity of crude extracts of *S. arvensis* L. leaf.

One kilogram of dried *S. arvensis* L. leaf was extracted by successive maceration with *n*-hexane, ethyl acetate, and ethanol. From each solvent, different extract weights were obtained. Each of the *S. arvensis* L. extracts was screened for the presence of phytochemicals. The ethanol extract contained flavonoids, alkaloids, terpenoids, saponins, and polyphenols, while the ethyl acetate extract included flavonoids, alkaloids, terpenoids, and polyphenols, and the *n*-hexane extract contained flavonoids, alkaloids, and terpenoids.

The Wilstatter "cyanidin" test confirmed the presence of flavonoids, while testing of the extract showed the

Table 7 Parasitemia, growth, and inhibition percentage of *Sonchus arvensis* L. leaves ethyl acetate extract against *Plasmodium berghei*

Sample	Dose (mg/kg)	Mean % Parasitemia		Mean % growth	Mean % inhibition	ED ₅₀ (mg/kg)
		Day 0	Day 4			
Ethyl acetate extract of <i>S. arvensis</i> L. leaves	1	1.51 ± 0.07	7.44 ± 0.21	5.93 ± 0.17	ND	46.31 ± 9.36
	10	1.42 ± 0.07	5.39 ± 0.43	3.97 ± 0.44	32.86 ± 7.50	
	100	1.51 ± 0.07	5.09 ± 0.56	2.57 ± 0.12	56.32 ± 2.64	
	200	1.46 ± 0.09	3.96 ± 0.68	1.36 ± 0.12	77.48 ± 2.93	
Na-CMC	-	1.44 ± 0.12	7.36 ± 0.24	5.91 ± 0.31	ND	
Chloroquine diphosphate	10	1.48 ± 0.09	0.02 ± 0.01	ND	ND	

Noted: The data have been represented as mean ± standard deviation (SD), *n* = 7. The Na-CMC: sodium carboxymethyl cellulose. ND = not detected

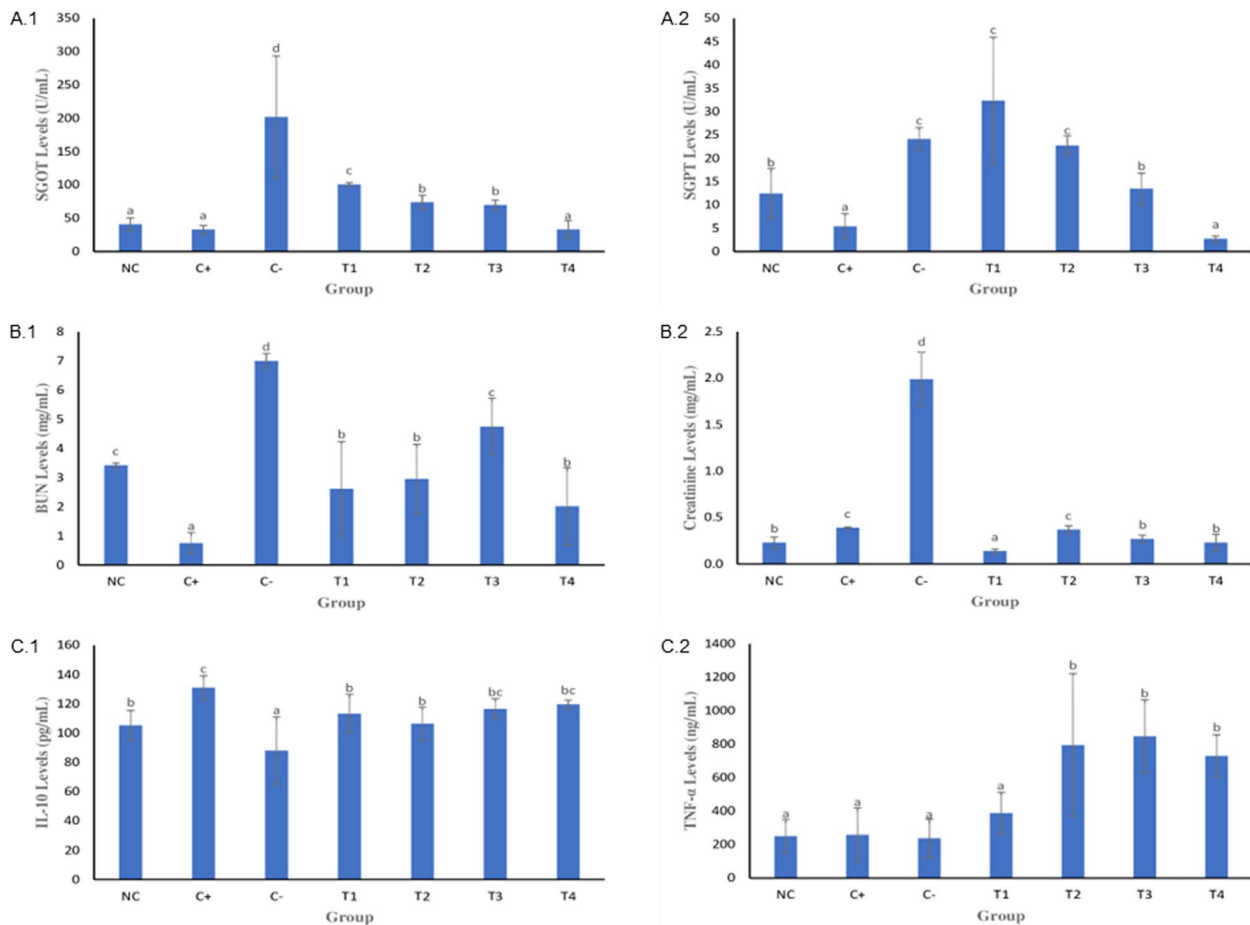


Fig. 2 Serum SGOT, SGPT, BUN, creatinine, IL-10, and TNF α levels of mice infected with *P. berghei* strain ANKA after treatment with *S. arvensis* L. leaf ethyl acetate extract. SGOT (A.1); SGPT (A.2); BUN (B.1); creatinine (B.2); TNF α (C.1); TNF α IL-10 (C.2); CN: normal control (healthy/untreated) group; C + : positive control; C-: negative control; T1: 1 mg/kg; T2: 10 mg/kg; T3: 100 mg/kg; T4: 200 mg/kg. The values followed by the same letter (superscripts) show no significant difference in the one-way analysis of variance (ANOVA) continued with Duncan Multiple Range Test (DMRT) for IL10 and TNF α , with a nonparametric independent *t*-test for SGOT and SGPT, and Kruskal–Wallis continued with Mann Whitney test for BUN and creatinine data. The significance level was set at 0.05

presence of alkaloids, as indicated by the formation of a white precipitate after the addition of Mayer reagent. The Liebermann–Burchard test results confirmed the presence of terpenoids, as indicated by the yellow color of the solution. After adding a few drops of 10% FeCl₃, the color of the solution changed to dark green, indicating the presence of tannins. Meanwhile, the presence of saponins was confirmed if the foam extract did not disappear after the addition of distilled water and shaking [11].

Polyphenols were present in the ethanol extract, whereas relatively large amounts of terpenoids were confirmed in the ethyl acetate and *n*-hexane extracts. These findings are consistent with similar studies conducted by Khan [25] and Seal [26]. Many triterpenoids have been isolated from the *n*-hexane extract of *S. arvensis* L. [16]. Additionally, some phytochemicals may be responsible for the various activities of *S. arvensis* L. For example,

flavonoid and phenolic compounds possess antioxidant activities [25], saponins have anti-inflammatory activities [27], and terpenoids exhibit antimicrobial activities [16].

Furthermore, *S. arvensis* L extract showed antioxidant activities. The ethyl acetate and ethanol extracts exhibited potent antioxidant activities (IC₅₀ < 50 μ g/mL) [28], with IC₅₀ value 8.27 \pm 4.93 μ g/mL and 12.36 \pm 10.40 μ g/mL respectively. While *n*-hexane extract had moderate antioxidant activity (101 > IC₅₀ < 250 μ g/mL) [28]. The IC₅₀ value (the antioxidant activity) of ethyl acetate extract was lower than ascorbic acid as standard (22.63 \pm 1.40 μ g/mL) (Table 3). Moreover, compared to the other studies, the leaf extract from *S. arvensis* L was lower than those of plants and callus *Trifolium pratense* L. [29], *Callisia fragrance* leaf juice [30], and *Centella asiatica* L. leaf [31] that reported has antioxidant activity. The potent antioxidant activity of the *S. arvensis* L.

extract was probably due to the presence of active ingredients with antioxidant activities, such as polyphenols and flavonoids. These findings are similar to those of previous studies of different plant sources [15, 25, 26, 32].

The antioxidant activity of the ethyl acetate extract was as good as the in vitro antimalarial effect. In general, an IC_{50} value less than 10 $\mu\text{g/mL}$ is considered to indicate the high activity, while $10 < IC_{50} \leq 25$ $\mu\text{g/mL}$ can be regarded as moderately active and values > 25 $\mu\text{g/mL}$ are deemed inactive [33, 34]. All plant extracts in this study presented the IC_{50} values < 10 $\mu\text{g/mL}$; therefore, they were primarily considered as the new candidates for antimalarial-drug development. The IC_{50} values of the ethyl acetate extract, *n*-hexane, and ethanol extracts were 2.916, 5.119, and 8.026 $\mu\text{g/mL}$, respectively. The industry standardizes the IC_{50} value of in vitro antiplasmodial activity, a pure compound is said to be active as antiplasmodial activity if the IC_{50} value is below 10 $\mu\text{g/mL}$ [6].

The toxicity of *S. arvensis* L. extracts were evaluated by calculating the ratio of cytotoxicity with human hepatic cell lines (CC_{50}) to in vitro antiplasmodial activity expressed as IC_{50} (selectivity index $SI = CC_{50}/IC_{50}$). A higher SI, theoretically, indicates greater drug effectiveness and safety for the treatment of plasmodial infections. An ideal drug would be cytotoxic only at very high concentrations and have antiplasmodial activities at low concentrations, thus yielding a high SI value and eliminating the plasmodial target at concentrations well below the cytotoxic concentration [35]. The IC_{50} values of extracts toxicity were 1420.88 ± 20.88 , 778.77 ± 10.53 , and 437.39 ± 7.46 , $\mu\text{g/mL}$, and then the SI value were 277.57 ± 5.77 , 97.03 ± 13.13 , and 150 ± 3.62 for *n*-hexane, ethanol, and ethyl acetate extract respectively. de Souza et al. [36] mentioned that “the natural product has been suggested that the $SI > 10$ indicate a favorable safety window between the effective concentration against the parasite and the toxic concentration to human cell”. So, all *S. arvensis* L. leaf extracts exhibited low toxicity. Nurianti et al. [37] found that an ethyl acetate extract of *S. arvensis* L had no toxic effects, and Harun et al. [38] revealed that an ethanol extract of *S. arvensis* L. was not toxic to healthy male albino rats. The antioxidant activities suggest that these extracts are relatively non-toxic because oxidative stress represents an imbalance between the production of free radicals and the ability of a biological system to readily detoxify reactive intermediates or repair the resulting damage [39].

Moreover, the ethyl acetate extract of *S. arvensis* L. was chosen for the assessment of in vivo antiplasmodial activity because it exhibited the highest antioxidant and in vitro antiplasmodial activities, with $IC_{50} = 8.27$ and 2.92 $\mu\text{g/mL}$ respectively. In vivo antiplasmodial activity can normally be classified as moderate, good, and very

good if an extract displayed percentage inhibition equal to or greater than 50% at a dose of 500, 250, and 100 mg/kg BW per day, respectively [40]. *P. berghei*-infected mice given orally 50–250 mg/kg/day of extract exhibiting inhibition percentage $> 60\%$ are considered to be active or very active, and those exhibiting inhibition percentage $> 30\%$ are considered to be moderately active [33, 34]. Based on this classification, the ethyl acetate extract of *S. arvensis* L. showed excellent in vivo antiplasmodial activity below 100 mg/kg/day with an ED_{50} of 46.31 ± 9.36 mg/kg. The ED_{50} of ethyl acetate extract of *S. arvensis* L. was higher than the ethanolic extract of *H. annuus* root has an ED_{50} value of 10.6 ± 0.2 mg/kg [41] but lower than the *Tagetes erecta* L. and *Synedrella nodiflora* (L.) Gaertn. extract can significantly suppress parasitemia in malaria-infected mice by 50.82% and 57.67% respectively at 400 mg/kg BW dose [40]. Compared to another Asteraceae member, the ethyl acetate extract of *S. arvensis* L. could be developed as an antiplasmodial agent.

Furthermore, blood was collected from the experimental mice to determine the nephroprotective, hepatoprotective, and immunomodulatory activities after 7 days of treatment with ethyl acetate extract of *S. arvensis* L. Many studies have reported that *S. arvensis* L. extracts exhibited antioxidant [25], hepatoprotective [13], nephroprotective [42], and immunomodulatory [43] activities. The present study was conducted to assess the effect of an ethyl acetate extract of *S. arvensis* L. against *P. berghei* infection in mice.

An increase in SGPT and SGOT serum levels indicates liver damage [15], and a rise in BUN and creatinine levels suggests a failure of the kidneys or their possible malfunction [39]. The results showed that the ethyl acetate extract protected the liver and kidneys by reducing SGOT, SGPT, creatinine, and BUN levels.

Overall, the serum levels suggested that the ethyl acetate extract of *S. arvensis* L. showed nephroprotective, hepatoprotective, and immunomodulatory activities in mice infected with *P. berghei*. The result is very interesting because the pathogenesis caused by *P. berghei* is multifactorial and has not been well characterized. There were several hypotheses suggesting that erythrocyte cytoadherence, proinflammatory response, nephrotoxicity, and oxidative stress are involved in the pathogenesis of *P. berghei* [44, 45]. Free heme-mediated oxidative stress, in which free heme is produced by parasites that consume hemoglobin during the intra-erythrocytic phase, has been implicated in lipoprotein oxidation and serious kidney damage [46]. In addition, malaria infection is caused by parasites and host factors, where there will be microvascular disturbances in the host's body. *P. berghei* parasites will infect erythrocytes and activate cytokines of phagocytic cells and endothelial cells to produce TNF- α , IL-10, IFN- γ , and free radicals (ROI, ROS, and NO). Free

radicals are molecules with one unpaired electron in their outer orbit which makes the molecule unstable [42]. Free radicals can cause oxidative stress. It has implications for various pathological conditions [48]. The involvement of oxidative stress can cause the amount of antioxidant status to decrease [42]. Oxidative stress condition is defined as imbalance condition between antioxidants and free radicals, where the state of free radicals is higher than antioxidants [14]. The number of antioxidants decreases because the body used to balance the high free radicals due to the presence of parasites. The more severe the infection from *P. berghei*, the use of antioxidants in the body will increase, causing the number of antioxidants in the body to decrease [42]. The biochemical data of serum of mice infected *P. berghei* supported that the *S. arvensis* L. ethyl acetate extract is active as antiplasmodial. Particularly, the *S. arvensis* L. leaf ethyl acetate extract increases the mice immune response to *P. berghei* infections. It is very valuable for the further investigation of the in vivo antioxidant activity and cytotoxicity of the *S. arvensis* L. leaf as antiplasmodial drug candidate.

The comprehensive tests and discussions in this study confirmed that ethyl acetate extract possessed antiplasmodial both in vitro and in vivo with nephroprotective, hepatoprotective, and immunomodulatory activities in mice infected with *P. berghei*. This study highlighted that *S. arvensis* L. crude extract had antimalarial activity. In summary, the results suggest that ethyl acetate extract of *S. arvensis* L. could be used to develop new antimalarial drugs in the future from a natural resource.

Conclusion

The results of this study confirmed the antiplasmodial activity of ethyl acetate extract of *S. arvensis* L. both in vitro and in vivo as well as the antioxidant, nephroprotective, hepatoprotective, and immunomodulatory activities with low toxicity. It was strongly suggesting the potential as an antimalarial drug. These findings lay a foundation for further investigations of new antimalarial compounds for future pharmaceutical applications. Further research, including bioassay-guided fractionation, was also recommended to identify new antimalarial drug candidates.

Abbreviations

BUN	Blood urea nitrogen
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TNF α	Tumor necrosis factor alpha
IL-10	Interleukin 10
IC ₅₀	Half maximal inhibitory concentration
ED ₅₀	Median effective dose
DPPH	2,2-Diphenyl-1-picryl-hydrazyl-hydrate
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide

Acknowledgements

The authors would like to acknowledge Universitas Airlangga Rector Scholarship. The authors also would like to thank Nindy Tresiana Putri, Rizal Adistya Putra Pradana, and Manikya Pramudya for their support in the in vivo antimalarial assays, Shilfiana Rahayu, Hikma, and Talita for coordinating the preparation of the raw plant extracts studied and whole blood analysis of mice. Then, we also would like to thank to Prof. Dr. Aty Widayawaruyanti, M.Si., Apt., Head of Center for Natural Product Medicine Research and Development, Institute of Tropical Diseases, Universitas Airlangan, Surabaya, Indonesia, for providing the human hepatic cell lines (Huh7it-1 cells line) for cytotoxicity assay.

Authors' contributions

DKW: conceived and conducted the experiments, analysed the data, and wrote the manuscript, SW: assisted the plant extractions and screened the phytochemicals, WB: assisted the experiments and interpreted the results, SPAW: analysed the results of biochemistry of blood and interpreted the results. WE: helped with in vitro and in vivo antimalarial assay design. HP: assisted the collection, identification, and classification of plant material, HP: assisted with conception and material preparation, and SP was the primary author of the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Universitas Airlangga, Contract No. 405/UN3.14/PT/2020.

Availability of data and materials

The datasets generated and analyzed during the current study are not available online due to funding policy however they are available from the corresponding authors or first author on reasonable request.

Declarations

Ethics approval and consent to participate

Applicable. Experimental research and field studies on plants were in compliance with relevant national, and international guidelines and legislation. The permission was obtained from Taman Husada Graha Famili (Medicinal Plant Garden of Graha Famili) Surabaya, East Java, Indonesia, managed by Universitas Airlangga and PT. Intiland Development Tbk., Surabaya, East Java, Indonesia, with the Memorandum of Understanding number 3001/UN3.1.8/2014 and the Memorandum of Activity number 142/GFV-PM HSG/SRT/HH/VIII/2021. The study was reported in accordance with ARRIVE guidelines (<https://arriveguidelines.org>). This study was also carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The study protocol was approved by the Institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine of Universitas Airlangga (Surabaya, East Java, Indonesia) (approval no. 499/HRECC.FODM/XI/2020). All surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 28 April 2022 Accepted: 2 February 2023

Published online: 14 February 2023

References

1. World Health Organization. Guidelines for the Treatment of Malaria. 3rd ed. Italy: WHO Press, World Health Organization; 2015.
2. World Health Organization. World Malaria Report 2021. Geneva, Switzerland: WHO Press, World Health Organization; 2021.
3. APMEN. The Asia pacific malaria elimination network (APMEN). 2020. <https://www.apmen.org/>. Accessed 25 Jan 2021.
4. Aguiar AC, Santos RD, Figueiredo FJ, Cortopassi WA, Pimentel AS, Franca TC. Antimalarial activity and mechanisms of action of two novel

- 4-aminoquinolines against chloroquine-resistant parasites. *PLoS One*. 2012;7(5):e37259. [10.1371/journal.pone.0037259](https://doi.org/10.1371/journal.pone.0037259).
5. Davanco MG, Aguiar ACC, Dos Santos LA, Padilha EC, Campos ML. Evaluation of antimalarial activity and toxicity of a new primaquine prodrug. *PLoS ONE*. 2014; 9(8): e105217. doi: <https://doi.org/10.1371/journal.pone.0105217>
 6. Tajuddeen N, Van Heerden FR. Antiplasmodial natural products: an update. *Malar J*. 2019;18(404):1–62. <https://doi.org/10.1186/s12936-019-3026-1>.
 7. Katiyar D, Singh K, Ali M. Phytochemical and pharmacological profile of *Pterocarpus marsupium*: a review. *J Pharm Innov*. 2016;5:31–9.
 8. Waiganjo B, Moriasi G, Onyancha J, Elias N, Muregi F. Antiplasmodial and cytotoxic activities of extract of selected medicinal plants used to treat malaria in Embu County, Kenya. *J Parasitol Res*. 2020;2020:1–12.
 9. Haidara M, Haddad M, Denou A, Marti G, Bourgeade-Delmas S, Sanogo R. *In vivo* validation of antimalarial activity of crude extracts of *Terminalia macroptera*, a Malian medicinal plant. *Malar J*. 2018;17:68. <https://doi.org/10.1186/s12936-018-2223-7>.
 10. Wahyuni DK, Shilfiana Rahayu, Putut Rakhmad Purnama, Triono Bagus Saputro, Suharyanto, Nastiti Wijayanti et al. Morpho-anatomical structure and DNA barcode of *Sonchus arvensis* L. *Biodiversitas*. 2019; 20:2417–26. doi: <https://doi.org/10.13057/biodiv/d200841>.
 11. Delyan E. Analysis of composition of volatile compounds of field sow thistle (*Sonchus arvensis* L.) leaf using the method of gas chromatography with mass-detection. *J Pharm Innov*. 2016; 5:118–21.
 12. Yuliarti W, Kusriani D, Isolasi FE. Identification and antioxidant activity of phenolic acid from tempuyung (*Sonchus arvensis* L.) leaf with 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) method. *Chem Inform*. 2013; 1:294–304.
 13. Hendriani R, Sukandara EY, Anggadiredja K. Sukrasno. *In vitro* evaluation of xanthine oxidase inhibitory activity of *Sonchus arvensis* leaf. *Int J Pharm Pharm*. 2014; 6:501–3.
 14. Imelda I, Azaria C, Lucretia T. Protective effect of ethanol extract of tempuyung leaf (*Sonchus arvensis* L.) against gentamicin induced renal injury viewed from blood ureum level. *Med Health*. 2017; 1:575–82. doi: <https://doi.org/10.28932/jmh.v1i6.555>.
 15. Hendriani R, Sukandara EY, Anggadiredja K. Sukrasno. *In vitro* evaluation of xanthine oxidase inhibitory activity of selected medicinal plants. *Int J Pharm Clin*. 2015; 8:235–8.
 16. Rumondang M, Kusriani D, Fachriyah E. Isolation, identification and antibacterial test of triterpenoid compounds from n-hexane extract of tempuyung leaf (*Sonchus arvensis* L.). *Pharm Sci*. 2013; 05:506–7.
 17. Wahyuni DK, Purnobasuki H, Kuncoro EP, Ekasari W. Callus induction of *Sonchus arvensis* L. and its antiplasmodial activity. *Afr J Infect Dis*. 2020; 14:1–7. doi: <https://doi.org/10.21010/ajid.v14i1.1>.
 18. Wahyuni DK, Rahayu S, Zaidan AH, Ekasari W, Prasongsuk S, Purnobasuki H. Growth, secondary metabolite production, and *in vitro* antiplasmodial activity of *Sonchus arvensis* L. callus under dolomite [CaMg(CO₃)₂] treatment. *PLoS ONE*. 2021; 16(8): e0254804. doi: <https://doi.org/10.1371/journal.pone.0254804>.
 19. Hanoon LK, Joshi SDS, Yasir AK, Prasad AM, Alapati KS. Phytochemical screening and antioxidant activity of *Pseuderanthemum malabaricum*. *J Pharmacogn Phytochem*. 2019;8:972–7.
 20. Lin J, Li X, Chen L, Lu W, Chen X, Han L, et al. Protective effect against hydroxyl radical-induced DNA damage and antioxidant mechanism of [6]-gingerol: A Chemical Study. *Bull Korean Chem Soc*. 2014;35:1633–8. <https://doi.org/10.5012/bkcs.2014.35.6.1633>.
 21. Trager W, Jensen JB. Human malarial parasites in continuous culture. *Science*. 1976;193:673–5.
 22. Fonseca AG, Dantas LLSFR, Fernandes JM, Zucolotto SM, Lima AAN, Soares LAL et al. *In vivo* and *in vitro* toxicity evaluation of hydroethanolic extract of *Kalanchoe brasiliensis* (Crassulaceae) leaf. *J Toxicol*. 2018; 6849765:1–8. doi: <https://doi.org/10.1155/2018/6849765>
 23. Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J Immunol Methods*. 1983;65(1–2):55–63. [https://doi.org/10.1016/0022-1759\(83\)90303-4](https://doi.org/10.1016/0022-1759(83)90303-4).
 24. Peters W, Portus JH, Robinson BL. The chemotherapy of rodent malaria. XXII. The value of drug-resistant strains of *P. berghei* in screening for blood schizontocidal activity. *Ann Trop Med Parasitol*. 1975; 69(2): 155–171.
 25. Khan RA. Evaluation of flavonoids and diverse antioxidant activities of *Sonchus arvensis* L. *Chem Cent J*. 2012;6:1–7.
 26. Seal T. Quantitative HPLC analysis of phenolic acids, flavonoids, and ascorbic acid in four different solvent extracts of two wild edible leaf, *Sonchus arvensis* and *Oenanthe linearis* of North-Eastern region in India. *J App Pharm Sci*. 2016;6:157–66. <https://doi.org/10.7324/JAPS.2016.60225>.
 27. Poudel BK, Sah JP, Subedi SR, Amatya MP, Amatya S, Shrestha TM. Pharmacological studies of methanolic extracts of *Sonchus arvensis* from Kathmandu. *J Pharmacognosy Phytother*. 2015;7:263–7. <https://doi.org/10.5897/JPP2015.0359>.
 28. Prieto JM. Procedure: Preparation of DPPH radical, and antioxidant scavenging assay. Prieto's DPPH Microplate Protocol. 2012. Available: <https://www.researchgate.net/file.PostFileLoader.html?id=503cd1c9e39d5ea4d11000043&assetKey=AS%3A271744332435456%401441800305338>. Accessed 30 March, 2021.
 29. Esmaili AK, Taha RM, Mohajer S, Banisalam B. Antioxidant activity and total phenolic and flavonoid content of various solvent extracts from *in vivo* and *in vitro* grown *Trifolium pratense* L. (Red Clover). *BioMed Res Int*. 2015; 643285:1–11. doi: <https://doi.org/10.1155/2015/643285>.
 30. Olennikov DN, Zilfikarov IN, Toropova AA, Ibragimov TA. Chemical composition of *Callisia fragrans* wood juice and its antioxidative activity (*in vitro*). *Chem Plant Raw Mater*. 2008;4:95–100.
 31. Yahya MA, Nurrosyidah IH. Antioxidant activity of ethanol extract of gotu kola (*Centella asiatica* L.) with DPPH method (2,2-diphenyl-1-picryl-hydrazyl-hydrate). *Journal Halal Product and Research*. 2020; 3:106–112. doi: <https://doi.org/10.20473/jhpr.vol3-issue.2.106-112>.
 32. Putra BRS, Kusriani D, Fachriyah E. Antioxidant compound isolation from tempuyung (*Sonchus arvensis* L.) leaf ethyl acetate fraction. *J Kim Sains Apl*. 2013;16:69–72.
 33. Upadhya HC, Sisodia BS, Cheema HS, Agrawal J, Pal A, Darokar MP. Novel antiplasmodial agents from *Christia vespertilionis*. *Nat Prod Commun*. 2013;8:1591–4. <https://doi.org/10.1016/j.jpnp.2012.11.034>.
 34. Lima RB, Rocha e Silva LF, Melo MR, Costa JS, Picanço NS, Lima ES. *In vitro* and *in vivo* antimalarial activity of plants from the Brazilian Amazon. *Malar J*. 2015; 14:508. doi: <https://doi.org/10.1186/s12936-015-0999-2>.
 35. Mellado-García P, Maisanaba S, Puerto M, Prieto AI, Marcos R, Pichardov S, Cameán AM. *In vitro* toxicological assessment of an organosulfur compound from *Allium* extract: cytotoxicity, mutagenicity and genotoxicity studies. *Food Chem Toxicol*. 2017;99:231–40. <https://doi.org/10.1016/j.fct.2016.12.007>.
 36. De Souza GE, Bueno RV, de Souza JO, Zanini CL, Cruz FC, Oliva G, Guido RC, Caroline ACA. Antiplasmodial profile of selected compounds from Malaria Box: *In vitro* evaluation, speed of action and drug combination studies. *Malar J*. 2019; 18(404):447–459.
 37. Nurianti Y, Hendriani R, Sukandara EY, Anggadiredja K. Acute and subchronic oral toxicity studies of ethyl acetate extract of *Sonchus arvensis* L. leaf. *Int J Pharm Pharm*. 2014; 6:343–7.
 38. Harun N, Fitri V, Karningsih D. Effect of ethanol extract *Sonchus arvensis* Linn. Leaf on acute toxicity in healthy male albino rat (*Rattus norvegicus*). *J Phys Conf S*. IOP Conference Series. 2019; 1179:012163 IOP Publishing. doi: <https://doi.org/10.1088/1742-6596/1179/1/012163>.
 39. Flora G, Gupta D, Tiwari A. Toxicity of lead: a review with recent updates. *Interdiscip Toxicol*. 2012;5:47–58. <https://doi.org/10.2478/v10102-012-0009-2>.
 40. Chaniad P, Techarang T, Phuwaroanpong A, Na-ek P, Viriyavejakul P, Punsawad C. *In vivo* antimalarial activity and toxicity study of extracts of *Tagetes erecta* L. and *Synedrella nodiflora* (L.) Gaertn. from the Asteraceae family. *Evid Based Complement Altern Med*. 2021; 1270902:1–9. doi: <https://doi.org/10.1155/2021/1270902>.
 41. Ekasari W, Pratiwi DW, Amanda Z, Suciati WA, Arwati H. Various parts of *Helianthus annuus* plants as new source of antimalarial drugs. *Evid Based Complement Altern Med*. 2019;2019:7390385. <https://doi.org/10.1155/2019/7390385>.
 42. Imelda A, Sekarwana N. Protective Effect of ethanolic extract of *Sonchus arvensis* L. in gentamicin-Induced acute tubular necrosis on wistar rats. *Indonesian J Pharm*. 2018; 29:86–93. doi: <https://doi.org/10.14499/indonesianjpharm29iss2pp86>.
 43. Sukmayadi AE, Sumuwi SA, Aryanti AD. Immunomodulatory activity of tempuyung (*Sonchus arvensis* Linn.) leaf ethanolic extract. *Int J Biosci Technol*. 2014; 1:1–8.
 44. Somsak V, Chachiyo S, Jaihan U, Nakinchat S. Protective effect of aqueous crude extract of neem (*Azadirachta indica*) leaf on *Plasmodium*

berghei-induced renal damage in mice. *J Trop Med*. 2015; 961205. doi: <https://doi.org/10.1155/2015/961205>

45. Elias RM, Costa MC, Barreto CR, Silva RC, Hayashida C, Castoldi A, Camara NS. Oxidative stress and modification of renal vascular permeability are associated with acute kidney injury during *P. berghei* ANKA infection. In F. Costa (Ed.). 2012; 7(8):1–11.
46. Kumar S, Bandyopadhyay U. Free heme toxicity and its detoxification systems in human. *Toxicol Lett*. 2005;157:175–88.
47. Jeney V, Balla J, Yachie A, Varga Z, Vercellotti GM. Pro-oxidant and cytotoxic effects of circulating heme. *Blood*. 2002;100:879–87.
48. Valko M, Leibritz D, Moncol J, Cronin MTD, Mazur J, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Inter J Biochem Cell Biol*. 2007; 39:44–84.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions





**UNIVERSITAS AIRLANGGA FACULTY OF DENTAL MEDICINE
HEALTH RESEARCH ETHICAL CLEARANCE COMMISSION**

ETHICAL CLEARANCE CERTIFICATE

Number : 499/HRECC.FODM/XI/2020

Universitas Airlangga Faculty Of Dental Medicine Health Research Ethical Clearance Commission has studied the proposed research design carefully, Declared to be ethically appropriate in accordance to 7 (seven) WHO 2011, and therefore, shall herewith certify that the research entitled :

"Test for The Antiplasmodial Activity of Tempuyung Leaf Extract (*Sonchus arvensis*) in mice Exposed to *Plasmodium berghei*"

Principal Researcher : RIZAL ADISTYA PUTRA PRADANA

Unit/Institution/Place of Research : - Faculty of Science and Technology,
Universitas Airlangga, Surabaya

CERTIFIED TO BE ETHICALLY CLEARED



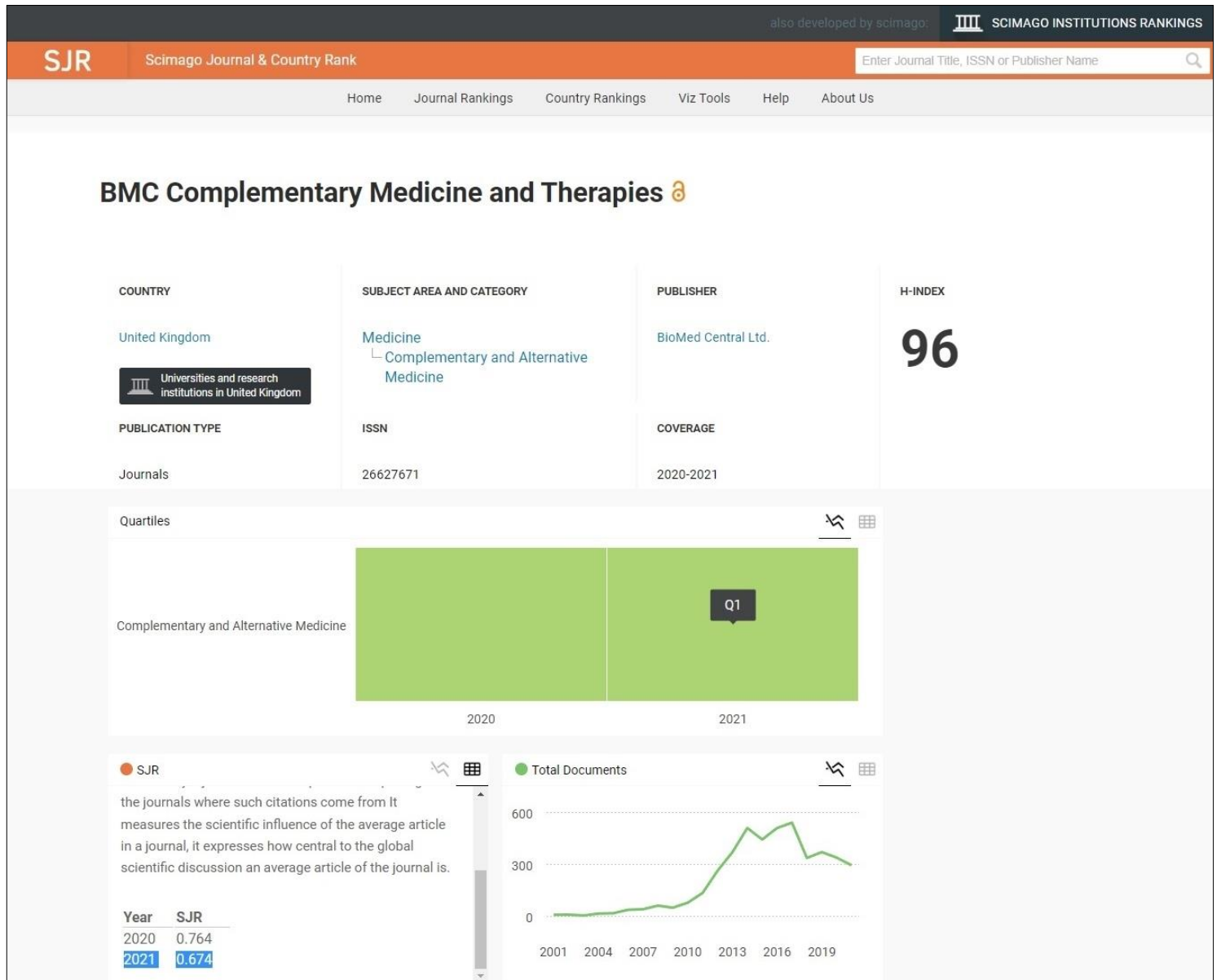
Surabaya, November 9, 2020

Chairman,

Prof. Dr. IGA ENGUS NARMADA, drg., Sp.Ort(K)

Official No.195601071981031003

Bukti – Subject Area and Category, Quartile dan SJR



Bukti – Scopus Coverage, Publisher dan ISSN



Scopus Preview

Author Search

Sources



Create account

Sign in

Source details

Feedback > Compare sources >

BMC Complementary Medicine and Therapies

Formerly known as: BMC Complementary and Alternative Medicine

Open Access ⓘ

Scopus coverage years: from 2020 to Present

Publisher: Springer Nature

E-ISSN: 2662-7671

Subject area: Medicine: Complementary and Alternative Medicine

Source type: Journal

View all documents >

Set document alert

Save to source list

CiteScore 2021

6.2 ⓘ

SJR 2021

0.674 ⓘ

SNIP 2021

1.471 ⓘ

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



$$6.2 = \frac{8,367 \text{ Citations 2018 - 2021}}{1,347 \text{ Documents 2018 - 2021}}$$

Calculated on 05 May, 2022

CiteScoreTracker 2022 ⓘ

$$5.1 = \frac{5,782 \text{ Citations to date}}{1,133 \text{ Documents to date}}$$

Last updated on 06 June, 2022 • Updated monthly

CiteScore rank 2021 ⓘ

Category	Rank	Percentile
Medicine Complementary and Alternative Medicine	#9/93	90th